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About the 23rd IMS Annual Meeting

The 23rd International Myeloma Society Annual Meeting, under the auspices of the International Myeloma Society (IMS), is devoted to fostering scientific and clinical echange on the latest breakthroughs in multiple myeloma and related plasma cell disorders. Scientific programming at the 23rd IMS Annual Meeting will cover the latest genomic advances, new drug targets and agents, immunotherapeutic approaches including Car T-cell therapies, and more.

This book compiles the abstracts fom oral and poster session presentations at the 23rd IMS Annual Meeting held at the Metro Toronto Convention Centre in Toronto, Canada from September 23–26, 2026. The abstracts ae reproduced as submitted by the author and accepted by the Scientific Program Committee. They appear in oder of abstract code and track.

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The purpose of this society is to promote research, education, clinical studies (including diagnosis and treatment), workshops, conferences, and symposia on all aspects of multiple myeloma worldwide.

The IMS is a membership organization comprised of basic research scientists, and clinical investigators in the field along with physicians and other healthcare practitioners.

IMS is governed by a Board of Directors representing practices from around the world and encourages and promotes the study of this expanding field though its annual meeting.

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Abstracts of the 23rd International Myeloma Society Annual Meeting

Clinical Lymphoma, Myeloma & Leukemia Vol. 26, No. S2, S1–S392, 2026

ORAL PRESENTATIONS

OA-01

5-Year Sustained Minimal Residual Disease (MRD) Negativity and Survival with Daratumumab Maintenance (D-maint) in Transplant-Eligible (TE) NDMM: CASSIOPEIA Registry

Jill Corre[1], Pieter Sonneveld[2], Sonja Zweegman[3], Cyrille Touzeau[4], Aurore Perrot[1], Cyrille Hulin[5], Bertrand Arnulf[6], Michel Delforge[7], Thomas Dejoie[8], Lionel Karlin[9], Nathalie Meuleman[10], Laure Vincent[11], Jean-Richard Éveillard[12], Cécile Sonntag[13], Mohamad Mohty[14], Xavier Leleu[15], Margaret Macro[16], Yuping Chen[17], Alba Tuozzo[17], Carla de Boer[17], Fredrik Borgsten[17], Melissa Rowe[17], Ariane Boumendil[18], Philippe Moreau[4]

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Introduction: CASSIOPEIA showed daratumumab, bortezomib, thalidomide, dexamethasone (DVTd) induction/autologous stem cell transplantation/consolidation improved outcomes vs VTd in TE-NDMM. D-maint led to prolonged progression-free survival (PFS) from 2nd randomization (2R) vs observation (OBS) (median PFS [mPFS] not reached vs 46.7 mo; HR 0.53; P < 0.0001), with sustained MRD negativity (neg) ≥12 mo (10^{-6}) in 56% (DVTd+D-maint) vs 37% (DVTd+OBS) pts. This interim analysis of the IFM202303/MMY0010 registry (follow-up [FU] study) presents long-term survival and MRD analyses. **Methods:** Pts alive at CASSIOPEIA study completion were eligible for the registry. Efficacy analyses used a data cutoff of 19 Sep 2025; median FU (mFU) was ~102.9 mo from 1st randomization (1R) and ~93.5 mo from 2R. MRDneg was assessed at 10^{-5} and 10^{-6} in bone marrow post-consolidation. Sustained MRDneg with complete response or better (≥CR) was defined as MRDneg during the analysis period, with no positive result in between, and before subsequent tx or disease progression. Net survival was estimated using the Pohar-Perme method, with expected survival derived from French general population life tables. **Results:** 802/835 eligible pts (96%) were enrolled in the registry, reflecting high retention. From 1R, mPFS was significantly prolonged with DVTd vs VTd (87.8 vs 54.7 mo; HR 0.62 [95% CI 0.53–0.72]; P < 0.0001) and overall survival was significantly improved (HR 0.61 [0.47–0.77]; P < 0.0001). At 96 mo, net survival was 94.3% (95% CI 90.7–98.0%) with DVTd vs 80.7% (95% CI 76.4–85.2%) with VTd. A maximum likelihood excess hazard model confirmed a significantly higher excess mortality in the VTd arm (excess HR 2.40 [95% CI 1.47–3.91]; P < 0.001). Duration of FU from 2R was well balanced across arms (mFU: 93.5 mo D-maint vs 93.4 mo OBS). From 2R, D-maint significantly prolonged mPFS (91.7 vs 44.6 mo; HR 0.52 [0.44–0.62]; P < 0.0001) and PFS2 (HR 0.72 [0.57–0.91]; P = 0.0062) vs OBS. When divided by tx arm from 2R, a trend favoring D-maint vs OBS was seen in DVTd- and VTd-treated pts; DVTd+D-maint showed the best PFS outcomes (mPFS not reached; 52.6% of patients alive and progression-free at 96 mo). 5-y sustained MRDneg (≥CR, 10^{-5}) rates were 23.1% (DVTd+D-maint), 17.9% (DVTd+OBS), 15.5% (VTd+D-maint), and 5.6% (VTd-OBS), with significantly higher rates in pts receiving D-maint vs OBS in the VTd arm (OR 3.23, P = 0.0007). These 5-y sustained MRDneg findings are further explored and data will be presented, including landmark PFS from last MRDneg assessment in pts with 5-y sustained MRDneg. **Conclusions:** After >8.5 y mFU with 96% retention, CASSIOPEIA registry data confirm deep and durable benefit of daratumumab tx. DVTd reduced risk of progression vs VTd by 38% and mortality by 39%. D-maint demonstrated prolonged mPFS and PFS2 vs OBS. 5-y sustained MRDneg was higher with D-maint vs OBS, and correlated with higher 96-mo PFS rates. These data demonstrate that D-maint is crucial for maintaining MRDneg after consolidation, and key to long-term disease control.

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OA-02

A CD4-Dominant, T-Helper-Skewed T Cell State Underlies Movement and Neurocognitive Toxicity After BCMA-Directed CAR-T Therapy in Multiple Myeloma

Theresia Akhlaghi[1], Mateo Mejia Saldarriaga[1], David Jayabalan[1], Joshua Kassner[1], Frank Costanzo[1], Kameisha Gulgar[1], Christian Gordillo[2], Sarah Wesley[2], Roger Pearse[1], Giorgio Inghirami[1], Ran Reshef[2], Ruben Niesvizky[1], Mark Bustoros[1]

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Introduction: Movement and neurocognitive toxicity (MNT) is a serious complication of B-cell maturation antigen (BCMA) chimeric antigen receptor T cell (CAR-T) therapy, yet its mechanism is unresolved and predictive pre-treatment biomarkers limited. **Methods:** We retrospectively analyzed 105 patients with relapsed/refractory multiple myeloma treated with cilta-cel (n = 87) or ide-cel (n = 18) at our institutions. CD4 and CD8 cells were measured by flow cytometry at apheresis. Single-cell RNA sequencing and proteomics were performed on PBMCs/serum from 29 patients at apheresis and peak expansion (days 9–15 post-infusion [post-tx]). This work was funded by the International Myeloma Society Translational Award. **Results:** Thirteen patients (12.4%) developed MNT. Apheresis CD4/CD8 ratio was higher in MNT+ patients; ratio >1.6 predicted MNT (AUC 0.80), similar to post-infusion maximum absolute lymphocyte count (ALCmax; AUC 0.78). In multivariable analysis adjusting for age, prior lines, extramedullary disease, ALCmax, and response to bridging (≥PR vs < PR or none), ratio >1.6 remained an independent predictor (OR 12.7, p = 0.02). In MNT+ patients with available CSF flow cytometry, T cells were predominantly CD4+ (mean CD4:CD8 20:1) in cilta-cel patients, with >50% expressing BCMA CAR; a single ide-cel case showed a different composition (CD4:CD8 = 0.9:1, 24% BCMA CAR). scRNA-seq confirmed elevated CD4/CD8 ratio in MNT+ patients (baseline 3.8 vs 1.1, p < 0.001; post-tx 2.8 vs 0.8, p = 0.005). MNT+ patients also had increased CAR-T expansion at ALCmax (50.5% vs 11.4% CAR+ cells, p = 0.004) and higher CD4 CAR+ cells. Dissecting T cell subsets post-tx revealed expansion of CD4 central memory (38.6% vs 17.6%, p = 0.007) and CD4 effector-memory (20.9% vs 10.7%, p = 0.027) and decreased CD8 effector-memory (2.4% vs 7.7%, p = 0.002) and CD8 TEMRA (1.2% vs 16.2%, p < 0.001) subsets in MNT+ patients. Functionally, MNT+ patients showed a post-infusion shift towards a T follicular helper-like signature (Tfh-2 p < 0.001, Tfh-1 p = 0.003, T peripheral helper p = 0.011), seen in both the CAR+ and endogenous CAR − compartments. MNT+ patients had an increased inflammatory signaling at baseline, with T cell upregulation of TNF-α/NF-κB (q = 0.001), type-I interferon response (q = 0.003), IL-2/STAT5 signaling (q = 0.011), and inflammatory response (q = 0.026). At ALCmax, MNT+ T cells showed enrichment of cell-cycle programs (G2-M Checkpoint CD8 q = 0.014; E2F Targets q = 0.055), consistent with their increased CAR-T expansion. Proteomics is ongoing to delineate the cytokine profile. **Conclusions:** Apheresis CD4/CD8 ratio >1.6 is an independent pre-infusion predictor of MNT. MNT+ patients showed greater CAR-T expansion, higher CD4 CAR+ cells, and CD4-dominant CSF infiltration. The T cell compartment showed helper-T-skewed programming in both CAR+ and bystander T cells, and elevated baseline inflammatory signaling. These findings support apheresis CD4/CD8 ratio as a pre-infusion screening biomarker and identify T cell phenotypes and states contributing to MNT.

OA-03

A Fixed-Duration, Modified Cevostamab Dosing Regimen Induces Durable Remissions That Continue After Completion in BCMA-Naïve Pts With Relapsed/Refractory Multiple Myeloma (RRMM): CAMMA 1 Arm A Results

Amrita Y. Krishnan[1], Henning Schade[2], Simon J. Harrison[3], Suzanne Trudel[4], Ameet Mishra[5], Sammy Chebon[6], Tulika Tyagi[5], Divya Samineni[5], Leanne Richardson[7], Ravi Vij[8]

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Introduction: Cevostamab is a first-in-class FcRH5xCD3 bispecific antibody. In a Phase I study, fixed-duration cevostamab induced durable responses in late-line RRMM, with more pronounced activity in BCMA-naïve pts, when initiated with single, double or triple step-up dosing in C1 and continued Q3W at the 160 mg target-dose (TD) in C2–17 (Richter et al. ASH 2024). Anti-tumor activity could be improved by increasing the intensity of target dosing (QW) in the initial cycles, while convenience could be improved by decreasing the intensity in later cycles. Arm A of the Phase Ib CAMMA 1 study (NCT04910568) is evaluating the safety, PK and activity of a fixed-duration, modified cevostamab dosing regimen in RRMM. We report data for BCMA-naïve pts. **Methods:** Eligible pts were those with RRMM for whom no established therapy was available or appropriate. Cevostamab was initiated with a single step-up dose (3.6 mg) on C1D1 and continued at TD (90 mg) QW in C1–2, Q2W in C3–6 and Q4W in C7–13 unless disease progression (PD) or unacceptable toxicity occurred; each cycle was 28 days. **Results:** As of 23 January 2026, 24 BCMA-naïve pts had been enrolled (median age: 66.5 years); 33.3% (7 of 21 evaluable pts) had high-risk cytogenetics (t(4;14), t(14;16) or del(17p)) and 8.3% had extramedullary disease. The median number of prior lines was 4. Most pts (87.5%) were refractory to their last line; 62.5% were triple-class refractory and 37.5% were penta-drug refractory. Median follow-up was 47.5 months. The objective response rate was 70.8%,

the VGPR+ rate was 58.3% and the CR+ rate was 33.3%. Median time to first PR was 1.0 month, VGPR was 3.3 months and CR+ was 9.7 months. Median DOR was 46.5 months (95% CI: 9.0, NE). Eleven pts who achieved PR+ completed the planned 13 cycles of treatment. Ten pts had responses lasting ≥40 months after initiation, 7 of whom were in CR+ at the end of treatment. Median PFS among all pts was 12.4 months (95% CI: 2.8, NE). Grade (Gr) 3–4 AEs occurred in 70.8% of pts; Gr 3–4 AEs in ≥10% were neutropenia (54.2%) and anemia (29.2%). Gr 3–4 infections occurred in 33.3%. Nine pts (37.5%) received IV immunoglobulin. CRS occurred in 75.0% (Gr 1, 50.0%; Gr 2, 20.8%; Gr 3, 4.2%); CRS occurred after the step-up dose (14 pts) and initial TD (8 pts) only. CRS was managed with tocilizumab in 7 pts and steroids in 4 pts. AEs leading to cevostamab withdrawal occurred in 2 pts (assessed as cevostamab related: pneumonia; not related: hemophagocytic lymphohistiocytosis and acute myeloid leukemia). Gr 5 AEs excluding PD occurred in 2 pts (not related: sepsis and cerebrovascular accident). **Conclusions:** A fixed-duration, modified cevostamab dosing regimen induces durable remissions that continue after treatment completion in BCMA-naïve pts with RRMM. Safety was manageable. Exposure-response analyses evaluating the relationship between the modified regimen, VGPR+ rates and DOR are ongoing and will be presented, as will data on B-cell recovery kinetics.

OA-04

A Novel Analytical Approach to Addressing the Challenge of Assessing Overall Survival in Myeloma Trials in the Context of a Rapidly Evolving Treatment Landscape

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Introduction: Multiple myeloma is a relapsing-remitting cancer. Patient outcomes have improved over the last decades through the introduction of novel agents. This has led to the use of PFS and more recently MRD negativity as surrogate endpoints for OS for licencing and early adoption of novel therapies. However, OS results remain of critical interest. OS analysis requires patients to be followed up for many years. In this time post-relapse treatment practices can change resulting in a non-homogenous population. This makes it hard for researchers to conclude from a conventional ITT analysis whether (the lack of) an OS effect is because of the trial intervention or post-relapse treatment. Here we present a novel analytical approach to quantify the effect of post-relapse treatment to aid clinical interpretation and ensure OS conclusions from trials stay relevant in an evolving treatment landscape. **Methods:** Myeloma XI+ was a UK randomised phase III trial for patients with newly diagnosed multiple myeloma eligible for autologous stem cell transplant. Between 2013 and 2016, 1056 patients were randomised between cyclophosphamide, thalidomide, and dexamethasone (CTD), cyclophosphamide, lenalidomide, and dexamethasone (CRD) or carfilzomib, cyclophosphamide, lenalidomide and dexamethasone (KCRD). At trial outset first relapse options included thalidomide, lenalidomide or bortezomib combinations. In 2019, a combination therapy including the monoclonal antibody (mAB), daratumab, became available on the NHS and was widely adopted in the UK. We therefore considered the OS effect of KCRD versus CTD/CRD if everyone who discontinued, without death, received subsequent treatment including a mAB. Two-stage estimation (TSE) was applied with a generalised gamma accelerated failure time model. Clinical experts guided variable selection. Re-censoring was implemented as a sensitivity analysis. **Results:** With a median follow-up of 101 months (IQR: 94,108), 48.2% (509/1056) of patients were recorded as receiving subsequent treatment. 15.1% (77/509) were reported to receive a mAB. Using TSE, the hazard ratio (HR, 95%CI) was 0.99 (0.79, 1.24). The equivalent ITT and re-censoring HRs were 0.96 (95%CI: 0.76, 1.21) and 0.96 (95%CI: 0.77, 1.22) respectively. **Conclusions:** This work provides a novel application of TSE in order to disentangle the effect of subsequent treatments on OS. In this example, if all patients received subsequent mAB the trial OS difference narrows. This is important for ongoing trials, especially in newly diagnosed populations, as current advances in myeloma therapy to include bispecific antibody therapies at relapse will impact OS treatment effects. Through the application of TSE as a sensitivity analysis in a clinical trial to complement the conventional ITT analysis, researchers can be confident in their conclusions. However, in order to apply the method, researchers must collect information on post-relapse treatment and patient and disease characteristics.

OA-05

An AI-Designed BCMA/FcRL5 Targeting TriTE Overcomes Antigen Escape and Outperforms BCMA-Directed Therapy in Multiple Myeloma

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Introduction: BCMA-directed immunotherapies have improved outcomes in multiple myeloma (MM), but their efficacy may be limited by heterogeneous antigen expression or loss, and treatment

resistance. FcRL5 is a B-lineage-restricted surface antigen broadly expressed in MM and Waldenström macroglobulinemia (WM), with minimal expression in healthy non-B cells, supporting its development as a selective therapeutic target. To address the limitations of single-antigen targeting, we developed a novel OR-gated BCMA/FcRL5 trispecific T-cell engager (TriTE) designed to enhance antitumor activity, broaden target coverage, and reduce susceptibility to antigen escape. **Methods:** BCMA/FcRL5 TriTE candidates were identified using a discovery platform integrating high-throughput functional screening with generative artificial intelligence–guided design. In vitro activity was evaluated by flow cytometry–based assays. In vivo efficacy was assessed in humanized MM mouse models. **Results:** Generative artificial intelligence–guided designs of antibody constructs were prioritized using a novel method based on T-cell effector performance against BCMA or FcRL5 single- or double-positive cells rather than affinity alone. We selected both BCMA and FcRL5 targeting antibodies and tested multiple constructs selecting the lead trispecific reagent termed CB-101. CB-101 induced greater tumor cell killing and T-cell activation than benchmark BCMA- or FcRL5-directed T-cell engagers in MM cell lines and primary MM samples naïve or treatment-resistant, while showing similar cytokine release. Potent activity was also observed in WM cell lines and primary WM samples, supporting the broader applicability of this dual-targeting approach. Importantly, TriTE activity was maintained in MM cells with CRISPR-based knockout of BCMA or low expression of FcRL5. Cytotoxicity was further enhanced in BCMA-knockout cells engineered to overexpress FcRL5; in this setting, CB-101 outperformed both Teclistamab and Cevostamab. In addition, the presence of soluble BCMA or FcRL5 did not significantly impair antitumor activity of CB-101. These results suggest that CB-101 is less vulnerable to clinically relevant BCMA escape mechanisms. In vivo, using humanized disseminated MM mouse models, CB-101 achieved greater antitumor efficacy than Teclistamab even at 10x lower doses. This led to a markedly prolonged survival with all TriTE-treated mice survived beyond 170 days compared to a median survival of 82 days with Teclistamab, demonstrating deep and durable disease control. **Conclusions:** CB-101, a BCMA/FcRL5 TriTE, demonstrated enhanced antitumor activity in vitro and in vivo, outperforming BCMA-directed therapy even at substantially lower doses and retaining efficacy in settings associated with antigen escape and drug resistance. Enabled by an AI-driven high-throughput discovery platform, this next-generation BCMA/FcRL5 TriTE with provocative preclinical data is now poised for clinical evaluation in MM and WM to improve outcomes.

OA-06

Anticoagulation for ThrOmbosis Prevention in Multiple Myeloma (ATOMM): Thromboprophylaxis in Elderly and Renal Impairment in a Large UK Real-World Cohort

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Introduction: We previously showed increasing use of DOACs for thromboprophylaxis in newly diagnosed multiple myeloma (NDMM), with low overall thrombotic rates compared with historic cohorts. However, thromboprophylaxis decision-making in elderly patients (pts) and those with renal impairment remains poorly characterised. **Methods:** UK-wide, retrospective observational study auditing thromboprophylaxis use in first 6 months' treatment of NDMM 1/1/21–1/8/24, collecting thrombosis and bleeding rates, excluding patients on treatment-dose anticoagulation. Anonymised clinical data was manually extracted from routine records with IMPEDE scores retrospectively calculated. Pts were stratified by age (< 80 y n = 1,968; ≥80 y n = 391) and creatinine clearance (CrCl) (≥50 n = 1,004; 30–49 n = 769; < 30 n = 581; unknown n = 5) calculated by Cockcroft-Gault equation. **Results:** 2,359 pts from 40 centres: median age 69 y (27–100), 58.8% male, 50.1% transplant-eligible (TE). Frontline therapy evolved during the study period from VTD/VCD triplets towards Dara-VTD in TE pts: 8% (2021), 76% (2022), 66% (2023), 70% (2024). IMiD use increased in non-TE pts from 2023 [Rd (21%), Dara-Rd (17%)] with Dara-Rd predominating in 2024 (75%). IMiD use overall was lower in pts ≥80 y (66% vs 78%, $p < 0.001$) and decreased with worsening renal function (86%, 79%, 55% for CrCl ≥50, 30–49, < 30 respectively; $p < 0.001$).

The proportion of pts classified as IMPEDE intermediate/high-risk decreased both with age (75% ≥80 y vs 84% < 80 y, $p < 0.001$) and worsening renal function (89%, 84%, 72% for CrCl ≥50, 30–49, < 30 respectively). Pts ≥80 y received less thromboprophylaxis (64% vs 78%), with lower LMWH use (18% vs 26%, $p = 0.008$) and higher aspirin/warfarin use (8% vs 4%, $p = 0.005$), while DOAC use was similar (73% vs 69%, $p = 0.2$). Thromboprophylaxis use declined with worsening renal impairment, with no prophylaxis in 14%, 24%, and 44% of pts with CrCl ≥50, 30–49, and < 30 respectively. Among pts receiving thromboprophylaxis, LMWH use was higher in CrCl < 30 than pts with CrCl ≥30 (33% vs 23%, $p < 0.001$) and less likely to receive DOACs (61% vs 72%, $p < 0.001$). DOACs predominated in CrCl ≥30 (72% in 30–49, 71% in ≥50).

80% (235/295) of IMPEDE intermediate/high-risk pts aged ≥80 y received thromboprophylaxis. 73% (304/415) of IMPEDE intermediate/high-risk pts with CrCl < 30 received thromboprophylaxis. Age was not independently associated with DOAC use after multivariable adjustment. Renal function was not significantly associated with venous/arterial thrombotic events or bleeding outcomes, even when adjusted for thromboprophylaxis. **Conclusions:** IMiD use was lower in elderly pts but increased over time, while remaining low in pts with CrCl < 30. Pts ≥80 y and those with CrCl < 30 were less likely to receive thromboprophylaxis even when classified as IMPEDE intermediate/high-risk, highlighting variation in guideline-recommended prophylaxis use in these subgroups. No clear association was observed between renal impairment and thrombotic or bleeding outcomes.

OA-08

Augmenting TRAIL-Dependent Apoptosis Enables BCMA CAR-T Cells to Overcome Resistance in Multiple Myeloma

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Introduction: BCMA-directed CAR-T cell therapy induces high initial response rates in multiple myeloma (MM), yet relapse remains common due to limited persistence, functional exhaustion, and/or tumor-intrinsic resistance. Transcriptomic analyses of anti-BCMA CAR-T cells from MM patients with durable remissions revealed elevated expression of TNFSF10 (TRAIL), BCL2L1 (BclxL), and CD28, implicating death receptor signaling and survival pathways in sustained antitumor activity. **Methods:** Anti-BCMA CAR-T cells incorporating 4-1BB and CD3ζ signaling domains were engineered to co-express either membrane-bound TRAIL or a chimeric TRAIL-CD28 fusion protein. CAR-T cell function was evaluated across a panel of MM cell lines, including models with acquired resistance. Chronic stimulation, low effector-to-target ratios, and repeated tumor rechallenge were used to model exhaustion. Validation of CAR-independent TRAIL-CD28 signaling was obtained via DR4 and/or BCMA coated plates. Off-tumor activity was evaluated using healthy donor PBMCs and iPSC-derived hepatocytes, and anti-tumor efficacy was assessed in MM mice models. **Results:** Genetic disruption of death receptor signaling in MM cells through deletion of FADD or expression of cowpox CrmA (caspase 8 inhibitor) significantly impaired killing by unmodified BCMA CAR-T cells, although to a degree lower than what observed with granzyme B inhibition, demonstrating a nonredundant role for death receptor–mediated apoptosis. TRAIL-armored CAR-T cells exhibited enhanced cytotoxicity across diverse MM models and maintained activity under exhaustion-inducing conditions and resistant models, including T cell–engager–resistant and NFκB-activated MM. Constitutive TRAIL expression induced limited CAR-T fratricide at high cell densities correlated with high rate of relapse in vivo; this was substantially mitigated by the TRAIL-CD28 chimera, which promoted sustained BclxL expression, and enhanced functional properties. Interestingly, TRAIL-CD28 armored CAR-T cells retained a central memory-like phenotype (CD62L+ CD45RA- cells with lower pAKT, lower pERK1/2, lower TOX, and higher TCF1) during the resting phase following chronic tumor cell stimulation. Moreover, BCMA-low and granzyme B–resistant MM cells overexpressing SerpinB9 remained sensitive to TRAIL-CD28–armored CAR-T cells. In vivo, TRAIL-CD28–armored CAR-T cells mediated superior tumor control (even after tumor rechallenge two months after initial CAR-T injection) in the mice bearing NFκB-activated MM cells. Importantly, CAR-T cells remained detectable in the bone marrow of rechallenged mice treated with the TRAIL-CD28 group, suggesting enhanced persistence compared with control groups. **Conclusions:** TRAIL-CD28 reinforcement enhances BCMA CAR-T cell cytotoxic durability and enables bypass of canonical resistance mechanisms in MM. TRAIL-CD28 signaling can further address potential fratricide while augmenting efficacy, supporting death receptor–guided armoring as a strategy to overcome relapse/refractory in MM.

OA-09

BCMA CAR T-Cell Therapy (Equecabtagene Autoleucel, Eque-Cel) for Multiple Myeloma in Chinese Clinical Practice: A Large Real-World Evidence of 281 Patients

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Introduction: Equecabtagene autoleucel (Eque-cel) is a fully human BCMA-targeted CAR T-cell therapy approved for relapsed/refractory multiple myeloma (RRMM). As pivotal trials enroll selected populations, real-world evidence in unselected, high-risk patients remains limited. We report effectiveness and safety from a large multicenter Chinese real-world cohort treated with Eque-cel across 65 clinical centers since its market launch on June 30, 2023. **Methods:** We analyzed 281 RRMM patients who received Eque-cel; 267 were response-evaluable. PFS and OS were estimated by Kaplan-Meier; CRS and ICANS were graded per ASTCT. Pre-lymphodepletion CAR-HEMATOTOX (CAR-HT) risk was recorded at baseline. Prespecified subgroups included age >70 y, anti-CD38 exposure, and CAR-HT risk. **Results:** Median age was 61 y (range 30–82; 18.7% ≥70 y); 59.4% male. Patients were heavily pretreated and high-risk: median 3 prior lines(Range 1–12); 69.4% triple-class and 27.4% penta-drug exposed; 46.9% prior ASCT; 84.0% prior anti-CD38; high-risk cytogenetics 82.4%; ISS III 50.5%; PCL 7.8%; extramedullary disease 47.0%. Pre-lymphodepletion CAR-HT was high in 75.3% of evaluable patients.

ORR was 95.9% (256/267), with CR/sCR 77.2% (sCR 42.7%) and ≥VGPR 86.9%; MRD negativity was 94.1% among evaluable patients. At a median follow-up of 10.97 months, median PFS and OS were not reached; 12-mo PFS and OS were 71.5% and 87.8%. Overall safety was manageable: any-grade CRS was 88.2%(with grade ≥3 was 3.8%); any-grade ICANS was 6.8%; No Parkinsonism was observed. Outcomes were consistent across higher-risk subgroups: effectiveness and safety in patients >70 y (n = 35; ORR 94.3%, 12-mo PFS 69.6%) and in anti-CD38–exposed patients (n = 223; ORR 96.0%, 12-mo PFS 68.5%) were comparable to the overall cohort, with no excess in grade ≥3 CRS or ICANS. CGS-defined high-risk disease was present in 53.1% (94/177) of cytogenetically evaluable patients; this subgroup retained high effectiveness, with ORR 98.9% and 12-mo PFS 65.1%. In contrast, CAR-HT stratified prognosis: high-risk patients (n = 107) had lower 12-mo PFS (60.3% vs 86.9%) and higher toxicity (grade ≥3 CRS 6.5%, ICANS 9.7%) than low-risk patients (n = 37; no grade ≥3 CRS or ICANS), despite similar high ORR. **Conclusions:** In 281 high-risk, heavily pretreated Chinese RRMM patients, Eque-cel achieved excellent effectiveness and favorable safety in routine practice, with no significant between-group differences in either effectiveness or safety by age (>70 y vs younger) or anti-CD38 exposure—including subgroups under-represented in the pivotal registration trial that nonetheless derived comparable, excellent benefit, thereby extending its applicability beyond the original trial population. In contrast, CAR-HT high-risk status stratified PFS and toxicity, supporting risk-adapted management.

OA-10

BMS-986453, a Dual-Targeting BCMA × GPRC5D Autologous CAR T Cell Therapy in Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM): Initial Results From a Phase 1 Trial

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Introduction: B-cell maturation antigen (BCMA) and G protein–coupled receptor class C group 5 member D (GPRC5D) are validated targets in MM. Simultaneous BCMA/GPRC5D targeting may overcome baseline antigen heterogeneity and treatment-related antigen loss. BMS-986453 is an investigational, dual-targeting BCMA × GPRC5D CAR T cell therapy. Here we report the first clinical results of the ph1, first-in-human, multicenter, open-label, dose-finding study of BMS-986453 in pts with RRMM (NCT06153251). **Methods:** Dose escalation and expansion included pts with ≥3 prior lines of therapy (pLOT), including a proteasome inhibitor, an immunomodulatory agent, and anti-CD38 therapy; prior anti-BCMA and/or GPRC5D therapies were allowed. After leukapheresis, pts received optional bridging therapy, then lymphodepletion, before a single infusion of BMS-986453. Primary objectives were safety, tolerability, and maximum tolerated dose (MTD) and/or recommended ph2 dose of BMS-986453. **Results:** At data cutoff (27Apr2026), 60 pts underwent leukapheresis and 58 (part A, 40; part B, 18) received BMS-986453 at doses of 25 (n = 21), 75 (n = 21), 150 (n = 14), and 300 (n = 2) million (M) CAR T cells. Median follow-up was 11.8 mo. Median age was 67 y, 33% had high-risk cytogenetics, and 26% had extramedullary disease. Pts had a median of 4 pLOT and 50% had triple-class refractory RRMM; prior

targeted therapy included BCMA (60%) and combined BCMA/GPCR5D (17%). Bridging therapy was given to 72%. Grade (G) 3/4 treatment-emergent adverse events (TEAEs) were reported in 98%; most common were neutropenia (88%) and thrombocytopenia (48%). Cytokine release syndrome (CRS) occurred in 78% (G3, 3.4%), immune effector cell–associated neurotoxicity syndrome in 3.4% (G3, 3.4%; no ≥G4), infections in 52% (≥G3, 21%), and weight loss in 10% (G3, 1.7%). There was 1 death due to CRS in the 300M cohort. Dose-limiting toxicities occurred in 19% pts (hematologic, 12%); MTD was not reached. Two pts (3.4%) had an other select neurotoxicity (n = 1 G1/resolved, n = 1 G2/ongoing). On-target, off-tumor TEAEs related to BMS-986453 occurred in 50%, including skin (19%), nail (36%) and oral (34%); all were ≤G2 except for 2 pts (3.4%) with G3 events which resolved. Pharmacokinetic analysis showed similar Tmax, Cmax, and AUC for 75M and 150M doses, both of which had greater peak and total exposure compared with 25M. Overall response rate (ORR) was 83% for all doses, 67% for 25M, and 94% for 75M/150M doses combined (n = 35; complete response rate [CRR] 71%). For pts with prior BCMA therapy (with/without GPRC5D), ORR was 77% for all (n = 35), 60% for 25M (n = 15), and 89% for 75M/150M (n = 19; CRR 58%). For BCMA/GPRC5D-naïve pts, ORR was 91% for all (n = 23), 83% for the 25M dose (n = 6), and 100% for 75M/150M (n = 16). In this latter group, ≥ very good partial response or better was 100%, CRR was 88%, 12-mo duration of response was 94%, and 100% were MRD-negative at the 10-5 threshold. **Conclusions:** BMS-986453 demonstrated favorable safety and efficacy in pts with RRMM.

OA-11

Cevostamab Plus Pomalidomide (Pom) and Dexamethasone (Dex) Induces Durable Remissions in BCMA-Naïve Patients With Relapsed/Refractory Multiple Myeloma (RRMM): CAMMA 1 Arm B Extended Follow-Up Data

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Introduction: FcRH5 is a membrane protein that is ubiquitously expressed on myeloma cells, independent of BCMA and GPRC5D expression. Cevostamab, a FcRH5xCD3 T-cell-engaging bispecific antibody, has shown encouraging activity as monotherapy in late-line RRMM, with more pronounced activity in BCMA-naïve pts. Combining cevostamab with anti-myeloma agents that augment T-cell activity could enhance efficacy. Initial data from the Arm B randomised dose-expansion stage of the Phase Ib CAMMA 1 study (NCT04910568) demonstrated that 70 mg and 105 mg cevostamab plus pom-dex have manageable safety and induce deep responses in BCMA-naïve pts with RRMM (Harrison et al. ASH 2025). We report extended follow-up data. **Methods:** Eligible pts were those with RRMM who had received ≥1 prior IMiD and ≥1 prior PI as part of ≥1 prior line. Pts were randomised (1:1) to 70 mg or 105 mg cevostamab given Q2W in C1–6 (28-day cycle) and Q4W in C7+. Pom (2 mg) was given on D1–21 and dex (20 mg) on D1, 8, 15 and 22 from C1+. Treatment was continued until disease progression (PD) or unacceptable toxicity. **Results:** As of 23 January 2026, 29 and 25 BCMA-naïve pts had been enrolled into the 70 mg and 105 mg cohorts, respectively (median age: 65 years in both cohorts). Among those, 10.3% and 32.0% had a conclusive assay result for high-risk cytogenetics (t(4;14), t(14;16) or del(17p)) and 13.8% and 12.0% had extramedullary disease. The median number of prior lines was 2 in both groups. Most pts were triple-class exposed (72.4% and 56.0%) and refractory to their last line (72.4% and 68.0%). Median time on study was 16.0 and 15.8 months in the 70 mg and 105 mg cohorts, respectively. Objective response rates were 86.2% and 88.0% and very good partial response or better rates were 75.9% and 76.0%. Median duration of response (DOR) and progression-free survival (PFS) were not estimable at data cut-off; 12-month rates were 87.2% and 77.3% for DOR and 78.6% and 75.1% for PFS. Rates of minimal residual disease (MRD)-negative complete response (CR) at the 10-5 level at any time were 92.3% (12/13 pts) in each arm among MRD-evaluable CR pts, and 41.4% (12/29) in the 70 mg cohort and 48.0% (12/25) in the 105 mg cohort among all efficacy evaluable pts. Grade (Gr) 3–4 adverse events (AEs) occurred in 82.8% and 96.0% of 70 mg and 105 mg pts, respectively. Gr 3–4 AEs in ≥15% were neutropenia (75.9%; 80.0%), anaemia (24.1%; 20.0%), thrombocytopenia (10.3%; 24.0%) and lymphopenia (3.4%; 16.0%). Gr 3–4 infections occurred in 17.2% and 36.0% and Gr 3–4 rash in 10.3% and 4.0%. CRS was all Gr 1 (53.8%) or Gr 2 (7.7%) in the subgroup of pts who initiated cevostamab with triple step-up dosing (n = 26). Gr 1 and Gr 2 ICANS occurred in 2 pts in the 105 mg cohort. Gr 5 AEs excluding PD occurred in 1 patient in each cohort (70 mg: septic shock; 105 mg: intracranial haemorrhage). **Conclusions:** Cevostamab plus pom-dex induces durable remissions in BCMA-naïve pts with RRMM. Updated data will be presented.

OA-12

Clinical Significance of Circulating Tumor Cells in Relapsed/Refractory Multiple Myeloma

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Introduction: Circulating tumor cells (CTCs) are increasingly recognized as a meaningful prognostic marker in newly diagnosed multiple myeloma (NDMM). Namely, the recently established CTC cutoffs of 0.02% and 2% identify high- and ultra-high-risk disease. However, its role in relapsed/refractory multiple myeloma (RRMM) remains uninvestigated. Thus, we evaluated the clinical significance of CTCs in a large series of RRMM patients including patients treated with anti-CD38 therapies. **Methods:** CTCs were assessed in 319 RRMM patients treated in Czech centers from 2022 to 2026 and included in the Czech registry of monoclonal gammopathies (RMG). Independent validation cohort included 240 patients enrolled in PETHEMA/GEM KyCyDex (NCT03336073) and SeliBorDara (NCT03589222) trials. CTCs were quantified by flow cytometry (FC) with median detection limit of 0.0007% in the exploratory and 0.0002% in the validation dataset. High-risk cytogenetics was defined by the presence of t(4;14), t(14;16), and/or del(17p). **Results:** CTCs were detectable in 71% of cases in the exploratory cohort and 89% in the validation cohort, with similar median (0.0056% vs. 0.0058%). Patients above the 0.02% cutoff had inferior outcomes with a median PFS of 11 vs. 22 months (mo) (HR = 1.55 [CI: 1.11–2.17], p = 0.009) and 6 vs. 21 mo (HR = 2.21 [CI: 1.61–3.04], p < 0.001) in the exploratory and validation cohorts, respectively. Median OS was 27 mo vs. not reached (NR) in both cohorts (p = 0.001 and p < 0.001 in validation). The prognostic impact of CTCs remained independent in multivariable Cox analysis adjusted for age, cytogenetic risk, and number of prior lines of treatment in both exploratory (HR = 1.61 [CI: 1.16–2.27], p = 0.004) and validation cohort (HR = 2.15 [CI: 1.56–2.96], p < 0.001). To increase the sample size, we merged both datasets. CTCs retained their significance across clinically relevant subgroups, including those defined by cytogenetic risk, prior lines, age, and ISS. Prognostic value was maintained among patients who had received anti-CD38 mAb treatment (n = 205) with a median PFS of 10 vs. 23 mo (HR = 1.98 [CI: 1.34–2.93], p < 0.001) and median OS of 30 mo vs. NR (HR = 2.16, [CI: 1.28–3.66], p < 0.001). Updated analysis in patients treated with T-cell redirecting therapy will be presented at the meeting. Furthermore, we tested the CTC cutoff for ultra-high-risk patients (≥2%) in the merged cohort. Patients above this threshold (n = 26) had a very poor prognosis with a median PFS of 4 vs. 17 mo (HR = 2.5 [CI: 1.61–3.91], p < 0.001) and an OS of 5 vs. NR (HR = 3.51 [CI:2.12–5.79], p < 0.001). **Conclusions:** CTCs assessed by FC are an independent prognostic biomarker in RRMM. CTC levels consistently stratify patients into distinct risk groups across disease subgroups and treatment settings, including anti-CD38 mAbs. Cutoffs established for smoldering and NDMM are also prognostic in RRMM. These findings support CTC use for risk stratification across all MM progression stages.

OA-13

Clinical Translation of LV169, a CD3-Targeted Lentiviral Vector for In Vivo Delivery of a BCMA-CAR Transgene to T Cells in Patients With Multiple Myeloma

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Introduction: BCMA-directed CAR T cell therapy has transformed the treatment of multiple myeloma, yet conventional autologous manufacturing imposes substantial logistical and clinical burdens. Direct in vivo CAR T cell engineering offers a compelling alternative paradigm. LV169 is a CD3-targeted lentiviral vector pseudotyped with chimeric VSV-G proteins detargeted from the LDL receptor and re-targeted to T cells via a surface-displayed CD3-specific scFv, enabling selective transduction of resting, niche-resident T cells in lymphoid tissues without ex vivo manipulation. **Methods:** LV169 was engineered to carry a novel BCMA-CAR construct comprising a fully human single-domain (nanobody) antigen-binding domain linked to 4-1BB and CD3ζ signaling domains. The CAR transgene is placed under a T cell-specific Lck promoter in reverse

orientation to eliminate CAR expression in producer cells and prevent off-target transduction of BCMA-positive cells. In vitro transduction efficiency and CAR T cell function were assessed in PBMC cultures from healthy volunteers and myeloma patients. In vivo efficacy was evaluated in a disseminated OPM-2 xenograft model using MHC-I/II double-knockout NSG mice engrafted with human PBMCs one week prior to a single intravenous dose of LV169-BCMA-CAR, administered three weeks after tumor engraftment. Tumor burden was monitored by luciferase imaging; circulating CAR T cells by flow cytometry; and serum cytokines by multiplex immunoassay. **Results:** LV169 specifically transduced resting T cells in PBMC cultures from both healthy donors and myeloma patients, generating BCMA-CAR T cells with low tonic signaling that efficiently killed BCMA-positive myeloma targets. Cytokine release was comparable to or lower than a clinically relevant benchmark CAR construct. In vivo, a single intravenous dose of LV169-BCMA-CAR induced durable responses: all treated mice achieved complete tumor clearance within 28 days, with kinetics correlating with LV particle dose; complete responses were observed even at the lowest dose tested. At 70 days post-treatment all mice remained tumor-free and fully resisted OPM-2 rechallenge, demonstrating long-lived functional immunity. Circulating CAR T cells were detectable by day 14, peaked between days 21–35, and contracted following tumor clearance,. Treatment was well tolerated with no evidence of severe cytokine release syndrome. IND-enabling studies were completed supporting safety and efficacy of LV169. **Conclusions:** LV169 enables efficient, selective in vivo BCMA-CAR T cell engineering without ex vivo manufacturing, producing durable anti-tumor responses with a favorable safety profile. A dose-escalation phase 1 trial is now initiating in patients with relapsed/refractory multiple myeloma, evaluating three dose levels. Primary endpoints are safety, tolerability, and maximum tolerated dose; secondary endpoints include pharmacokinetics and pharmacodynamics of in vivo-generated CAR T cells and determination of the recommended phase 2 dose.

OA-14

Clinically Significant Bone Disease Is Uncommon in Smouldering Myeloma Progressors Monitored With Modern Imaging: Findings From the Prospective Multi-Centre UK MRA COSMOS Study

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Introduction: With licensed treatment in high-risk smouldering myeloma(SMM), a surveillance approach needs careful monitoring plans that include regular whole body functional imaging to detect progression(PD) early and limit morbidity. We aimed to understand imaging patterns of progression in a prospectively followed cohort of patients with SMM. **Methods:** The UK MRA COSMOS study is a prospective multi-centre observational study in SMM(target = 750). Patients undergo baseline whole-body imaging at diagnosis; subsequent imaging is per IMWG guidelines and local practice. Patients exit the study at progression, defined locally. Patients meeting SLiM criteria are included if the local site elected not to treat as NDMM, MGUS patients can remain on study if they are entered to the study as presumed SMM. **Results:** Of 501 evaluable patients, 53 had progressed by the data cut-off (April 2026). Median follow up was 18 m, PD at median 13 m(5–51) from trial entry, median 22 m(6–189) from diagnosis. At study entry, 22/53(42%), 11/53(21%), 6/53 (11%) were Mayo 20/2/20 high/intermediate/ low risk, 10/53(19%) had SLiM disease, and 3/53(6%) MGUS. 25/53(47%) progressed with imaging changes (focal lesions(FL) and bone disease), 19/53 (37%) with biomarkers (SFLC ratio >100 or BM PC >60%), 6/53 (12%) had other CRAB features, 1/53(2%) MGCS, 1/53(2%) extramedullary disease. 43/53(81%) patients had imaging within two years of PD, 33/53(62%) within one year. Access to advanced imaging was high; 36/53(68%) underwent one or more surveillance WB-MRI or PET-CT. Among the 25 with imaging abnormalities at PD, 12(48%) had >1 FL only, 5(20%) had single lytic or mixed small lesions, while 8(32%) developed large lesions(>2 cm) or fractures. 7/8 of these were Mayo intermediate or high risk, 6/8 had biochemical change suggesting evolving disease before PD. All had surveillance imaging within two years of PD and 4/8 within one year. Of the 4 who had not had annual imaging, two were high risk with evolving disease, one was low risk and one >5 years from diagnosis. Of the patients imaged within the last year, one had a WB-CT and one had MRI spine only, potentially limiting earlier detection of FL or extra-spinal lesions. One patient required surgery for metastatic spinal cord compression and another emergency radiotherapy for cauda equina syndrome. **Conclusions:** Most COSMOS patients progressed with minor imaging abnormalities or biomarkers rather than clinically significant bone disease, supporting the value of modern surveillance imaging strategies. However, clinically significant bone disease still occurred in a minority(15% progressors, 1.6% cohort). Some cases appeared unavoidable with very recent whole-body imaging. Others may have been detected earlier through stricter adherence to surveillance

imaging and expanding guidance to those with evolving disease. Future work should focus on understanding the biology of skeletal progression to inform risk-adapted monitoring strategies.

OA-15

Dara-VRD Plus Tandem Autologous Stem Cell Transplantation Followed by Prolonged Consolidation for Primary Plasma Cell Leukemia: A French Phase II Prospective Trial

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Introduction: Primary plasma cell leukemia (PCL) is a rare and aggressive malignancy. Despite recent therapeutic advances in multiple myeloma, the prognosis of PCL remains poor, with a median survival of less than 3 years. Only a limited number of prospective trials have been conducted in this setting. **Methods:** The IFM group conducted a prospective phase II trial in patients with newly diagnosed PCL. The treatment strategy consisted of four cycles of DVRD (daratumumab, bortezomib, lenalidomide, dexamethasone) as induction, followed by a first autologous stem cell transplantation (ASCT). Patients then received two additional cycles of DVRD followed by a second ASCT. This was followed by prolonged consolidation including six cycles of DVRD (administered every two months) and at least one year of lenalidomide maintenance. The primary endpoint was hematological response (according to the IMWG response criteria for PCL) after induction. Secondary endpoints included cytogenetic evaluation, measurable residual disease (MRD) assessed by next-generation sequencing, progression-free survival (PFS), overall survival (OS), and safety. Preliminary data were analyzed after the second ASCT. **Results:** Twenty-nine patients were enrolled between February 2022 and September 2024. The median age was 59 years (range, 36–70), and the median creatinine clearance was 64 mL/min (range, 22–120). Three patients presented with extramedullary disease, 15 (56%) had high-risk cytogenetics (IMWG 2025), and 11 (26%) had t(11;14). As of May 2026, the median follow-up was 20 months (range, 0.7–36). Twenty-eight patients completed the induction phase. Overall, 23/29 patients (79%) achieved at least a very good partial response (VGPR), including 8 (28%) who achieved a complete response (CR) or better. Twenty-four patients underwent both the first and second ASCT. Among evaluable patients after the second ASCT (n = 22), 95% (n = 21) achieved at least VGPR, and 64% (n = 14) achieved CR or better. Seven patients (28%) achieved MRD negativity ($< 10^{-6}$) after induction, and 15 (52%) after the second ASCT. The principal serious adverse events were infections. A total of 6 patients died (5 from disease progression): 5 before the first ASCT, including 1 during induction, and 1 after the second ASCT. The median PFS has not yet been reached but 23 pts were alive at the time of analysis: they continued the programme and had not relapsed. **Conclusions:** These initial results suggest that DVRD combined with tandem ASCT is feasible and induces high hematological response rates in patients with PCL, a population with a particularly poor prognosis. This strategy may translate into improved survival outcomes. Future trials will explore combinations of DVRD and ASCT with anti-BCMA bispecific antibodies.

OA-16

Diffuse Bone Marrow Activity in Patients With Smouldering Multiple Myeloma: A WB-MRI Analysis

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Introduction: Smouldering Multiple Myeloma (sMM) is an asymptomatic plasma cell disorder with a variable yet significant risk of progression to symptomatic Multiple Myeloma (MM). Current prognostic models help stratify patients into risk categories but often lack dynamic markers that reflect ongoing disease biology. Diffuse marrow activity (DMA), a radiological finding observable especially via Whole Body MRI (WBMRI), has been proposed as a potential imaging biomarker, though its role in risk prediction remains underexplored in real-world sMM populations diagnosed with modern IMWG criteria. **Methods:** This retrospective study enrolled 100 patients diagnosed with sMM between 2014 and 2026 according to the IMWG criteria. Patients underwent WBMRI and/or PET/CT at baseline. DMA was defined as an ADC range between 550 and 750 $\mu m^2/s$ on WBMRI, meanwhile in PET/CT was defined as Deauville/score 3–4. Prognostic stratification was performed using 20/20/2 and PANGEA at diagnosis and last follow-up. Statistical analysis was conducted using SPSS v30.0 to correlate imaging findings with clinical and biochemical markers, time to progression (TTP), and risk evolution. These results regard the WBMRI subgroup of the study. **Results:** DMA was detected in 43% of patients overall, with higher sensitivity observed in WBMRI (71%)

compared to PET/CT (29%). 28 patients progressed to MM over a median follow-up of 20 months (range: 8–132), with a median TTP of 39.5 months. In the WBMRI subgroup (51%), 14 patients progressed to MM, of these 71% showed DMA at baseline. Mean TTP was 40 months but evaluating separately patients with and without DMA who progressed to MM, TTP differed significantly, with a median TTP of 28 months in DMA-positive patients compared to a median TTP of 70 months in the DMA-negative subgroup. Interestingly, in patients who did not progress, the expression of DMA correlated with a statistically significant increase in dFLC ratio and bone marrow infiltration. More importantly, DMA at baseline correlated with a higher PANGEA risk score compared to DMA negative patients. **Conclusions:** WBMRI is a cardinal radiological in patients with sMM. New findings suggest the use of DMA as prognostic biomarker. This study describes a subgroup of patients with sMM which underwent WBMRI and the results, despite the small numbers elucidate a radiological finding which potentially could be included as an independent prognostic tool. This subanalysis is part of a broader study (BisMMuto) which includes also patients undergoing PET/TC analysis.

OA-17

Discontinuation of Maintenance Therapy Guided by Minimal Residual Disease in Newly Diagnosed Multiple Myeloma: Long-Term Results of the GEM2014MAIN Study

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Introduction: Minimal residual disease (MRD) testing is an established prognostic factor in newly diagnosed multiple myeloma (MM), but its role to individualize treatment remains unknown. The aim of this study is to assess the long-term outcomes of MRD-guided discontinuation of maintenance in the GEM2014 clinical trial. **Methods:** The GEM2014MAIN clinical trial randomly assigned lenalidomide and dexamethasone (RD) vs. ixazomib plus RD (IRD) as maintenance therapy in patients who received 6-cycles of induction therapy with bortezomib, lenalidomide and dexamethasone (VRD), followed by high-doses of melphalan or busulfan/melphalan and 2 consolidation cycles with VRD (GEM2012MENOS65 trial). MRD was assessed by next generation flow cytometry with $2 \times 10\text{-}6$ sensitiviy after induction (T1), ASCT (T2) and consolidation therapy (T3), and then annually for 5 consecutive years (T4-T8). Patients who were MRDneg after 2 years of maintenance (T5) discontinued RD or IRD while those who were positive continued with RD for three additional years. **Results:** In total, 332 patients received RD (N = 161) or IRD (N = 171). Overall, 178 (53.6%) patients achieved MRD negativity (MRDneg) before maintenance. The median follow-up was 9.5 years from the start of maintenance therapy. As a time-dependent variable, achieving MRDneg at any timepoint was an independent prognostic factor to longer PFS (hazard ratio [HR] 0.13, $p < 0.001$), while high-risk cytogenetics (HR-CG) (HR 1.56, $p = 0.012$) and International Staging System (ISS) (2 vs.1 HR 1.98, $p < 0.001$; 3 vs. 1 HR 2.45, $p < 0.001$) were associated with inferior PFS. 271 (81.6%) of 332 patients completed two years of maintenance. 165 (49.7%) who were MRDneg discontinued therapy while 106 (31.9%) were MRD positive and continued maintenance. The median PFS at the T5 landmark was not reached vs. 3.5 years ($p < 0.001$) in patients with negative or positive MRD, respectively. The outcome of patients who were MRDneg at T5 using a 5-year landmark from maintenance discontinuation (N = 123) was analyzed. The 3-year PFS from this landmark was 89% vs. 70% ($p = 0.004$) for patients with sustained (N = 88, MRDneg at both T5 and T8) vs. unsustained MRDneg (N = 35, MRDneg at T5 but positive or missing at T8), respectively, without a plateau. Of the 165 patients who discontinued maintenance at 2 years due to MRDneg status, 84 (51%) remained alive and progression-free at the 7-year landmark, and only 3 patients showed disease progression and 1 died without progression. The impact of MRDneg on PFS in all landmarks was independent of the maintenance arm, ISS, extramedullary disease or HR-CG. **Conclusions:** Patients with MRDneg after two years of maintenance discontinued therapy and showed a significantly longer PFS than those with positive MRD that remained on maintenance. About half of the patients who were MRDneg at 2 years and

discontinued maintenance remained alive and progression-free after 7 years and could be considered operationally cured.

OA-18

Distinct Immune and Genomic Signatures Predict Resistance to Ibrutinib Therapy in Waldenström Macroglobulinemia

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Introduction: Despite recent advances in treatment strategies of Waldenström macroglobulinemia (WM)patients, the disease remains incurable. While several genomic features predict poor outcomes with ibrutinib, the contribution of immune dysfunction to tumor behavior remains unclear. **Methods:** The aim of this study was to identify and characterize the mechanisms of resistance of WM patients uniformly treated with standard BTK therapy, ibrutinib (IBR), by integrating single cell RNA seq (scRNAseq) and whole genome sequencing (WGS) profiling approaches.

We profiled 348,000 cells using scRNAseq on 82 longitudinal bone marrows from 37 WM patients before and after ibrutinib therapy as well as 2 healthy donors. The responder group (RG) who achieved at least partial response consisted of 24 patients while the non-responder group (NRG) consisted of 13 patients. **Results:** Our data identified distinct immune phenotypes associated with ibrutinib progression which were primarily characterized by the accumulation of T-effector cells, Tregs and pro-inflammatory M1-like monocytes, alongside a depletion of naïve T-cells. Specifically, we demonstrated the presence of highly enriched terminally differentiated GZMB CD8+ T-cells populations, SELL-expressing NK cells and IFN+ monocytes in the NRG, indicating that an expansion of these subpopulations with increasing disease severity, possibly affecting the interaction of WM cells with the immune system and the efficacy of ibrutinib therapy. On the other hand, responders displayed a more functionally competent T-cell repertoire through the expression of naïve-CD4+ and CD8+ T-cells. Following IBR treatment, the significant reduction of the Tregs and T-cell exhaustion indices, observed only in the RG, suggests that IBRs efficacy is potentially linked to an effect on the restoration of T-cell fitness. Furthermore, the post treatment pronounced expansion of the pro-inflammatory M1-like monocytic population observed in NRG, suggests a shift towards a more pro-inflammatory state and an IRAK-NFκB driven signaling that could sustain tumor support in a BTK-independent manner. The tumor architecture in progressing patients, exhibited a unique transcriptomic signature, also validated in an external cohort of 47 WM patients, driven by genes including LTB, NFKBIA, DUSP2, NR4A1, mainly involved in TNFα/NFκB signaling pathways, leading to shorter progression-free survival (PFS). Additionally, the Elastic Net classifier identified key genes like IRF4, NR4A1, MYC, BCL7A, and LTB that contributed most to ibrutinib resistance prediction with significant impact on PFS. Mutational profiling using WGS identified mutational signatures SBS1/SBS5 being significantly associated with poorer outcome. **Conclusions:** Finally, we showed that integrating tumor with immune cell compartments can significantly improve ibrutinib response prediction scoring highlighting potential mechanisms of resistance that could serve for the identification of predictive biomarkers for BTK-based therapy in WM.

OA-19

Double Hit Ultra-High Risk Myeloma Treated With Isa-VRD Plus Cyclophosphamide Induction and Isa-VRD Consolidation: QoL Analysis of the UKMRA RADAR Trial in Newly Diagnosed Transplant Eligible Patients

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Introduction: RADAR was designed to evaluate an intensive treatment strategy comprising Isatuximab-VRD- Cyclophosphamide induction, single autologous stem cell transplantation (ASCT), Isa-VRD consolidation, and Isa-R maintenance in patients with double-hit high-risk disease. We recently reported encouraging activity from this treatment pathway. Here we explore the longitudinal quality of life (QoL) in patients on this intensive pathway **Methods:** UK-MRA RADAR is a prospective, national, multi-centre, risk-adapted phase

II/III trial for patients with NDMM eligible for ASCT. Patients enter a high-risk pathway based on the presence of ≥2 HRCA (t(4;14), t (14;16), t(14:20), del(17p), del1p and gain(1q)). High-risk patients in v4 of the protocol (HRv4) received 4 × 21 day cycles of Isa-VRDc. Followed by an ASCT and then 4 × 21 day cycles of Isa-VRD consolidation and 28 day cycles of IsaR maintenance until progression. EORTC-QLQ-C30, EQ5D-3L and EORTC-QLQ-MY-20 questionnaires were completed at baseline, end of induction (EoI), 100 days post-ASCT and after 6, 12 and 24 months of post-ASCT treatment. Baseline adjusted mean values of subscales with 95% CI were calculated to understand the QoL of HRv4 patients. QoL completion was subject to patient withdrawal, non-compliance and immature follow-up as such 12 and 24 months of post-ASCT treatment are not analysed. **Results:** 70 patients were recruited to HRv4 between 1Sept22 and 4Sept23. Of the 70 patients in the cohort, QoL questionnaire completion rates decreased over time (baseline: 93%, EoI:71%, 100-days post-ASCT: 66%, 6-months: 54%, 12-months: 34%). We analysed data upto 6 months post ASCT due to data immaturity for later time points. For the majority of subscales (including physical, emotional, social and cognitive functioning), QoL improves up to 100-days post-ASCT. In the observed time frame, the change in global health status peaks at 15.93 (95%CI 8.46,23.4) points at 100 days post-ASCT and is maintained at 6 months post-ASCT treatment (13.82 (95%CI 3.29,24.34)). Similarly to a lesser extent, the disease symptoms subscale decreases by 13.73 (95%CI: − 20.09,-7.37) at 100 days post-ASCT which is again maintained at 6-months post ASCT treatment (−11.64 (95%CI: −18.89, −4.39)). The future perspective worries scale worsens over time, especially during active treatment with 100 days post-ASCT (95%CI: −10.25 (−19.58, −0.91) being the best scoring timepoint. Finally, despite the intensive regimen, the change in the side effect of treatment score from baseline stays low (±2 points) up until 6 months post-ASCT treatment. **Conclusions:** QoL outcomes observed in patients with double hit high risk disease receiving intensified ASCT-based therapy indicate this approach can deliver meaningful improvements in patient reported outcomes. As patients continue prolonged intensive consolidation and maintenance regimen ongoing longitudinal monitoring will assess if these benefits are maintained in the longer term.

OA-20

DREAMM-9 Patient-Reported Vision-Related Function with Extended Belantamab Mafodotin Dosing Intervals with Bortezomib, Lenalidomide, Dexamethasone (BVRd) in Transplant Ineligible Multiple Myeloma

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Introduction: Maintaining health-related quality of life (HRQoL) for patients (pts) with multiple myeloma (MM) with convenient administration and manageable safety is important due to potential for long first-line treatment duration. As previously reported in the phase 1 DREAMM-9 (NCT04091126) study in transplant-ineligible newly diagnosed MM (NDMM), cohorts with higher induction dose intensity (i.e., shorter planned dosing intervals) achieved deepest responses (complete response or better/minimal residual disease negativity] 68/55% for Q3/4W schedules, 88/54% Q6/8W, and 59/43% for Q9/12W or Q12W) whereas longer planned dosing intervals required fewer dose modifications (Usmani ASCO 2026, abstract 7503). We report ocular tolerability of BVRd via pt-reported outcomes (PROs). **Methods:** Adults received BVRd in 1 of 8 belantamab mafodotin (belamaf) dosing cohorts at an induction/maintenance schedule of Q3/4W (1.9, 1.4, 1.0 mg/kg), Q6/8W (1.9, 1.4 mg/kg), Q9/12W (1.9 for 1 dose then 1.4 mg/kg; 1.4 for 1 dose then 1.0 mg/kg), or Q12W (1.0 mg/kg). Primary endpoint was safety. Maximum post-baseline severity of blurred vision (severe/very severe [score 3/4]) was assessed using the PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE). Changes in vision-related functioning (VRF; ≥ minimal clinically important difference from baseline [12.5 points]) were assessed using the Ocular Surface Disease Index. **Results:** As of June 2, 2025, 118 pts were enrolled. Median duration of follow-up was 15.9–47.1 months. Across all cohorts, 92% of Grade ≥2 ocular events (best-corrected visual acuity changes and/or slit lamp findings) resolved (Usmani ASCO 2026, abstract 7503). Longer dosing intervals (Q9/12W or Q12W) consistently had the lowest proportion of pts reporting severe/very severe blurred vision (range 25–32%) compared to the Q6/8W (58%) and Q3/4W (range 67–92%) groups. VRF profile was favorable in the Q6/8W and Q9/12W or Q12W groups, generally staying below the threshold for clinically important difference. After Week 24, between-group differences were modest, with no consistent evidence of sustained worsening in any group. **Conclusions:** BVRd has high efficacy and is well tolerated highlighting the promise of this

regimen. Ocular events were transient and pts in the Q9/12W or Q12W group had less severe blurred vision than the Q3/4W group. Extended dosing schedules were generally not associated with meaningful deterioration of VRF. With BVRd, higher belamaf dose intensity at induction is optimal to achieve deep responses, while longer dosing intervals during maintenance improve tolerability and maintain HRQoL. An induction/maintenance phase dosing strategy for NDMM belamaf regimens may improve tolerability while maintaining efficacy and is currently being used in ongoing phase 3 DREAMM-10 and PrE1005 studies. **Funding:** GSK (209664). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

OA-21

Dynamic Changes in Plasma Cell and Immune Niches Underlie CAR-T Response in Multiple Myeloma

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Introduction: Autologous chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen (BCMA) has shown promising clinical efficacy in relapsed/refractory multiple myeloma (RRMM), although relapse remains common. We aimed to characterize dynamic changes in the plasma cell (PC) niches and their microenvironment following CAR-T therapy and correlate them with progression-free survival (PFS). **Methods:** We performed Xenium spatial transcriptomic profiling on bone marrow (BM) biopsies from RRMM patients treated with BCMA CAR-T products. The cohort includes 63 BM biopsies from 33 patients, comprising 28 paired pre- and post-CAR-T samples, including 2 with additional early pre-CAR-T biopsies, and 5 singletons. Spatial analyses assessed cellular composition, cell-cell proximity, cellular neighborhoods (CNs), and transcriptional alterations. Long- and short-PFS groups were defined using a 1-year PFS cutoff. **Results:** Spatial proximity analysis revealed a marked post-treatment decline in PC-PC interactions, with closer proximity of vascular smooth muscle cells and basophil/eosinophil/mast populations to residual PCs, suggesting remodeling from tumor-dominated aggregates toward stromal and innate immune-associated BM architecture. Residual PCs showed reduced BCMA expression, highlighting potential antigen escape under selective pressure. We identified 13 recurrent CNs, including PC/T, PC/stromal, and myeloid/stromal enriched niches. The PC/T enriched CN contained PCs, CD4 and CD8 T cells, monocytes, and macrophages. After CAR-T therapy, this niche showed increased FGL2 CD4 T cells and reduced LAMP3 activated macrophages, suggesting a shift toward an immune-stalled state. While PC burden alone was not predictive of efficacy, differential microenvironmental remodeling correlated with PFS. Short-PFS patients showed increased post-CAR-T PC expression of TCL1A and STC2, suggesting tumorigenic and stress-response programs. In contrast, long-PFS patients showed increased T cell cytotoxicity and exhaustion markers after therapy, particularly within the PC/T enriched CN, indicating stronger anti-tumor T cell stimulation. Pre-CAR-T short-PFS samples were enriched for a dysfunctional PC/T-enriched CN, where $CD8^+$ T cells showed terminal exhaustion features, including elevated TIM3 and reduced CD3E, and monocytes showed decreased HLA-DQB2, indicating impaired antigen presentation. Macrophages in the niche showed elevated CD80 expression compared to pre-treatment long-PFS samples, suggesting suppressive signaling in the T-cell compartment. High-density PC regions in short-PFS patients were enriched for KRAS expression, potentially reflecting resistance to immune-mediated clearance. **Conclusions:** These findings demonstrate that pre-CAR-T cell states and spatial organization are associated with therapeutic efficacy, and that anti-BCMA CAR-T therapy reshapes tumor and immune compartments in the BM. Spatial reorganization of PC and T-cell niches underlies therapeutic response and PFS in multiple myeloma.

OA-22

Dysregulated RAS Signaling Modulates Apoptotic Dependencies and Therapeutic Response in Multiple Myeloma

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Introduction: Activating RAS mutations are highly prevalent in Multiple Myeloma (MM), but their impact on therapeutic response remains poorly understood. Our previous work showed that dysregulated RAS signaling can influence apoptotic priming and dependencies on BCL2 family proteins, as well as sensitivity to venetoclax (ven). **Methods:** We explored the effects of endogenous RAS mutations on drug sensitivity in two MM cell lines, MM1.s (KRAS G12A) and H929 (NRAS G13D), by assessing cell death via Annexin V/PI flow cytometry. Cells were treated with increasing concentrations (1–1000 nM) of a pan RAS(ON) inhibitor (RMC-7977) alone and in combination with 5 μM lenalidomide (len). To directly interrogate the effects of RAS activation on therapeutic responses, we generated an NRAS overexpression (OE) model in an NRAS wild-type (WT) cell line, KMS12-PE. NRAS Q61 K and NRAS WT were introduced via GFP-tagged lentiviral transduction, then sorted on GFP positivity. Western blot for phospho-ERK

indicated that only the NRAS Q61 K OE cells had pathway activation and this was inhibited by RMC-7977. Cell death was assessed after treatment with ven alone or in combination with 500 nM dexamethasone (dex), MCL1 inhibitor, AZD5991 (1–1000 nM), melphalan (1–30 μM), or bortezomib (1–1000 nM). **Results:** MM1s cells exhibit limited induction of apoptosis with RAS inhibition (~10% of cells), and the addition of len increased sensitivity (~20%). H929 cells were sensitive to RAS inhibition (EC50 78 nM) and further sensitized by the addition of len (EC50 33 nM). These data suggest combinations with IMiDs may be most effective in cells with proapoptotic response to single-agent RAS inhibition. Mutant NRAS Q61 K OE decreased sensitivity to ven (EC50 481 nM) when compared to the GFP control (EC50 65 nM) and the NRAS WT OE (107 nM), consistent with observed BCL2 priming that we recently published (PMID:41481388). The addition of dex sensitized both GFP (EC50 23 nM) and NRAS WT OE (EC50 32 nM), but not NRAS Q61K OE (EC50 506 nM). We also found that NRAS Q61K OE was less sensitive to MCL1 inhibition (EC50 255 nM) when compared to GFP (EC50 87 nM) and NRAS WT OE (EC50 134 nM), suggesting that mutant NRAS is not resulting in a switch to MCL1 dependence. These findings, together with decreased ven sensitivity, indicate that RAS activation is shifting dependency away from BCL2, but not towards MCL1, which has been reported to be a mechanism of ven resistance in leukemia. Finally, we also observed NRAS Q61K-induced resistance to melphalan but not bortezomib. **Conclusions:** These studies demonstrate that dysregulated RAS signaling can modulate apoptotic dependencies in MM, shifting away from BCL2 and towards alternate survival pathways. This shift can also alter therapeutic response to both novel targeted agents and select standard of care therapies suggesting that rational therapeutic combinations can be considered.

OA-23

Epigenetic Reactivation of ASS1 Drives Arginine Metabolic Adaptation in Multiple Myeloma

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Introduction: Argininosuccinate synthetase 1 (ASS1) encodes the rate-limiting enzyme for arginine synthesis. Most immune cells lack ASS1 and rely on extracellular arginine, whereas some multiple myeloma (MM) subtypes express ASS1 and synthesize arginine de novo. Given the role of ASS1 in metabolic plasticity, we investigated ASS1regulation and function in MM. **Methods:** EpiATLAS chromatin state data (n = 2,897) were obtained from the IHEC. RNA-seq from healthy B-cell differentiation (GSE148924) and 2 NDMM cohorts were analyzed as log2(TPM+1) and batch-corrected by limma. The ASS1 cut-off was set as the largest expression gap, with differential expression analyzed by DESeq2 and pathway enrichment by Enrichr. 2 CCND1 knockout (KO) t(11;14) U266B1 clones were generated by CRISPR/Cas9 and profiled by ChIP-seq (H3K4me3/H3K4me1/H3K27ac), ATAC-seq and RNA-seq alongside wild-type (WT). DTAC treatment [PMID: 40619689], LC-MS metabolite profiling, ATF4 siRNA knockdown, lentiviral cyclin D1 over-expression, RT-PCR and western blotting were used to define the regulatory and metabolic consequences of ASS1 activation. **Results:** EpiATLAS data demonstrated a poised ASS1 promoter (high H3K4me3 and H3K27me3) across hematopoietic lineages. Elevated ASS1 expression in transitional preplasmablasts (prePBs) vs. other B-cell stages ($p = 0.01$) suggested a transient metabolic and developmental plasticity. Despite a poised chromatin state across many hematologic malignancies, ASS1 expression was heterogeneous in MM: highest in the CD1 subgroup of t(11;14) (median log2(TPM +1) 7.1 vs. 3.7, $p < 0.001$). Within t(11;14), high ASS1 expression was associated with amino acid metabolism and mTORC1 signaling, and reduced B-cell activation and NF-kB inflammatory programs. Cyclin D1 deletion in U266B1 reduced ASS1 transcript and protein levels ($p < 0.0001$). CCND1 re-expression in KO restored ASS1, while DTAC-mediated cyclin D1 degradation reduced ASS1 protein, supporting a positive regulatory relationship. ATAC-seq footprinting identified increased ATF4 occupancy in WT vs. KO and an ATF4 motif at ASS1 promoter. ATF4 correlated with ASS1 in expression across two patient cohorts and was elevated in the CD1 MM ($p < 0.0001$) and prePBs ($p = 0.02$). ATF4 knockdown in U266B1 reduced ASS1 expression by ~2-fold ($p < 0.0001$). WT U266B1 showed increased arginine and ornithine, and reduced citrulline and aspartic acid vs. ASS1-low KO. KO cells had impaired growth, reduced further by arginine depletion. Cox modeling confirmed a significant association between increasing ASS1 expression and poorer survival in t(11;14) ($p = 0.01$), but not in other subgroups. Public proteomic data [PMID: 38942927] showed higher ASS1 in t(11;14) PCL vs. t(11;14) MM ($p < 0.05$). **Conclusions:** ASS1 is a reactivated metabolic gene in MM that promotes cell growth under nutrient stress and may support independence from the microenvironment. Targeting arginine metabolism may represent a therapeutic vulnerability in ASS1-expressing MM.

OA-24

Etentamig Combined With Pomalidomide Plus Dexamethasone (Pom+Dex) in Relapsed/Refractory Multiple Myeloma (RRMM) After 1–3 Prior Lines of Therapy: A Phase 1b Dose-Escalation and Safety Expansion Study

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Introduction: Etentamig is being developed as a next-generation differentiated B-cell maturation antigen (BCMA) × CD3 bispecific T-cell engager composed of a bivalent BCMA-binding domain with a high-avidity, low-affinity CD3-binding domain potentially reducing cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life enabling convenient monthly (Q4W) dosing from the start. Arm A Kilimanjaro study data (NCT05259839) showed deep responses with low CRS rates (35%) when pom+dex are combined with etentamig without step-up dosing (SUD) in heavily pretreated (≥3 prior lines of therapy [PLT]) patients (pts) with RRMM. We report safety and efficacy from Arm E of the Kilimanjaro study, which evaluated the same combination but in pts with earlier-line (1–3 PLT) RRMM and 1 SUD. **Methods:** Arm E of this multi-arm, open-label, multicenter, Phase 1b dose-escalation and -expansion study enrolled pts ≥18 years old with RRMM after 1–3 PLT, including lenalidomide. At Cycle (C) 1 Day (D) 1, etentamig was initiated with a 2 mg SUD, followed by 60 mg on C1D4. From C2 onwards, pts received their cohort-designated dose (20, 40, or 60 mg) Q4W with pom (4 mg, D1–21) and dex (40 mg, weekly). Responses were investigator assessed (IMWG 2016 criteria). **Results:** At data cutoff (Jan 7, 2026), 58 pts received etentamig plus pom+dex (20 mg: n = 25; 40 mg n = 25; 60 mg: n = 8). Median age (range) was 67 (43–86) years. International Staging System at study entry was I, II, III, or not evaluable in 19 (33%), 23 (40%), 12 (21%), and 4 (7%) pts, respectively. Pts received a median (range) of 2 (1–3) PLT with 26% triple-class refractory (immunomodulatory drug, proteosome inhibitor, anti-CD38 monoclonal antibody) and 16% were pom-refractory. At data cutoff, 50 (86%) remained on therapy. Progressive disease (n = 4 [7%]) and adverse events (AEs; n = 3 [5%]) were the most common reasons for treatment discontinuation. Most common Grade (G) 3–4 hematologic treatment-emergent AEs were neutropenia (52%) and lymphopenia (21%). Consistent with prior data, G3–4 infection (19%) and any grade CRS rates (24%) were low (G1: 17%; G2: 7%; no G3 events). One G1 immune effector cell-associated neurotoxicity syndrome event was reported. Four fatal AEs were observed, but none were reported as possibly related to etentamig by investigator. After a median (range) follow-up of 6 (1–9) months, the objective response and ≥very good partial response rates (95% CI) were 88% (77–95) and 59% (45–71), respectively, across dose levels. Median progression-free survival and median duration of response are not reached. **Conclusions:** Consistent with the previously reported Arm A data, the etentamig plus pom+dex combination led to deep responses. Considering the shorter Arm E follow-up time, the introduction of a single SUD, as well as delayed pom administration in Arm E, further reduced CRS and infection risk, mirroring etentamig monotherapy rates. These data support further exploration of the regimen in a randomized Phase 3 study.

OA-25

Evaluation of a Vision-Related Anamnestic Tool (VRAT) to Guide Belantamab Mafodotin Dosing With Bortezomib and Dexamethasone for Multiple Myeloma: Interim Results From the UKMRA ProMMise D Trial

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Introduction: Belantamab Mafodotin (Belamaf), bortezomib, and dexamethasone (BVd) is approved for RRMM, however ocular

adverse events (AEs) lead to frequent dose reductions and interruptions with Q3W Belamaf. The vision-related anamnestic tool (VRAT) is a patient-reported 9-item questionnaire for ocular symptoms and activities of daily living. Validation of the VRAT to inform Belamaf dosing may reduce the need for ocular assessments, reducing the treatment burden. **Methods:** ProMMise D is an ongoing phase II two-stage trial investigating if BVd can be safely given using the VRAT without mandated eye examinations. Belamaf was given using a less frequent schedule of 2.5 mg/kg in cycle 1 then 1.9 mg/kg Q8W with weekly bortezomib and dexamethasone for 6 months, then Belamaf Q12W. Here we report interim findings from Stage 1 with Belamaf dosing guided by both VRAT and eye examination to assess correlation. Stage 2 will evaluate VRAT-led dosing only without mandated eye examinations. **Results:** 39 patients have enrolled with a median age of 71 (range 52–83) and a median of 2 prior lines (range 1–3). 35 (89.7%) had received at least 1 dose at the time of analysis. The median follow-up was 5.0 months with a median of 6 treatment cycles; for those >6 cycles, median follow-up was 9.9 months with a median of 10.5 cycles. Q8W belamaf dosing was well tolerated with few treatment interruptions. 36 (16.9%) treatment cycles were delayed of the 213 total given. The median number of Belamaf doses was 3.0 (range 1.0–4.0). Only 3 of 35 (8.6%) patients required Belamaf dose reduction for AEs. 7 (20%) had a dose of Belamaf delayed due to ocular AEs. 8 (22.9%) patients required bortezomib dose reductions and 12 (34.3%) had a dose omitted due to AEs. 25 had at least 1 joint VRAT and ocular examination from cycle 3 with a total of 51 joint VRAT and ocular examinations used to inform Belamaf dosing decisions. Treatment was interrupted due to 9 (17.6%) joint assessments. 13 (23.2%) VRAT results indicated potential ocular AEs for which to withhold Belamaf, of which 2 (15.4%) were confirmed by ocular examination. Only 1 (1.8%) grade 3 ocular AE was not identified by the VRAT (G3 keratopathy and reduced visual acuity) at cycle 5. However, the VRAT was positive at cycle 3, which in Stage 2 would have led to a dose hold. Ocular AEs were reported in 21 (60.0%) with 10 (28.6%) grade 3 events (0 grade 4). Peripheral neuropathy was reported in 8.6%; all grade 1–2. Other AEs were: thrombocytopenia: 25.7% (grade 3–4: 20.0%); neutropenia: 5.8% (grade 3–4: 2.9%); and infections: 28.6% (grade 3–4: 5.7%). **Conclusions:** The symptom based VRAT approach demonstrated a low rate of false negative results demonstrating its potential to detect significant ocular AEs. Belamaf at Q8W dosing resulted in a low rate of G3–4 ocular events, leading to few dose delays and reductions. Funding: GSK: funding and Belamaf supply. Myeloma UK: through the UKMRA-MUK-concept and access research programme.

OA-26

Feasibility of MRD-adapted Deferral of Autologous Stem Cell Transplantation in Newly Diagnosed Multiple Myeloma: Clinical and Translational Results from the Phase II MILESTONE Study

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Introduction: Minimal residual disease (MRD) is a dynamic prognostic marker for progression-free survival (PFS) and overall survival (OS) in newly diagnosed multiple myeloma (NDMM). Emerging data suggests that the benefit of upfront autologous stem cell transplantation (ASCT) may be minimal in patients (pts) achieving MRD-negative responses following induction. We prospectively evaluated the feasibility of using post-induction MRD status to guide ASCT deferral in transplant-eligible NDMM. **Methods:** MILESTONE (NCT04991103) is a prospective phase II trial in NDMM with quadruplet induction (DVRd x6 cycles) followed by MRD-adapted transplant deferral. The primary endpoint is the rate of ASCT deferral based on post-induction MRD status (next-generation sequencing using ClonoSEQ® 10-5 threshold). Longitudinal immune profiling using multiparametric immune phenotyping and cytokine analyses was performed across treatment phases to identify biomarkers associated with MRD kinetics. **Results:** Twenty pts were enrolled between 11/2021 and 5/2023 [(median age 69 years, 50% male, 45% minorities, 15% with high-risk FISH abnormalities [t(4;14), t(14;16) and del17p]. Five pts (25%) achieved MRD negativity (< 10-5) following induction and deferred ASCT per protocol. At a median follow-up of 42.3 months, 2 pts progressed, no deaths occurred. The cumulative MRD-neg CR rate < 10-5 is 85% and < 10-6 is 55%. The sustained MRD neg (< 10-5) is 60% and (< 10-6) is 35%. MRD negativity was associated with broad remodeling of the immune microenvironment. The baseline sBCMA/BAFF ratio at screening strongly correlated with BM plasma cell burden and outperformed measurements of either cytokine alone. Increasing CXCL9/sBCMA ratio following consolidation was associated with lower MRD burden post ASCT. Exploratory immune analyses identified distinct CD8+ T-cell differentiation states associated with response depth. Expansion of CD57posPD-1neg effector-memory CD8+ T cells between screening and maintenance correlated with lower MRD levels, whereas expansion of PD-1pos or CD11c/CD16-defined EMRA CD8+ subsets correlated with higher residual disease burden. Favorable MRD responses were also associated with down-modulation of classical monocytes between screening and post-induction timepoints, along with shifts in naïve/transitional B-cell populations, and expansion of CD11c+CD57negCD56bright NK-cell subsets. **Conclusions:** MILESTONE study demonstrates the feasibility of

using post-induction MRD status to guide ASCT deferral in NDMM. Longitudinal immune profiling revealed dynamic immune remodeling and distinct cytokine and immune cell signatures associated with MRD depth. These findings suggest that baseline immune contexture influences response and may inform future immune- and risk-adapted strategies as T-cell–redirecting therapies move into earlier lines of therapy, including NDMM. MRD-adapted transplant deferral is being tested in the prospective randomized MASTER-2 trial, paired with comprehensive immune profiling.

OA-27

Fifteen-Month Follow-Up from a Pivotal Trial of GR1803 in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: GR1803, a BCMA-CD3 bispecific antibody, showed promising efficacy in relapsed/refractory multiple myeloma (RRMM). GR1803–002 (NCT06566547) is a phase 2, open-label, single arm study evaluating the efficacy and safety of GR1803 in patients with RRMM. **Methods:** Eligible patients had triple-class exposed RRMM (proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody). The patients were received intravenous GR1803 with a priming regimen (30 μg/kg on cycle (C) 1 day (D) 1 and 90 μg/kg on C1D4) followed by 180 μg/kg on C1D8, on a weekly (C1-C9) and every 2 weeks (C10+) schedules. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) per International Myeloma Working Group 2016 criteria. The second endpoints were median duration of response (mDOR), median progression-free survival (mPFS), overall survival (mOS), and side effects. **Results:** A total of 116 patients were enrolled and received GR1803. The median age was 62.0 years (range, 42 to 79). Patients had undergone a median of 4 previous lines of therapy (range, 3 to 8). Among the cohort, 40.87% had extramedullary disease, 85.22% were stratified high risk according to Mayo Stratification of Myeloma and Risk-adapted therapy (mSMART) 3.0, 21.74% had ISS stage III disease. At a median follow-up of 14.32 months, treatment continued for 71 patients. The ORR was 79.13%, 53.04% with complete response (CR) or better, 72.17% with very good partial response (VGPR) or better. The MRD-negativity rate among patients with a CR or better was 96.72%. Among patients with extramedullary disease, ORR was 72.34%, 34.0% with CR or better. mDOR, mPFS and mOS were not yet reached. The estimated 12-month DOR, PFS, and OS rates were 76.65% (95% CI, 65.64 to 84.53), 68.82% (95% CI, 58.75 to 76.91), 79.45% (95% CI, 70.69 to 85.85), respectively. 14 patients discontinued study treatment due to treatment-emergent adverse event (TEAE). 15 patients died due to TEAE. Hematologic TEAE (any grade/grade 3/4) included neutropenia (93.10%/75.00%), lymphopenia (73.28%/72.41%), thrombocytopenia (73.28%/27.59%), and anemia (56.90%/19.83%). Common infections (≥10% any grade) were pneumonia (65.52%), upper respiratory tract infection (41.38%), bronchitis (13.79%), and urinary tract infection (12.07%). Grade 5 infection occurred in 10 pts (8.62%); with viruses being the most common pathogens. Cytokine release syndrome (CRS) occurred in 86.21% (0.86% were grade 3, none were grade 4), with almost all events occurring in priming doses and first target dose. There was one case of grade 1 immune effector cell associated neurotoxicity syndrome, which occurred on C1D2. **Conclusions:** GR1803 exhibited profound and sustained responses in RRMM, with high MRD negativity and excellent response in extramedullary RRMM. CRS and infections were generally manageable with established protocols and aligned with that of other BCMA-CD3 bispecific therapies.

OA-28

First-in-Human Phase Ia/Ib Study of QLS32015 (GPRC5D × CD3) in Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM): Updated Safety and Efficacy Data

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Introduction: QLS32015 is a novel cis-link GPRC5D × CD3 antibody with high GPRC5D/low CD3 affinity to enhance tumor bridging and reduce off-target activation. QLS32015 has shown a favorable safety profile and preliminary efficacy in pts with RRMM (Blood (2025) 146 (Supplement 1): 4049). At >12 months median follow-up, we report the mature PFS and updated safety and response data of QLS32015 monotherapy in RRMM. **Methods:** In the first-in-human, phase Ia/Ib study, subcutaneous QLS32015 was dose-escalated (2–100 μg/kg) in the Ia phase for up to 4 years. Three dose levels (36/54 μg/kg Q2W and 54 μg/kg Q4W) were selected for phase Ib expansion. Primary endpoint included the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and safety in phase Ia, and IMWG ORR in phase Ib. **Results:** As of April 7, 2026, 66 pts received QLS32015 (2–100 μg/kg; 32 pts at the RP2D [54 μg/kg Q2W]). Two DLTs were observed (one grade [Gr] 4 thrombocytopenia at 54 μg/kg Q2W and one Gr 3 herpes zoster at 100 μg/kg Q2W). MTD was not reached. The most common TRAEs were cytokine release syndrome (CRS; 86.4%). The majority of CRS were mild to moderate (Gr 1 [66.7%], Gr 2 [16.7%], Gr ≥3 [3.0%]). No ICANS occurred. At data cutoff, median follow-up was 12.6 months. In the full analysis set, median PFS was not reached (NR) (95% CI: 9.7–NR) at the RP2D and 14.0 months (95% CI: 7.5–NR) at all dose levels, with corresponding 12-month PFS rates of 70.4% (95% CI: 49.3–84.0) and 55.5% (95% CI: 41.7–67.2), respectively. At the RP2D, QLS32015 showed notable survival benefit: the median PFS was NR in pts with EMD or high-risk cytogenetics, and 14.1 months in pts with prior BCMA-targeted therapy. Median OS was immature, with 18-month OS rates of 80.7% (95% CI: 62.0–90.8) and 77.9% (95% CI: 65.5–86.3) in the RP2D and all-dose-level groups. Subsequently, updated ORRs were 81.3% (26/32, 95% CI: 63.6–92.8) at the RP2D and 75.8% (50/66, 95% CI: 63.6–85.5) at all dose levels, with the corresponding≥ VGPR rates of 62.5% (20/32; 95% CI: 43.7–78.9) and 53.0% (35/66; 95% CI: 40.3–65.4) and MRD-negative CR rates of 37.5% (12/32; 95% CI: 21.1–56.3) and 27.3% (18/66; 95% CI: 17.0–39.6), respectively. At the RP2D, QLS32015 induced remarkable and durable responses in poor-prognosis pts: ORRs were 90.0% (9/10) for prior BCMA-targeted therapy, 87.5% (7/8) for high-risk cytogenetics, and 75.0% (9/12) for EMD. Median DoR was NR (95% CI: 13.4–NR) at the RP2D and 13.4 months (95% CI: 11.6–NR) at all dose levels. QLS32015 showed dose-proportional exposure (t1/2: 19.8 days); at the RP2D, trough levels exceeded the in vitro EC90. **Conclusions:** QLS32015 showed a manageable safety profile with no reported ICANS. After ≥ 1 year of follow-up, QLS32015 yielded favorable PFS and a high ORR in the FAS and key subgroups (prior BCMA-targeted therapy, high-risk cytogenetics, or EMD), with the most pronounced effects at the RP2D. These findings support QLS32015 at 54 μg/kg Q2W as RP2D for further development in multiple myeloma.

OA-29

First-Year Results of Isatuximab–Iberdomide Maintenance in MRD-Positive Newly Diagnosed Multiple Myeloma Patients Included in the Phase 3 MIDAS Trial

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Introduction: In transplant-eligible newly diagnosed multiple myeloma (TE-NDMM), quadruplet induction followed by autologous stem cell transplantation (ASCT) is standard of care. Minimal residual disease (MRD) is a major prognostic factor and may guide treatment strategies. In the phase 3 MIDAS trial (Perrot et al, NEJM 2025), patients remaining MRD-positive after Isa-KRd induction received intensified maintenance with isatuximab (Isa) plus iberdomide (Iber) after single or tandem ASCT. While daratumumab plus lenalidomide maintenance has shown efficacy in recent studies (PERSEUS, AURIGA), no data are available regarding anti-CD38 combined with a CELMoD in maintenance. Here, we report first-year efficacy and safety results of Isa-Iber maintenance in MIDAS. **Methods:** MIDAS (NCT04934475) is an ongoing phase 3 trial evaluating an MRD-adapted consolidation and maintenance strategy in TE-NDMM patients treated with six cycles of isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd). Patients remaining MRD-positive after induction were randomized to single ASCT plus Isa-KRd consolidation (Arm C) or tandem ASCT (Arm D), followed by maintenance with monthly isatuximab and iberdomide for 3 years. Iberdomide was administered at 1 mg/day on days 1–21 of a 28-day cycle. Isatuximab was given at 10 mg/kg every 4 weeks, initially intravenously then subcutaneously. MRD was

assessed by next-generation sequencing at a sensitivity threshold of 10^{-6} in the intention-to-treat population. **Results:** Overall, 219 patients (108 in Arm C and 111 in Arm D) initiated Isa-Iber maintenance; 203 completed the first year of treatment.

The most common adverse events during maintenance were neutropenia (all grade: 46%; grade ≥3: 42%), infections (72%; grade ≥3: 18%), diarrhea (19%; grade ≥3: 1%), rash (16%; grade ≥3: 2%), and peripheral neuropathy (18%; no grade ≥3 events). No significant safety differences were observed between Arms C and D, and no unexpected toxicity signals emerged. After one year of maintenance, 55 patients achieved MRD conversion from positive to negative at the 10^{-6} threshold. MRD negativity rates at 10^{-6} improved from 40% post-consolidation to 58% after one year of maintenance in Arm C, and from 32% to 48% in Arm D. At the 10^{-5} threshold, MRD negativity rates increased from 67% to 76% in Arm C and from 62% to 70% in Arm D. During the first year of maintenance, 5 progressions and 1 death occurred in each arm. **Conclusions:** Maintenance with isatuximab plus iberdomide after Isa-KRd induction and single or tandem ASCT is feasible with a manageable safety profile. This combination induced substantial MRD conversion during the first year of maintenance in patients remaining MRD-positive after consolidation. These findings support further evaluation of anti-CD38 plus CELMoD-based maintenance strategies in high-risk NDMM patients.

OA-30

Hypogammaglobulinaemia (HG), Infection Risks and Effects of Immunoglobulin Replacement Therapy (IgG RT) in Multiple Myeloma (MM): A Registry Based Longitudinal Real-World-Analysis (RWA)

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Introduction: Infections are a leading cause of morbidity & mortality in MM pts. and HG predisposes to them. While pre-emptive IgG RT is standard in deeply immunosuppressive therapies (e.g. bispec. ABs) usually at a threshold of 500 mg/dl IgG, the effects of HG and IgG RT in "standard" MM therapies are unclear. **Methods:** We performed a comprehensive review from a national registry covering 1214 pts., recruiting 1045 pts. (86%) with ≥ 1 documented IgG measurement. Data were analyzed for missingness using standard myeloma & demographic variables and found to be missing at random. HG was defined as an IgG below the LLN, severe HG (sHG) as an IgG < 500 mg/dl. Analyzed risk factors (RFs) for infection were ECOG, age, ASCT, line of therapy, ISS stage, genetic and clinical high-risk features, use of IgG RT, and anti-CD38 antibodies. **Results:** 9870 IgG measurements were available in 1945 pts. median/pt = 7 (IQR 3–11), median interval of measurements was 3.4 mo. Data completeness ranged from 72–94%. The incidence of HG was found to be 46% with 15% sHG. Cumulative incidence of sHG increased with prolonged observation (12 mo. 14%, 24 mo. 21%, 36 mo. 27%). With anti-CD38 treatments an increase in HG was seen within 3 mo. from start of therapy, a nadir at 9–12 mo., and persistence with ongoing therapy. On multivariate analysis use of anti-CD8 antibodies, no. of previous therapies, status post ASCT, age and an ECOG ≥ 2 remained independent RFs. A time dependent cox model was developed showing the use of anti-CD8 to be the most important RF with an aHR of 2.1 (95% CI: 1.62–2.79), followed by ECOG aHR 1,46 (1,18–1.81), ASCT in the last 6 mo. aHR 1.43 (1.05–1.26), no. of lines of therapy (aHR 1.29 per line), and age (aHR 1.22 per 10a). Infection risk per pt/year was 16% with normal IgG levels, 32% in HG, and 64% in sHG. In a time-dependent cox model IgG < LLN vs. normal the aHR was 1.82, and 3.31 in normal vs. sHG. These effects were stable in sensitivity analyses. Effects of IgG RT 41% of pts. with sHG received either i.v. IgG or s.c.IgG within a median of 1.8 mo. after dropping below the threshold of 500 mg/dl. The use IgG RT resulted in significant decreases in severe infections (grade III° or higher) (aIRR 0.65) and a hospitalization (aIRR 0,72). **Conclusions:** HG and even more sHG are frequent complications in MM pts. with all types of effective anti-myeloma therapies resulting in high rates of infections per pt./year with a hazard rate of 3,31 in sHG. The most important risk factors are: the use of anti-CD8 antibodies, an ECOG ≥ 2, status post ASCT within 6 mo., number of previous therapies and age. IgG RT can mitigate these risks considerably with an impressive reduction of clinically meaningful endpoints as severe infections (aIRR 0.65) and hospitalizations (aIRR 0.72) and concordantly probably is a cost-effective measure. We therefore recommend that IgG RT should always be considered in severe HG, especially in elderly, frail, and advanced MM pts. independent of the type of MM therapy.

OA-31

Iberdomide Priming Enhances Anti-BCMA CAR-T Efficacy in Multiple Myeloma

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Introduction: Despite impressive responses to anti-BCMA CAR-T therapy in RRMM, suboptimal CAR-T expansion and T cell exhaustion remain critical mechanisms of resistance. Iberdomide

(Iber), a CELMoD agent with potent T cell immunostimulatory activity, represents a rational priming strategy. We have demonstrated that ex vivo Iber priming prior to CAR-T manufacturing yields products with superior proliferation, activation, and functionality. Here we report the first in vivo validation in NSG murine models and characterize the immunomodulatory effect of Iber+Dexamethasone (Dex) on the bone marrow (BM) of patients who progressed on anti-BCMA therapy. **Methods:** Anti-BCMA CAR-T cells were manufactured from T cells primed with 10 nM Iber or DMSO 24 hours prior to lentiviral spinoculation, followed by standard expansion. NSG mice engrafted with BCMA+ myeloma cells and subsequently treated with Iber-primed CAR-T, DMSO-CAR-T, or PBMC control; tumor burden was monitored longitudinally. To assess BM immune remodeling, paired BM mononuclear cells from patients progressing on anti-BCMA therapy (n = 21) were profiled at baseline and C2D15 using a custom high-dimensional spectral flow cytometry panel spanning innate and adaptive immune compartments. **Results:** Iber-primed CAR-T cells demonstrated superior in vivo anti-myeloma activity compared to DMSO-control CAR-T cells in NSG mice. Primed CAR-T cells exhibited enhanced tumor control with sustained remission resulting in increased overall survival (DMSO CAR-T median OS = 48 days compared to 85 days Iber-primed CAR-T cells $p < 0.001$). We next investigated the effect of Iber+Dex on the bone marrow compartment of patients progressing after BCMA-directed therapy (n = 21). Treatment with Iber+Dex was associated with a significant increase in NK cells ($p < 0.05$), γδ T cells, and CD8+ T cells ($p < 0.001$). Within the T cell compartment, Iber +dex promoted a shift to effector memory T cells ($p < 0.001$) with a decrease in TEMRA and naive T cells. We observed an increase of activated CD4+ and CD8+ T as denoted by augmentation of canonical markers- HLA-DR, CD69 and PD-1 ($p < 0.01$). These findings are consistent with our prior translational cohort, in which CAR-T cells manufactured from C2D1 Iber treated patient samples showed significantly greater proliferative capacity, increased activation, and enhanced cytotoxic function compared to baseline-manufactured products in vitro. **Conclusions:** Iber priming prior to CAR-T manufacturing enhances in vivo anti-myeloma efficacy in NSG models, providing preclinical validation. Comprehensive BM immune profiling demonstrates dynamic remodeling by Iber+Dex in patients progressing after BCMA-directed therapy. Together, these data support Iber-based priming as a strategy to improve anti-BCMA CART efficacy and enhance subsequent T cell-directed therapies. An ongoing clinical trial at our institute evaluating one cycle of Iber prior to apheresis will prospectively determine whether this approach optimizes CAR-T product quality and improves outcomes.

OA-32

IBI3003, a Novel Trispecific Antibody Targeting GPRC5D, BCMA and CD3, in Patients (Pts) With Relapsed or Refractory Multiple Myeloma (R/R MM): Results of a Phase 1 Study

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Introduction: Bispecific antibodies have redefined the therapeutic landscape of R/R MM. Dual-antigen targeting trispecific antibodies could overcome resistance mechanisms associated with tumor heterogeneity and treatment-induced antigen loss. Prior data from the dose-escalation study of IBI3003, a first-in-human study of a GPRC5D × BCMA × CD3 trispecific antibody, demonstrated a manageable safety profile and promising efficacy in heavily pretreated, high-risk R/R MM pts (Li, et al., 2025 ASH). Here, we report updated results of this study to include a longer follow-up period and additional pts from dose expansion. **Methods:** The phase 1 study (NCT06083207) enrolled triple-class exposed pts with measurable R/R MM who had failed at least 2 prior lines of therapy. In dose escalation, subcutaneous doses of IBI3003 ranging from 0.1 to 800 μg/kg QW were evaluated. In dose expansion, additional pts were randomized 1:1:1 to 120, 360 and 540 μg/kg QW (with 2 priming doses). For pts treated for ≥6 months and achieved ≥PR for ≥2 months, the regimen could be switched to Q2W maintenance dosing. Anti-tumor activity was assessed by 2016 IMWG criteria. **Results:** As of April 30, 2026, 102 pts were treated with IBI3003 (median age: 62.0 years; R-ISS stage III: 16.7%; mSMART high-risk: 52.9%; median lines of prior therapy: 4; extramedullary disease [EMD]:

53.9%; ≥60% plasma cells in bone marrow: 9.8%; triple-class exposed: 100%; penta-class exposed: 55.9%; prior anti-BCMA and/or GPRC5D therapy: 33.3%; refractory to last line of therapy: 88.2%). The median follow-up was 4.9 months (range: 0.8–13.1). In dose expansion, ORR was 52.4% for 120 μg/kg (N = 21), 70.6% for 360 μg/kg (N = 17) and 63.2% for 540 μg/kg (N = 19). The recommended phase 2 dose was identified as 360 μg/kg QW. In pts treated with 360 μg/kg from dose escalation and expansion (N = 26), ORR was 80.8% including 61.5% ≥VGPR and 34.6% ≥CR). In pts with 2–4 prior lines of therapy and treated with 360 μg/kg, ORR was 89.5% (N = 19). In pts with EMD and treated with 360 μg/kg, ORR was 69.2% (N = 13). In pts with baseline sBCMA ≥400 ng/mL and treated with 360 μg/kg (N = 4), ORR was 75.0%. Median DoR and PFS were not reached. Of 11 evaluable pts treated with ≥360 μg/kg, MRD negativity was 100%. TEAEs occurred in 99% pts (grade≥3 [G3+]: 88.2%). The most common non-hematologic TEAE (≥50%) was cytokine release syndrome (51.0%, all G1-G2). Infections occurred in 36.3% pts (G3+: 19.6%). GPRC5D oral TEAE occurred in 53.9% pts (no G3+). GPRC5D skin and nail TEAEs occurred in 59.8% pts including 2 pts with resolved G3 rash. No TRAE led to treatment discontinuation or death. Profound and durable sBCMA reductions were observed across dose groups, reaching >95% at 360 μg/kg after 3 cycles. **Conclusions:** IBI3003 continues to demonstrate encouraging durable responses, with a manageable safety profile, in heavily pretreated R/R MM pts. The efficacy and safety data support further exploration of IBI3003 in the ongoing phase III study.

OA-33

Immune Dysregulation in the Bone Marrow Following Autologous Stem Cell Transplant in Multiple Myeloma

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Introduction: Standard of care in multiple myeloma (MM) includes chemotherapy followed by autologous stem cell transplant (ASCT). The full scope of post-transplant (PT) bone marrow (BM) remodeling is poorly understood, especially within stromal niches not captured by dissociative methods. **Methods:** To characterize the interplay of BM-resident populations during transplant response, we conducted scRNAseq, CODEX proteomic imaging, and spatial Xenium transcriptomics on samples from 171 patients at new diagnosis of multiple myeloma (NDMM) and day 100 PT, alongside 35 age-matched donor controls. To mitigate therapy-dependent variation, we leveraged data collection from 82 enrollees of a phase II multicenter trial with uniform induction and ASCT. **Results:** PT MS4A1- early B cells undergo major reconstitution and restored spatial proximity to supportive myeloid and stromal niches, while the T cell compartment is characterized by relative expansion of cytotoxic CD8T cells correlated with improved progression-free survival (PFS). In contrast, PT myeloid cells displayed elevated immunosuppressive programs marked by HIF1A, CTLA4, and PDCD1 expression, and mesenchymal stromal cells retained inflammatory myeloma-associated BMP4hi/SERPINE1hi signatures indicating persistent stromal dysfunction. Spatial analyses reveal abnormal transcriptional states of myeloid cells and MSCs physically adjacent to PT plasma cells (PC), providing in situ demonstration of PC niche dysregulation in PT. Compared to the dramatic BM remodeling observed across paired timepoints, measurable residual disease (MRD) status had a relatively modest effect on PT samples. Microenvironmental alterations were observable only when comparing MRD- samples to MRD+ samples with high plasma cell (PC) burden, revealing that MRD+ samples exhibited significantly reduced CXCR4 expression in hematopoietic stem cells and elevated CD4:CD8T cell ratios. Inferred interaction analysis further suggested differential regulation of extracellular matrix and cell-adhesion pathways, with increased IL2 and decreased CD160 signaling in MRD+ high-PC-burden samples, consistent with altered niche remodeling and a less cytotoxic, more tolerant T cell environment conducive to relapse when combined with reduced tumor clearance. **Conclusions:** Integrating multi-omic profiling within a treatment-controlled clinical trial cohort reveals that persistent myeloid and stromal dysfunctions coexist with beneficial B and T cell reconstitution programs after ASCT, while MRD+ disease with residual PC burden is associated with focal niche remodeling and immune features that may influence PT treatment response in MM.

OA-34

Interim Report of Phase I Results of a Phase I/II, Open Label Study to Evaluate Safety, Tolerability, and Efficacy of Elranatamab in Patients With Relapsed AL Amyloidosis

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Introduction: AL amyloidosis is a rare and incurable plasma cell cancer that causes progressive organ failure due to deposition of involved free light chain (iFLC) fibrils. A deep and rapid normalization of iFLC is necessary for overall survival. However, there are no FDA-approved therapies for patients with relapsed AL amyloidosis. Elranatamab is a bispecific T-cell redirecting antibody targeting B-cell maturation antigen (BCMA) expressed by clonal plasma cells and CD3 on T cells. Elranatamab is FDA-approved for multiple myeloma patients but has not been prospectively evaluated

in AL amyloidosis patients. **Methods:** Adult patients with AL amyloidosis who had progressed or were refractory to at least 1 prior line of therapy, inclusive of daratumumab and/or cyclophosphamide/bortezomib/dexamethasone were eligible. Patients were excluded for overlapping multiple myeloma or previous BCMA exposure, with the exception of belanatamab mafodotin if it was not the last line of therapy before enrollment. Disease progression was defines as a difference between involved and uninvolved free light chain (dFLC) of at least 20 mg/L after at least 2 cycles of therapy. In phase I, two step-up doses are administered, 12 mg SQ on Day 1 and 32 mg SQ on Day 4. This is followed by weekly treatment doses of 76 mg SQ (Dose Level 0). If patients have achieved a very good partial response or better (≥VGPR) after 2 cycles, treatment was modified to every other week treatment (Day 1 and Day 15) starting Cycle 3. All patients received a fixed duration of 6 cycles. The primary objective of Phase I is to determine the recommended phase II dosing (RP2D). **Results:** At the data cut off, ten patients were enrolled in Phase I and received at least one full dose of elranatamab (range: 11–15). Three patients were female. The median age was 66 years old (range 54–70) with a median time since diagnosis of 32.7 months (5.2–145). The median prior lines of therapy were 2.5 (range: 1–5) with all patients exposed to daratumumab and bortezomib. At screening, median NT-proBNP was 575 ng/mL (81–3512) and median hs-troponin T was 21 pg/mL (range:10–130). Cytokine release syndrome occurred in 7 patients (70%) (grade 1 = 4 patients and grade 2 = 3 patients). Tocilizumab was used in 3 patients, additional steroids used in 2 patients, and supplemental oxygen in 2 patients (37.5%). There were no neurotoxicity events. After a median follow-up of 12.4 months (3.2–18.1), all (100%) patients achieved a complete hematological response (CR). All (100%) patients achieved iFLC less than 10 after first cycle of treatment. In six patients where MRD testing via clonoseq was performed at the end of 6 cycles, 5 were MRD negative at 10-6 and one below limit of detection. **Conclusions:** Elranatamab demonstrated no new safety signals and rapid, deep and frequent hematological response in patients with relapsed, AL amyloidosis, representing a promising therapeutic option to address this critical unmet need.

OA-35

Investigation of the Impact of Peripheral Neuropathic Symptoms on Quality of Life in Patients With Smoldering Multiple Myeloma

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Introduction: Smoldering multiple myeloma (SMM) is considered an asymptomatic malignant disease with a high risk of progression to multiple myeloma (MM) requiring treatment. In addition to the classic manifestations of the disease, patients may also develop peripheral neuropathies, which can significantly impact their quality of life (QoL). Currently, there are few studies that address neuropathic symptoms in the context of SMM. The aim of this study was to investigate the influence of peripheral neuropathies on the health-related (HR)-QoL of treatment-naive SMM patients. **Methods:** A monocentric, prospective, non-interventional, observational study without randomization was conducted. Data was collected using the validated EORTC questionnaires QoL-C30, QoL-MY20 and QoL-CIPN. Evaluation was based on official scoring manuals, non-parametric statistical tests, including the Mann–Whitney U test, were performed to investigate differences in QoL between the groups (i.e., patients with and without neurological symptoms; PN vs. non-PN). Univariate and multivariable linear regression analysis were used to determine independent factors associated with neuropathic symptoms and QoL. **Results:** A total of 127 patients participated in the study between Aug-Oct 2025. Among these, 20 patients (16%) showed no neuropathic symptoms (non-PN), while 107 patients (84%) reported symptoms (PN). Patients without neuropathic symptoms exhibited a significantly higher global health status in comparison to those with symptoms (mean M (PN) = 62.54 (SD 22.27) vs. M (non-PN) = 81.25 (SD 19.09); $p < 0.001$). Even patients with moderate neuropathic symptoms had a significantly lower global health status as compared to patients with mild symptoms (Dunn; $p < 0.001$) or no symptoms (Dunn; $p < 0.001$). Furthermore, female patients experienced higher levels of sensory and motor symptoms. The presence of peripheral neuropathic symptoms was independent of patient characteristics and disease-specific parameters such as M protein level. In general, patients with sensory symptoms also exhibited significant motor and autonomic impairments. **Conclusions:** The majority of SMM patients are affected by PN, and neuropathic symptoms in patients with SMM have a significant adverse impact on HR-QoL. HR-QoL questionnaires are key tools in identifying SMM patients with high symptom burden in clinical routine, may guide clinical and therapeutic decision-making processes and prompt additional neurological diagnostics. Further research in patients with SMM and neuropathic symptoms is needed to confirm the results and understand possible causal relationships and differential diagnoses.

OA-36

Longitudinal Liquid Biopsy Monitoring Reveals Distinct Residual Disease Dynamics Beyond Bone Marrow MRD Assessment in Newly Diagnosed Multiple Myeloma

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Introduction: In Multiple Myeloma (MM) measurable residual disease (MRD) is conventionally assessed in the bone marrow (BM), where sustained MRD negativity at a sensitivity of $\geq 10^{-5}$ predicts improved outcomes. However, BM evaluation is invasive and may not fully capture the systemic and heterogeneous distribution of the disease. Circulating biomarkers therefore represent promising, less invasive alternatives for MRD monitoring. **Methods:** We designed a longitudinal study comparing BM MRD assessment by NGS with peripheral blood (PB)-based monitoring using ctDNA (by ULP-WGS), circulating MM cells (CMMCs by flow cytometry) and M-protein (by MALDI-TOF mass spectrometry, MS). These biomarkers were serially evaluated in 60 newly diagnosed MM patients (pts), including 50% treated with daratumumab-based quadruplets before autologous stem cell transplantation. BM assessments were performed every 6 months, while PB biomarkers were monitored monthly for 12 months. Longitudinal biomarker dynamics were quantified using slope and AUC from interpolated serial measurements. **Results:** After a median follow-up of 58 months, 27 pts experienced disease progression with a median time to progression of 27 months. BM MRD negativity rates were comparable in pts with and without progression (28% vs. 29%, respectively), prompting investigation of whether PB monitoring could provide complementary information. Analysis of longitudinal trajectories identified three recurrent patterns across biomarkers: 1) persistent detectability, 2) rapid decline to sustained undetectability, and 3) fluctuating detectability. BM-MRD and MS showed highly concordant disease dynamics, likely reflecting complementary assessment of the same clonal marker through the IgH/IgK rearrangement and the corresponding M-protein. In contrast, CMMCs and ctDNA were frequently discordant with BM-MRD. To investigate the significance of this discordance, we performed unsupervised clustering of pre-maintenance biomarker profiles, identifying three pt subgroups: one characterized by concordantly negative PB biomarkers and BM-MRD negativity, experienced no disease progression. The remaining two displayed concordantly positive BM-MRD and MS results but differed in CMMC status and ctDNA kinetics and were associated with lower complete response rates and higher rates of disease progression (64% and 44%, respectively). These findings suggest that concordant negativity across PB and BM biomarkers identifies pts at very low risk of progression, while discordance may reveal residual disease not captured by BM-MRD, likely reflecting spatial heterogeneity and the limited representativeness of a single BM aspirate. **Conclusions:** Overall, MS and BM-MRD provided highly concordant measures of residual disease while CMMCs and ctDNA contributed complementary information, particularly when assessed longitudinally. Integrating PB biomarkers with BM-MRD may improve characterization of residual disease dynamics and risk stratification in MM. Thanks to AIRC19-IG22059, BolognAIL OdV.

OA-37

Long-Term Follow-Up of the Phase II EMN15/HOVON147 Trial: Carfilzomib-Lenalidomide-Dexamethasone Versus Lenalidomide-Dexamethasone in Patients With High-Risk Smoldering Multiple Myeloma

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Introduction: Patients with high-risk smoldering multiple myeloma (HR-SMM) have a substantial risk of progressing to symptomatic multiple myeloma. We assessed the efficacy and safety of fixed-duration treatment with carfilzomib–lenalidomide–dexamethasone (KRd) versus lenalidomide–dexamethasone (Rd) in this population. **Methods:** HOVON147/EMN15 is a prospective, multicenter, open-label, randomized, phase II trial conducted at five European centers. Adults with HR-SMM, defined by Mayo 2008 and/or PETHEMA criteria, were randomly assigned (2:1) to receive KRd or Rd. Rd consisted of lenalidomide (25 mg) on days 1–21 and weekly dexamethasone (40 mg) in a 28–day cycle, whereas KRd consisted of intravenous carfilzomib (20/56 mg/m2) on days 1, 8, and 15 in addition to Rd. Patients were treated with nine induction cycles, followed by 24 cycles of lenalidomide (10 mg) maintenance in patients without disease progression. The primary endpoint was minimal residual disease (MRD) negativity after induction, assessed centrally by next-generation flow cytometry (sensitivity 10^{-5}). Secondary endpoints included MRD negativity after four cycles, overall response rate, progression-free survival (PFS) and progression to multiple myeloma, progression-free survival 2, overall survival, duration of response, and safety. The data cutoff for analysis was April 17, 2026. **Results:** Between Jan 2, 2019, and Sep 27, 2023, 58 patients were enrolled, of whom 57 were eligible. 35 (61%) patients were assigned to receive KRd and 22 (39%) patients to Rd. After induction therapy, MRD negativity was achieved in 20 (57%) patients following KRd treatment compared with 1 (5%) patient in

the Rd group (odds ratio 0.04, 95% confidence interval [CI] 0.00–0.28; p < 0.0001). After a median follow-up of 54 months, KRd significantly improved PFS compared with Rd (hazard ratio (HR) 0.25, 95% CI 0.10–0.60); median PFS was not reached in KRd versus 22.4 months in Rd (95% CI 13.7 – not reached). Progression to symptomatic multiple myeloma was observed in 2 (6%) patients in the KRd group, compared with 8 (36%) patients in the Rd group (HR 0.13, 95% CI 0.03–0.62). Grade 3–4 adverse events (AEs) occurred more frequently in the KRd group (82% vs. 62%). Grade ≥3 non-hematological AEs were more common with KRd (82% vs. 57%), grade ≥3 hematological AEs occurred at similar frequencies (15% in KRd vs. 19% in Rd). Serious adverse events were reported in 62% of patients receiving KRd and 52% receiving Rd. No treatment-related deaths occurred. **Conclusions:** Although KRd demonstrated efficacy by significantly increased rates of MRD negativity and prolonged PFS compared with Rd in patients with HR-SMM, the higher incidence of grade 3–4 AEs during KRd treatment raises important concerns regarding its tolerability in this otherwise asymptomatic population without myeloma-defining end-organ damage. These findings warrant careful consideration before adopting KRd in this specific HR-SMM population.

OA-38

Long-Term Outcomes With Sustained Minimal Residual Disease (MRD) Negativity in Belantamab Mafodotin–Treated Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM): An Update From DREAMM-8

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Introduction: B-cell maturation antigen (BCMA)–directed therapies have changed the RRMM treatment landscape. In the phase 3 DREAMM-8 trial (NCT04484623), BCMA-directed antibody-drug conjugate (ADC) belantamab mafodotin plus pomalidomide and dexamethasone (BPd) demonstrated significant progression-free survival (PFS) benefit and higher rates of complete response (CR)–based MRD negativity vs triplet pomalidomide, bortezomib, dexamethasone (PVd) in pts with RRMM and ≥1 prior line of therapy (LOT). As MRD negativity predicts improved survival in MM, this long-term, postbaseline update describes clinical outcomes and characteristics of pts with sustained MRD negativity. **Methods:** Pts with ≥1 prior LOT including lenalidomide were randomized 1:1 to BPd or PVd. The primary endpoint was PFS (independent review committee assessed); PFS2 was investigator assessed. CR-based sustained MRD negativity (≥12 mo) was an exploratory endpoint. Pts with ≥CR were tested for MRD negativity by next-generation sequencing (10^{-5} threshold). **Results:** At data cutoff (July 7, 2025; median follow-up 35.8 mo), pts in the intention-to-treat population treated with BPd (n = 155) were >4 × more likely vs those treated with PVd (n = 147) to achieve ≥ CR + MRD negativity (27.7% vs 6.1%) and sustained MRD negativity (15.5% vs 2.7%). In pts with ≥ CR (BPd, n = 67; PVd, n = 25), rates of MRD negativity were also higher with BPd vs PVd (64.2% vs 36.0%), as were rates of sustained MRD negativity (55.8% vs 44.4%) among all ≥CR + MRD negative pts. Pts with sustained MRD negativity had durable PFS in both arms; 1 of 24 and 0 of 4 pts experienced PFS events with BPd and PVd, respectively. In pts without sustained MRD negativity, median PFS was 21.1 mo with BPd (HR vs sustained MRD negative, 0.04; 95% CI, 0.01–0.32) and 10.2 mo with PVd (HR vs sustained MRD negative, not estimable [NE]). Sustained MRD negativity was also associated with durable PFS2 in both arms; 2 of 25 and 0 of 4 pts experienced PFS2 events with BPd and PVd, respectively. In pts without sustained MRD negativity, median PFS2 was 20.2 mo with BPd (HR vs sustained MRD negative, 0.08; 95% CI, 0.02–0.33) and 9.3 mo with PVd (HR vs sustained MRD negative, NE). Findings were similar in pts with vs without ≥CR + MRD negativity. Of BPd-treated pts, those with MRD negativity (n = 43) received 1–3 prior LOT, of which most (74.4%) had 1. MRD-positive pts (n = 112) received up to 6 prior LOT, of which 44.6% received 1 and 17.0% received >3. Almost 40% of pts with CR-based MRD negativity had high-risk cytogenetics. **Conclusions:** Pts receiving BPd vs PVd were >4 × more likely to achieve sustained MRD negativity, which was associated with improved PFS and PFS2. Within the BPd arm, MRD negative vs positive pts more often had 1 prior LOT, further supporting the use of BPd, a BCMA-directed ADC regimen, in earlier LOTs for RRMM, including in pts with high-risk cytogenetics. Sponsorship: GSK (study ID 207499) Copyright statement © 2026 American Society of Clinical Oncology, Inc. Reused with permission.

OA-39

Low-Dose BCMA × CD3 Bispecific Antibody CM336 Induces Rapid and Universal Deep Hematologic Responses in Newly Diagnosed Systemic AL Amyloidosis: Primary Analysis of the Prospective Phase 2 AL-003 Trial

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Introduction: Systemic immunoglobulin light-chain (AL) amyloidosis arises from clonal plasma cells with cardiac involvement driving early mortality. Approximately 40% of patients still fail to reach a deep response, and early deaths remain a major unmet need, particularly in patients with advanced cardiac disease. BCMA/CD3 bispecific antibodies have shown high response rate in relapsed/refractory AL amyloidosis. We conducted the first prospective trial evaluating a BCMA/CD3 bispecific antibody (CM336) as frontline therapy in newly diagnosed AL amyloidosis. **Methods:** AL-003 (NCT07151690) is a single-center, single-arm phase 2 trial of CM336, a humanized BCMA/CD3 bispecific antibody, in adults with previously untreated systemic AL amyloidosis. CM336 was administered subcutaneously in 28-day cycles for up to 12 cycles. During cycles 1 through 4, patients who had received at least two cycles of weekly therapy, had a partial response or better, and had a very good partial response or better by the end of cycle 4 were switched to 80 mg every 2 weeks during cycles 5 through 12. Primary endpoints were the ≥VGPR rate and safety. **Results:** As of the April 7, 2026 data cutoff, 21 patients had been enrolled, of whom 19 had completed at least one hematologic response assessment and constituted the efficacy and safety analysis population. The median baseline dFLC was 319.76 mg/L (range, 53–2543). 85.7% (18/21) had cardiac involvement, 76.2% (16/21) renal involvement. All 19 evaluable patients achieved ≥VGPR, including CR in 13 (68.4%) and VGPR in 6 (31.6%). Hematologic responses were extremely rapid: median time to ≥PR was 9.5 days (range, 5–40) and median time to CR was 108 days (range, 7–193). Among patients with at least one next-generation flow cytometric MRD assessment, all achieved MRD negativity at 10^{-5} (100%). Among 17 patients evaluable for organ response, organ response was achieved in 15 (88%). Cardiac response occurred in 11 of 15 evaluable patients (73%) at a median of 35 days (range, 14–106). Renal response occurred in 12 of 13 evaluable patients (92%) at a median of 38 days (range, 14–50). The most common treatment-emergent adverse events were lymphopenia (84.2%; grade 3–4 in 68.4%), hypogammaglobulinemia (78.9%; no grade 3–4) and leukopenia (68.4%; grade 3–4 in 21.1%). CRS occurred in 2 patients (10.5%), all of grade 1–2 severity, with no grade ≥3 events. 5 patients (26.3%) had grade 3 infections; no grade ≥4 infections were reported. **Conclusions:** In this first prospective frontline trial of a BCMA/CD3 bispecific antibody in newly diagnosed AL amyloidosis, low-dose CM336 produced unprecedented depth and speed of response: 100% of evaluable patients achieved ≥VGPR and median time to hematologic response was only 9.5 days. Cardiac and renal organ responses occurred within the first 5 to 6 weeks of treatment in the majority of evaluable patients. The safety profile was manageable. These results support BCMA/CD3 bispecific antibody therapy as a potential new frontline option for AL amyloidosis.

OA-40

Mechanical Loading of the Bone During Induction Therapy Improves Bone Regeneration in Newly-Diagnosed Multiple Myeloma Patients (GMMG-HD8-INDEX Trial)

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Introduction: Even though a full recovery of bone lesions in multiple myeloma (MM) is unlikely, certain mechanisms of bone regeneration can be observed during induction therapy (IND), such as osteosclerosis of bone lesions. In this study we hypothesized that bone healing might be further improved by mechanical loading during IND, when regenerative mechanisms are already activated. **Methods:** A total of 50 newly-diagnosed MM patients were randomized to an intervention (IG) and a standard of care group (SOC). Following orthopedic principles of bone and fracture healing, patients in the IG received an individualized resistance training plan (2–3x/week) with the intent to increase mechanical loading and thus promote bone healing. Bone marrow biopsies were collected at initial diagnosis (T0) and after IND (T1) for RNA sequencing. Whole body CT-scans were conducted at T0 and after autologous stem cell transplantation (T2). A blinded assessment of bone changes was performed by two independent radiologists. Lumbar spine bone density was measured in Hounsfield units. Osteolytic lesions were

evaluated for maximum width, intralesional calcification, and osteosclerosis. Osteolyses were evaluated in the lumbar spine and pelvis as high mechanical loading sites (HML), and in the skull or sternum as lower mechanical loading sites (LML). **Results:** The median width of osteolyses decreased in both groups, though more in the IG than in SOC at HML sites (−13.86% vs. −6.7%, $p < 0.05$). Osteosclerosis was more often identified in the IG than in SOC at both HML (77.5% vs. 44.4%) and also LML sites (62.5% vs. 25%, $p < 0.05$), suggesting that additional to mechanical loading there might also be a systemic effect of resistance training on bone regeneration. Intralesional calcification, a further sign of bone regeneration, was detected in 5 patients, all of whom were in the IG. Loss of bone density was identified in both groups, though significantly greater in the SOC (median −22,53% vs. −9.55% in IG, $p < 0.05$). Bisphosphonate therapy was similar in both groups and the total dexamethasone dose was higher in the IG. Matched pair analysis of patients in remission at T1 revealed higher gene expression associated with bone remodeling and mechanical loading in the IG (e. g. RUNX2, WWTR1, WNT10B). **Conclusions:** Our data show that individually adapted mechanical loading in the form of resistance training improves bone remodeling mechanisms in newly-diagnosed MM patients.

OA-41

Mitigating Cilta-cel-Associated Delayed Neurotoxicity in Patients with High Lymphocyte Expansion: A Prospective Observational Comparative Study of Prophylactic Cyclophosphamide

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Introduction: Immune effector cell-associated delayed neurotoxicity (DNT), including parkinsonism syndrome (PKS) and cranial nerve palsies (CNP), occurs in 10–15% of patients (pts) treated with ciltacabtagene autoleucel (cilta-cel) and is associated with substantial morbidity and mortality. Among pts who develop a high post-infusion absolute lymphocyte count (ALCpeak ≥3 × 109/L; ALChi) DNT rates increase to 25–30%. We previously demonstrated that prophylactic dexamethasone (PPX DEX) administered at ALChi did not reduce DNT incidence. We prospectively evaluated whether prophylactic cyclophosphamide (PPX CTX) mitigates DNT. **Methods:** We conducted a prospective observational single-arm study using a binomial design (one-sided $\alpha = 0.10$, power 90%) to test whether a single dose of PPX CTX 500 mg administered at ALChi reduces DNT incidence by 90%. Prespecified comparators were a historical cohort (HIS) without prophylaxis (HIS; ALChi104/229) and a PPX DEX cohort (ALChi 65/136; DEX 10 mg twice daily for ≥3 days). DNT incidence, event-free survival (EFS), and ALC kinetics were assessed. Peripheral blood (PB) and bone marrow (BM) immune composition were evaluated by flow cytometry. **Results:** In PPX CTX cohort, 39/101 had ALChi and received CTX. Demographics, CRS/ICANS, and response to bridging were similar among the ALChi across cohorts. PPX CTX pts had a trend for lower disease burden that was not statistically significant. PPX CTX did not reduce DNT or PKS incidence among ALChi pts compared with HIS or PPX DEX cohorts (% DNT (%PKS): CTX 26% (8%), HIS 22% (9%), DEX 23% (8%); p = ns). DNT-free EFS or PKS-free EFS were comparable across cohorts. Notably, 3/4 PKS events in the PPX CTX cohort were clinically mild, and 2 improved/resolved with corticosteroids ± IVIG. To date, no PKS-related death was observed in the PPX CTX cohort. Given the limited number of cases and short follow-up, this suggests an improvement compared with a total PKS-associated mortality rate of 36% (5/14) in our comparator cohorts.

CNP and PKS cases showed CD4-predominant T cell expansion (CD4/CD8 >1). The proportion of CD4-predominant cases was numerically higher in PKS compared to CNP at pre-Apheresis (10/14 (71%) vs 16/20 (80%), p = 0.69), pre-LD (10/10 (100%) vs 10/15 (67%), p = 0.12) and month 1 (10/16 (63%) vs 14/27 (52%), p = 0.45).

PPX CTX did not significantly alter ALC expansion kinetics compared to PPX DEX. The ALC decrease after expansion was similar across 3 cohorts (ALC AUC: HIS, Day 11 to 30; DEX and CTX, intervention to Day 30). No statistical differences of CD4/CD8T cell distribution on Day 14, month 1 and 3 have been observed across cohorts. **Conclusions:** Single-dose PPX CTX was safe but did not reduce ALC expansion, DNT incidence, or PKS following cilta-cel, but may affect severity of PKS. Our findings support further development of biologically informed, risk-adapted prevention strategies and suggest that refinement of intervention targets may be required.

OA-42

MRD Depth by NGS and Distinct Clonotypic Patterns Below the Limit of Detection Predict Divergent Relapse Risk After Sustained Remission

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Introduction: Measurable residual disease (MRD) testing by next-generation flow (NGF) and next-generation sequencing (NGS) has dramatically improved disease monitoring and serves as an early surrogate for survival. However, there are conflicting data regarding the optimal MRD depth and modality for predicting long-term disease control. While many trials use MRD at 10^{-5} as an endpoint, results between 10^{-5} and 10^{-6} or below the limit of detection (LOD) at 10^{-6} have unclear prognostic significance. Biologically, these states may reflect true low-burden disease or non-malignant plasma cell clones detected by highly sensitive assays, and their clinical impact is incompletely understood. **Methods:** We evaluated MRD results for patients at our center who achieved sustained MRD-negative (neg) remission lasting ≥24 months, either by NGF (10^{-5}) or by NGS via clonoSEQ (10^{-6}). NGF samples without concurrent NGS assessment are termed NGF-neg only. We divided NGS samples into 1) NGS-neg; 2) NGS below LOD with detection of highly unique clonal rearrangements, termed NGS-LOD+; and 3) NGS below LOD with detection only of less unique clonotypic sequences, termed NGS-LOD0. This information is available in the standard clonoSEQ report: NGS-LOD+ samples have a reported range with a minimum of >0 (reflecting likelihood of low-level disease), while NGS-LOD0 results are assigned a range with a minimum of 0 (reflecting possible background). Association between MRD and progression was evaluated using a time-dependent Cox proportional hazards model, adjusted for IMS/IMWG genomic risk, ISS, and age, in which each MRD result was treated as a time-varying covariate from that timepoint until the next assessment. **Results:** A total of 2,116 unique MRD assessments (1083 NGS, 1033 NGF) were included from 418 patients, with a median of 5 timepoints per patient. Compared to NGS-neg, NGS-LOD0 showed no significant difference in relapse risk (aHR 2.43, $p = 0.35$). In contrast, both NGS-LOD+ (aHR 10.62, $p < 0.001$) and NGF-neg only (aHR 6.03, $p = 0.004$) had significantly higher relapse risk, though lower than MRD positive (aHR 22.72, $p < 0.001$). Using a composite endpoint of relapse or MRD resurgence, NGS-LOD0 again showed no significant difference (aHR 1.36, $p = 0.60$), whereas NGS-LOD+ (aHR 10.56, $p < 0.001$) and NGF-neg only (aHR 4.87, $p < 0.001$) had significantly increased risk compared to NGS-neg. In our cohort, patients whose MRD status was confirmed at least once as NGS-neg or NGS-LOD0 had significantly decreased relapse risk compared to those with exclusively NGS-LOD+ or NGF-neg only results (aHR 0.13, $p < 0.001$). **Conclusions:** After sustained remission, MRD negativity by NGS demonstrated significantly reduced relapse risk compared to NGF. Further, while NGS-LOD0 functioned similarly to true NGS negativity, NGS-LOD+ represented an intermediate risk state for subsequent relapse or MRD resurgence. These data support enhanced prognostic stratification across distinct MRD states and may help better identify candidates for treatment de-escalation.

OA-43

Multi-Center Phase II Trial of Iberdomide and SQ Daratamumab as Post-ASCT Maintenance Therapy in Pts with Multiple Myeloma (the IBEX Trial): Initial Safety Analysis and Interim Efficacy Results.

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Introduction: Maintenance therapy after autologous stem cell transplant (ASCT) improves progression-free survival (PFS) and overall survival (OS) in multiple myeloma (MM). Lenalidomide (LEN) is standard maintenance therapy. Addition of an anti-CD38 antibody such as daratumumab (DARA) increases MRD(−) responses and further improves outcomes. Iberdomide (IBER) is a Cereblon E3-ligase modulator (CELMoD) with greater CRBN-binding affinity than LEN, resulting in enhanced target protein degradation, increased immune activation, and direct anti-MM activity (including LEN-resistant disease). IBER and DARA also demonstrate synergistic anti-MM activity. IBEX is a multicenter phase II trial evaluating IBER plus DARA as post-ASCT maintenance. We report a prespecified safety analysis and preliminary efficacy data. **Methods:** Pts with MM who received anti-CD38-containing induction therapy followed by ASCT were eligible. IBER was given on days 1–21 of 28-day cycles (max 26 cycles). The starting dose was initially 1 mg/d, later amended to 0.75 mg/d following EXCALIBER-Maintenance dose-optimization results. DARA 1800mg SQ was administered qw (C1–2), q2w (C3–6), then q4w (C7+). All pts received aspirin unless anticoagulated. The original 1o endpoint, MRD conversion from (+) to (−) by ClonoSEQ NGS (10^-5), was revised to sustained MRD negativity. Forty-two MRD-evaluable pts are required. Secondary endpoints: MRD conversion, 12- & 24-mo PFS/OS, change in IMWG response category, PRO/QoL, and safety. Safety monitoring uses a continuously assessed Pocock-type stopping boundary defined by grade(Gr)3+ nonheme or Gr4+ heme adverse events (AEs) at least possibly related to treatment. **Results:** As of May 31, 2026, 18 pts had received treatment. Initial IBER dose was 1.0 mg in 10 pts and 0.75 mg in 8. Med treatment duration: 15 cycles (range, 1–25). For the safety analysis, the stopping boundary was 10 events. No treatment-related Gr4 heme AEs occurred. Five Gr3 nonheme AEs were observed (3 infections, 1 fever, 1 rash). The most common treatment-associated AE was neutropenia (9 pts; all Gr3). The most common nonheme AE was upper respiratory infection (7 pts; Gr1/2/3: 3/2/2); three additional infections occurred (Gr1/2/3: 2/0/1). Diarrhea was uncommon and

mild (4 pts, all Gr1). No thromboembolic events or secondary malignancies occurred. Five pts required dose reductions. Seventeen pts were MRD(+) at enrollment; among 9 evaluable at 12 mos, 5 converted to MRD(−), 4 remained MRD(+). Two pts improved their IMWG response category. Only 1 pt developed progressive MM: a new PET/CT-detected bone lesion despite concurrent MRD-negative marrow assessment. **Conclusions:** Post-ASCT maintenance with IBER plus DARA is feasible and safe. Neutropenia was manageable at the doses used in IBEX. Improvements in IMWG response and MRD conversion were observed despite pre-ASCT quadruplet induction. Enrollment is ongoing. Updated safety and efficacy results will be presented.

OA-44

Multi-Omic Characterization of Teclistamab Resistance Reveals Diverse Evolutionary Trajectories in RRMM: Results From the RESISTEC Trial

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Introduction: The introduction of teclistamab, a BCMA × CD3 bispecific antibody, has revolutionized the treatment of relapsed/refractory multiple myeloma (RRMM). However, primary resistance in 30% of patients remains a critical clinical challenge. Within the scope of the RESISTEC clinical trial (NCT05945524), we applied a high-resolution, multi-omic approach to uncover the molecular drivers of primary resistance to teclistamab. **Methods:** We characterized the genomic and transcriptomic features of RRMM patients by comparing Responders (R) versus Non-Responders (NR), before teclistamab therapy. Three complementary techniques were integrated: 1) bulk panel sequencing (n = 40) to identify translocations, mutations, copy number alterations, and ploidy; 2) single-cell targeted DNA sequencing (MissionBio Tapestri; n = 55) to quantify the subclonal heterogeneity and study their evolutionary patterns; 3) single-cell RNA sequencing (10X Genomics; n = 36) to evaluate transcriptomic shifts, including pathway enrichment analysis and RNA velocity inference. **Results:** Bulk sequencing highlighted hyperdiploidy and t(11;14) as hallmarks of response. Conversely, NR patients exhibited high-risk genomic traits, including chromosome 1 abnormalities combined with t(4;14), high-risk LP score, but also EPHA3 mutations, and monoallelic deletions of XBP1, TRAF3, and TNFRSF17 (BCMA; $P < 0.05$). Within the bulk signal, single-cell analysis revealed profound clonal complexity. We found that high heterogeneity (i.e. >3 subclones) was associated with NR patients ($P = 5.83e\text{-}3$). We observed patient-specific branched evolutions, where distinct subclones harbored independent high-risk alterations (e.g. convergent 1p and 17p losses) within the same tumor. Leveraging scRNA-seq data, we showed that TNFRSF17 expression is significantly lower in NR than in R. RNA velocity analysis highlighted striking patient-specific effects over time, such as: 1) decreased TNFRSF17 and HLA-A/B/C expression, suggesting immune evasion; 2) increased BCL2 and MCL1 expression, promoting cell survival; 3) decreased PRDM1 and XBP1 expression, driving dedifferentiation ($P < 0.05$). **Conclusions:** Our findings demonstrate that primary resistance to teclistamab is not driven by a key universal driver. Integrating bulk and single-cell multi-omics data enables more accurate insights into complex biological mechanisms and regulations. This approach reveals that high subclonal heterogeneity and evolutionary trajectories of distinct high-risk populations are key features of tumor aggressiveness. Genomic alterations or transcriptomic downregulations of TNFRSF17 are significantly associated with NR patients, but only partially uncover resistance mechanisms. In the absence of such defects, aggressive tumors are characterized by a wide spectrum of changes. This inter- and intra-patient heterogeneity underscores the critical need for personalized, high-resolution monitoring to anticipate resistance and adapt therapeutic strategies early.

OA-45

Myeloma Precursors Erode Durable Immunity Through Tumor Burden–Dependent Depletion of APRIL

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Introduction: The asymptomatic precursor states of multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM), affect 3–5% of adults over 50. Infection is a leading cause of morbidity and mortality across

the myeloma spectrum, often exceeding treatment toxicity and disease progression. Although clinically silent, these patients are now the target population for early-intervention cancer vaccines and immunotherapies. Whether their immune systems can mount and maintain effective responses to such interventions remains undefined. **Methods:** We studied a prospective cohort of 731 participants: healthy donors (HD, n = 129), MGUS (n = 249), SMM (n = 273), MM (n = 80). We paired an mRNA vaccine challenge (SARS-CoV-2 spike) with childhood measles, mumps, and rubella (MMR) serology to probe humoral generation and maintenance. Profiling included 1,940 spike-IgG ELISAs; scRNA-seq of 1,109,633 PBMCs (n = 114); scTCR-seq (n = 82) with ClusTCR co-clustering vs spike (n = 1,463) and CEF (n = 2,286) references; Olink plasma proteomics (n = 51); and IFN-γ ELISPOT (HD vs SMM, n = 10 each). **Results:** Across the disease spectrum, immunity collapsed in a coordinated, stage-dependent manner. Vaccine-induced IgG titers waned twice as fast in SMM as MGUS ($\beta = -0.0085$ vs -0.0043 log-titer/day; $p = 0.038$) and were not rescued by a third dose (SMM $q = 1.5 \times 10^{-5}$, $r = 0.41$). Most strikingly, decades-old immunity was eroding in plain sight: SMM patients had reduced titers to childhood mumps ($p = 0.007$) and rubella ($p = 0.049$) vaccines, exposing failure of plasma-cell maintenance, not de novo generation. Plasma proteomics revealed a unifying mechanism: APRIL, the survival cytokine of long-lived plasma cells, was progressively depleted in SMM ($q = 0.026$) with near-perfect inverse correlation to tumor burden (Spearman $\rho = -0.96$, $p = 7.3 \times 10^{-6}$); myeloid TNFSF13 transcription was intact, pinpointing consumption by clonal plasma cells, not impaired production. An APRIL-responsive survival module was downregulated in normal B cells of SMM ($p = 0.006$) and replicated in an independent bone-marrow plasma-cell scRNA-seq cohort ($p = 0.0095$). The defect extended beyond antibodies: SMM patients failed to expand vaccine-specific T cell clonotypes (CEF preserved; ELISPOT spike $p = 0.0029$, CERI $p = 0.25$), and post-vaccination IL-1β, IL-18, RIG-I, NUB1, and MMP7 induction was lost across the continuum (HD $r = 0.82$–0.88). **Conclusions:** Myeloma precursors harbor a multilayered immune deficit unified by tumor-burden–dependent depletion of APRIL: clonal plasma cells consume the survival cytokine of their normal counterparts, eroding decades-old humoral memory while compromising de novo T cell and innate responses. Our findings reframe MGUS and SMM not as inert pre-malignant states but as states of progressive immune erosion years before diagnosis, with direct implications for cancer-vaccine eligibility, adjuvant choice (e.g., STING/TLR ligands), and infection prevention in this population.

OA-46

NKp30 is Expressed on Natural Killer (NK) Cells of Multiple Myeloma Patients and Can be Potently Activated by [GPRC5DxNKp30] and [CD38xNKp30] Bispecific NK Cell Engagers

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Introduction: Natural Killer (NK) cells are potent immune cells of the innate immune system, which distinguish healthy from virus-infected or malignantly transformed cells by activating and inhibitory receptors recognizing a multitude of ligands. Important activating NK cell receptors are for example the Fc γ receptor IIIa (FcγRIIIa) that is engaged, e.g., by daratumumab, and NKp30. NKp30 is activated by binding its ligand B7-H6. Importantly, tumor cells often downregulate or shed activating ligands to evade NK cell recognition. In multiple myeloma (MM), NKp30 – in contrast to other activating receptors – is not downregulated on the patients' NK cells, making NKp30 an attractive receptor for the development of novel NK cell engagers (NKCEs). Thus, the aim of our work was to design bispecific NKCEs activating NKp30 to redirect NK cells against MM cells. **Methods:** Mononuclear cells from bone marrow aspirates of MM patients were analyzed via flow cytometry. Two IgG-like, NKp30-binding NKCE either harboring a Fab derived from CD38 antibody daratumumab or G protein-coupled receptor family C group 5 member D (GPRC5D) antibody talquetamab and equipped either with a silent or an active Fc domain were produced in CHO-S cells. NK cell-induced myeloma cell killing was measured in 51Cr release assays using MM cell lines and myeloma cells from patients as targets. Fratricide was tested with freshly isolated NK cells from the same donor. Phagocytosis was analyzed with pHrodo-labeled MM cells and monocyte-derived M0 macrophages by live cell imaging. NK cell-induced cytokine release was measured in ELISA. **Results:** Flow cytometric analyses of newly diagnosed and relapsed/refractory (RR) MM patients revealed consistent expression of NKp30 on the patients' NK cells. Of note, the natural ligand of NKp30, B7-H6, was absent on MM cells of all patients. NKCEs targeting either CD38 [CD38xNKp30] or GPRC5D [GPRC5DxNKp30] were produced and bound myeloma cells comparable to daratumumab and talquetamab, respectively. Both, [GPRC5DxNKp30] and [CD38xNKp30], induced effective NK cell-mediated killing of MM cell lines and MM patient cells. Of note, [GPRC5DxNKp30] mediated potent killing of MM cells with low levels of CD38 that could not be lysed by daratumumab or [CD38xNKp30]. NK cell fratricide induced by [CD38xNKp30xFcγR] was comparable to daratumumab. An active Fc in general further enhanced the anti-myeloma effects and additionally induced robust phagocytosis of MM

cells. NKCE-triggered cytokine release of NK cells was significantly lower than observed with talquetamab and T cells. **Conclusions:** NK cell-based immunotherapies might be a promising strategy for RRMM patients especially after T cell-directed therapies. NKp30 is an important receptor stably expressed on NK cells of MM patients irrespective of disease stage, which can be potently activated by our novel bispecific NKCEs. Our data additionally suggest a good safety profile and support further investigation.

OA-47

NSD2 Expression Remodels DNA Methylation, Creating a Targetable Epigenetic Dependency in t(4;14) Multiple Myeloma

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Introduction: t(4;14) translocations cause overexpression of NSD2, which catalyzes di-methylation of histone H3 lysine 36 (H3K36me2), and is associated with poor outcome. However, the mechanisms by which NSD2-mediated chromatin changes create specific epigenetic vulnerabilities in this subtype remain poorly understood. **Methods:** DNA methylation (DNAm) data from the MMRF CoMMpass trial were determined by Whole Genome Bisulfite Sequencing. CRISPR/Cas9 was used to generate isogenic models: targeting the translocated allele only (TKO) in KMS11 and KMS18, and complete ablation (KO) in KMS28BM and KMS26. Analyses included BH3 mitochondrial profiling, DNA methylation analysis, and RNA-seq (with ribosomal RNA depletion). Cell sensitivity to decitabine (DAC) and the DNMT1 inhibitor GSK-3685032 were evaluated via flow cytometry (Annexin V and live/dead staining). KMS11 NTKO and TKO models were used for CUT&Tag and DNAm analysis. **Results:** CoMMpass patient data revealed significantly higher DNAm levels in the t(4;14) subtype compared to other MM subtypes ($p = 1.17e-12$). In isogenic models, NSD2 depletion (TKO/KO) resulted in reduced DNAm ($p < 0.05$), with H3K36me2 and DNAm loss co-occurring at the same genomic regions (OR = 1.85, $p < 1e-15$). NSD2-replete cells demonstrated significantly higher sensitivity to DAC ($p < 0.01$) and to DNMT1 inhibition ($p < 0.05$). Specifically, DAC treatment induced mitochondrial priming in KMS18 NSD2-replete cells but not in TKO cells ($p < 0.001$).

RNA-seq analysis revealed that while DAC downregulated cell cycle and MYC targets in both genotypes, the induction of interferon (IFN) response genes was significantly more robust in NSD2-replete cells (FDR< 0.0023 vs. FDR >0.08 in TKO/KO). This was associated with increased transcription of endogenous retroviruses (ERVs), specifically in the NSD2-replete cells, suggesting that DAC-induced transcription of ERVs drives an IFN signaling in t(4;14) MM. Correspondingly, these ERVs exhibited higher levels of DNAm in NSD2-replete KMS11 cells (FDR< 0.01) and in t(4;14) patient samples from CoMMpass. **Conclusions:** NSD2-mediated increases in H3K36me2 promote DNAm via recruitment of the DNMT3A/B PWWP-domains, creating a distinct epigenetic state in t(4;14) MM. This high-methylation state creates a dependency that can be exploited by DNA hypomethylating agents; inhibiting DNAm in t(4;14) leads to ERV de-repression, triggering viral defense pathways (IFN signaling) and apoptosis. Overall, NSD2 creates an epigenetic dependency in t(4;14) MM that can be therapeutically exploited with DNA hypomethylating agents. These findings support the use of DNA methylation inhibitors as a targeted translational strategy for NSD2-high multiple myeloma.

OA-48

Outcomes of Anti-BCMA CAR-T-Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma and CNS Involvement Based on a Multicenter Real-World Study With Extended Follow-Up

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Introduction: Central nervous system involvement of multiple myeloma (CNS-MM) is rare and associated with poor outcomes. Evidence for BCMA-directed CAR T-cell therapy in CNS-MM remains limited as pivotal trials largely excluded CNS disease despite potential efficacy. Here, we report real-world outcomes of commercially available anti-BCMA CAR T-cells (idecabtagene vicleucel (IC), ciltacabtagene autoleucel (CC)) in an extended follow-up of 25 patients (pts) with CNS-MM. **Methods:** Only pts with intradural and/or intraparenchymal lesions by MRI/CT of brain/spine or detection of MM cells in the CSF were regarded as MM-CNS pts. Endpoints included overall response rate (ORR), CNS response, progression-free survival (PFS), overall survival (OS) and safety. **Results:** Between July 2022 and April 2026, 25 CNS-MM pts were

treated with either IC (n = 15) or CC (n = 10). Median age at infusion was 60 (47–72) and 62 (37–76) years, respectively. Median time from diagnosis to CAR T-cell therapy was 6.0 (3.5–13.6) years for IC and 5.4 (0.7–9.0) years for CC. Median prior lines of therapy were 4 (1–11) and 3 (1–9), including 14/15 and 8/10 pts with ≥triple-class refractory status. High-risk cytogenetics per 2025 renewed IMWG classification were balanced among both groups (7/15 IC; 6/10 CC). Across the entire cohort, leptomeningeal disease and parenchymal lesions were present in 14/25 and 12/25 pts, respectively, distributed equally across IC and CC. At the time of bridging, active CNS disease was present in 23/25 pts. CNS-directed therapy before CAR-T included systemic (20/25 pts), intrathecal (13/25 pts) or radiation therapy (12/25 pts) and surgery (3/25 pts). Median number of bridging regimens was 1 (1–3) in both subgroups. Best achieved CNS response after bridging was CR/PR in 15/25 pts. CAR-T application was generally safe and manageable with only 2 pts experiencing ≥grade 3 CRS (both IC) and 4 pts with grade 1 ICANS (2 each for IC and CC). Deep responses (≥VGPR) following CAR T-cell therapy were achieved in 16/20 pts (response assessment pending in n = 5 due to short follow-up). Median PFS and OS were 6.3 vs. 13.9 months (p = 0.95) and 13.0 vs. 13.9 months (p = 0.88) for IC and CC, respectively. Noting the limitations in sample size and statistical power for this study, CNS disease control before CAR-T infusion trended with a more favorable PFS after CAR-T (mPFS 10.5 vs. 6.3 months, p = 0.21). At data cut-off, progressive disease (PD) was observed in 8/15 IC and 4/10 CC pts, including CNS relapses in 3 and 2 pts, respectively. 6/15 IC and 4/10 CC pts had died, all due to PD except for 1 pt with secondary sarcoma. **Conclusions:** BCMA-directed CAR T-cell therapy shows clinically meaningful activity with manageable toxicity profile in CNS-MM regardless of the specific CAR product. While outcomes remain inferior to those in non-CNS MM, our findings highlight the need for CNS remission during bridging therapy to optimize CAR-T outcome in this under-represented subgroup of high-risk pts.

OA-49

Overall Survival, Progression and Non-Relapse Mortality With Teclistamab Plus Daratumumab (Tec-Dara) vs Dara-Based Triplets in Relapsed/Refractory Multiple Myeloma (RRMM): MajesTEC-3 Post Hoc Analysis

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Introduction: Tec-Dara showed significant survival benefits vs Dara + dexamethasone + pomalidomide/bortezomib (DPd/DVd) in MajesTEC-3 in early-line RRMM, a setting in which disease progression is the leading cause of death. The marked improvement in PFS (HR = 0.17; 95% CI 0.12–0.23) resulted in substantially different treatment (tx) exposure between arms (median tx duration, 32.4 mo with Tec-Dara vs 16.1 mo with DPd/DVd). This post-hoc analysis evaluated cumulative incidence of progression (CIP) and non-relapse mortality (NRM) and their contribution to observed OS. **Methods:** Patients (pts) had 1–3 prior lines of therapy (LOT), including a proteasome inhibitor and lenalidomide (len; len-refractory if 1 prior LOT) with progression on/after last LOT. Pts refractory to anti-CD38 were excluded. Pts were randomized 1:1 to Tec-Dara (n = 291) or DPd/DVd (n = 296). In the Tec-Dara arm, tx was administered in 28-day cycles (C) of Tec with step-up dosing followed by 1.5 mg/kg QW in C1–2, 3 mg/kg Q2W in C3–6, and 3 mg/kg Q4W in C7 onward, in combination with Dara (administered per the approved schedule). DPd/DVd were administered per approved schedules. OS was a key secondary endpoint with HR reported from Cox regression model. Since the proportional hazards assumption was violated, a prespecified analysis of restricted mean survival time (RMST) was also conducted. Competing risk analyses for CIP and NRM were performed using Fine-Gray sub-distribution hazard models (sHRs) and Gray's test. **Results:** At median follow up of 34.5 mo, there were 46 deaths in Tec-Dara vs 98 in DPd/DVd (ITT analysis set). Tec-Dara significantly improved OS vs DPd/DVd (HR = 0.46; 95% CI 0.32–0.65; P < 0.0001); estimated 36-mo OS rates were 83.3% vs 65.0%. Proportional hazards assumption was not met. OS curves intersected at ~10 mo with no OS difference ≤10 mo (HR = 1.08; 95% CI 0.64–1.81). Beyond 10 mo, OS favored Tec-Dara (HR = 0.22; 95% CI 0.13–0.38), corresponding to a 78% reduction in the hazard of death. CIP was markedly lower in Tec-Dara vs DPd/DVd (sHR = 0.10; 95% CI 0.07–0.16; P < 0.0001); estimated 36-mo CIP was 8.7% vs 62.1%. There were 24 progressions in Tec-Dara vs 171 in DPd/DVd (18 vs 72 resulted in death). Death without prior progression occurred in 28 Tec-Dara vs 26 DPd/DVd pts. NRM was similar in Tec-Dara vs DPd/DVd (sHR = 1.16; 95% CI 0.69–1.98; P = 0.6), with estimated 36-mo NRM of 10.2% vs 9.0%. RMST analysis (area under the OS curve) confirmed superior OS of Tec-Dara (difference 2.15 mo; 95% CI 0.54– 3.77; P = 0.009). **Conclusions:** Tec-Dara significantly improved OS over DPd/DVd in pts with RRMM and 1–3 prior LOT. This analysis demonstrates that the observed OS benefit is driven by a

profound reduction in disease progression, the leading cause of mortality in RRMM. Despite early curve crossing, Tec-Dara did not increase NRM. The findings underscore the safety and clinically meaningful and durable survival benefit of Tec-Dara, supporting Tec-Dara as a new standard-of-care as early as 2L RRMM.

OA-50

Persistent Mucosal CAR-T Cells and Interferon-Driven Inflammation Drive BCMA-Targeted CAR-T Therapy–Associated Enterocolitis

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Introduction: BCMA-targeted chimeric antigen receptor (CAR) T-cell therapies have transformed outcomes in multiple myeloma but can cause a severe enterocolitis in about 6% of cases with mortality in >30% of cases. We present insights from the first multi-comic and multimodal analysis of CART colitis with healthy individuals and asymptomatic CART patient controls. **Methods:** Intestinal biopsies from the small intestine and colon were analyzed from 11 normal volunteers, 7 asymptomatic BCMA CAR-T–treated controls (CAR-TCTRL), and 10 multiple myeloma patients with CAR-T–associated enterocolitis (CAR-TEC). in addition to anti-Camelid staining, single-cell RNA sequencing data were analyzed using a custom reference genome incorporating the cilta-cel CAR construct to identify and transcriptionally profile CAR-T cells. Immune and stromal compartments were further characterized by multiparameter flow cytometry, immunohistochemistry, immunofluorescence, systemic IgA, soluble BCMA (sBCMA), and fecal calprotectin. **Results:** BCMA CAR-T therapy induced profound mucosal plasma-cell and B-cell depletion in all CAR-TEC subjects and in a subset of CAR-TCTRL, indicating that deep humoral depletion is a shared consequence of therapy but is not sufficient alone to cause enterocolitis. Asymptomatic CAR-TCTRL showed selective loss of long-lived and IgA2 plasma cells and switched memory B cells yet retained homeostatic transcriptional programs, whereas CAR-TEC mucosa exhibited near-complete plasma-cell absence together with expansion of highly cytotoxic and TH17-skewed T cells. Using the custom genome construct, scRNA showed that persistent BCMA CAR-T cells were mapped to cytotoxic and NK-like clusters in the gut. CAR-TEC patients displayed an interferon-inducible, JAK-STAT-enriched, trafficking-competent phenotype, in contrast to low-level, transient mucosal CAR-T detection in most CAR-TCTRL. Myeloid, stromal, endothelial, epithelial, and glial remodeling in CAR-TEC converged on interferon- and NF-kB-driven activation, loss of homeostatic signaling, with ligand-receptor networks including MIF-CD74-CXCR4 and gut-homing endothelial programs that may recruit and retain cytotoxic CAR-T cells. Systemically, persistent loss of IgA and sBCMA together with elevated fecal calprotectin defined a high-risk inflammatory signature. In two refractory CAR-TEC patients, JAK inhibition with upadacitinib was associated with clinical improvement, reduced fecal calprotectin, decreased mucosal CD14 monocytes CAR-T infiltrates. **Conclusions:** Our data establish CAR-TEC as an interferon-imprinted mucosal immune failure state arising from the intersection of deep B-cell depletion, stromal-endothelial breakdown, and persistent tissue-resident CAR-T cells. The inclusion of asymptomatic CAR-T controls highlights protective mucosal programs not evident from case-only studies and identifies practical biomarker and therapeutic hypotheses for risk stratification and mechanism-based intervention.

OA-51

Phase 2 Study of Talquetamab (Tal), Daratumumab (D), and Lenalidomide (R) as Induction Therapy in Patients (pts) With Transplant Eligible Newly Diagnosed Multiple Myeloma (TE-NDMM): MajesTEC-5

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Introduction: Tal, a first-in-class anti-GPRC5D × CD3 bispecific antibody, demonstrated robust efficacy in pts with relapsed/refractory multiple myeloma. The immunomodulatory effects of D prime the immune system, leading to activation and expansion of cytotoxic T cells and may enable synergistic efficacy when combined with Tal. We

report the first results from Arm E evaluating Tal plus D+R during induction in pts with TE-NDMM as part of the multi-arm phase 2 GMMG-HD10/DSMM-XX/MajesTEC-5 trial. **Methods:** Eligible pts aged 18–70 years with TE-NDMM received Tal-DR induction therapy: Tal 0.8 mg/kg SC Q4W, preceded by 3 step-up doses in cycle (C)1; D 1800mg SC QW in C1–2 and Q2W in C3–6; oral R 25 mg in C2–6; and dexamethasone 20 mg in C1–2 only. Pts then received high-dose chemotherapy + autologous stem cell transplant (ASCT). **Results:** 20 pts (median age: 57.5 yrs; high-risk cytogenetics: 30%) received Tal-DR induction therapy. As of March 2026, 17/20 pts were still on study treatment with a median follow-up of 12.5 months. 19/20 pts completed stem cell mobilization, with a median yield of 6.4×10^6 CD34 cells/kg; 18 underwent successful ASCT. Median time to neutrophil and platelet engraftment was 14 days. All pts experienced ≥1 adverse event (AE). Grade (gr) 3–4 AEs and SAEs occurred in 13/20 and 11/20 pts, respectively. Cytopenias were the most common gr 3–4 AEs (n = 11/20), including neutropenia (n = 6/20). CRS was reported in 14/20 pts (all gr 1/2); no ICANS was reported. Gr 3–4 infections occurred in 4/20 pts. AEs of decreased weight occurred in 8/20 pts with 3/20 pts experiencing ≥20% weight loss from baseline. Taste changes ([maximum toxicity of gr 2] n = 16/20), nail (n = 4/20), skin (n = 3/20), and rash (n = 11/20) disorders were gr 1/2, except 2 pts with gr 3 rash (n = 1) and eczema (n = 1). Ataxia/balance disorders occurred in 3/20 pts (all gr 1/2); symptoms resolved in 2 pts and are ongoing in 1 pt. 4/20 pts discontinued Tal due to an AE (vertigo [n = 2], balance disorder [n = 1], and eczema [n = 1]) and continued the remaining study drugs. Deaths occurred in 2 pts, 1 due to trauma and 1 due to rapid disease progression at C3. ORR (95% CI) was 85% (62–97), with 65% (41–85) and 85% (62–97) achieving a complete response or better and very good partial response or better, respectively. 18/20 pts achieved minimal residual disease (MRD) negativity at 10^{-5} prior to ASCT. In 16 pts, MRD negativity was confirmed at subsequent time points. Two pts became MRD-positive after C6 but converted back to MRD negativity after ASCT, while 2 pts remained MRD-positive throughout treatment. **Conclusions:** Tal-DR induction demonstrated promising early efficacy results in TE-NDMM, with rapid, deep responses and high MRD-negative rates. The gr 3–4 infection rate was lower than previously reported for the teclistamab induction therapy arms of this study, and no new safety signals emerged. This suggests pts at high risk for infection may benefit from targeting non-BCMA myeloma antigens. However, 4/20 pts discontinued Tal due to AEs.

OA-52

Phase I/II Study of Mezigdomide and Elranatamab for Relapsed/Refractory Multiple Myeloma Patients (MELT-MM): Updated Results From Part 1

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Introduction: Despite significant advances, multiple myeloma (MM) remains incurable. Mezigdomide is a novel CELMoD with enhanced tumoricidal and immunomodulatory effects via rapid Ikaros/Aiolos degradation. Elranatamab is an approved BCMA × CD3 bispecific antibody for R/R MM. We evaluated the combination of mezigdomide with elranatamab. Preclinical data show high tumor burden limits elranatamab cytotoxicity, and mezigdomide rescues this by augmenting T-cell effector function and attenuating PD-1/TIGIT upregulation. **Methods:** MELT-MM (NCT06645678) is an ongoing, open-label, multinational phase I/II study. Part 1 assessed safety, tolerability, and preliminary efficacy to define recommended phase 2 doses (RP2Ds). After an elranatamab lead-in (cycle 0), treatment was administered in 28-day cycles: elranatamab weekly (cycles 1–6), biweekly (cycles 7–12, PR or better), and monthly (cycles 13–24, CR or better); mezigdomide on days 1–21 at 0.3 mg or 0.6 mg. Eligible patients had R/R MM after ≥2 prior lines including a proteasome inhibitor and lenalidomide, were anti-BCMA–naïve, ECOG PS ≤2, with measurable disease. **Results:** From December 2024 till data cutoff (April 2026, median follow-up 10 months), 15 patients enrolled; 13 evaluable for safety and efficacy (2 excluded: 1 consent withdrawal, 1 progression before mezigdomide). Seven received 0.3 mg and 6 received 0.6 mg. Median age was 69 years (range 51–76), with a median of 4 prior lines (range 2–7); 53.8% had prior anti-CD38 antibody and 30.8% prior non-BCMA bispecific antibodies. Extramedullary disease was present in 30.8%. Cytokine release syndrome occurred in 10 patients (76.9%; all grades 1–2). No ICANS were observed. Hematologic toxicities were consistent with the known safety profile of mezigdomide. There were no febrile neutropenia events. Most common non-hematologic adverse event was fatigue (all grades 84.6%; grade 3–4 7.7%). Six (46.2%) experienced infection of any grade. Of note, cytomegalovirus disease occurred in 2 patients. Two dose-limiting toxicities were observed in the 0.6 mg cohort (grade 4 thrombocytopenia; grade 3 acute kidney injury), both reversible. Correlative analyses are ongoing to evaluate the relationship between Ikaros/Aiolos degradation and T-cell activation and exhaustion. Overall response rate was 100% (13/13) with ≥complete response (CR) in 92.3% (12/13), consistent across mezigdomide dose levels and prior treatment exposure. Among 8 patients with stringent CR and available minimal residual disease (MRD) data, 7 (87.5%) achieved MRD negativity. Median time to first response was 17 days (range 14–45). Median PFS was not reached. **Conclusions:** Mezigdomide plus elranatamab demonstrates profound and rapid antimyeloma activity with a manageable safety profile. Both 0.3 mg and 0.6 mg were selected as RP2Ds. Part 2 will proceed as a 1:1 randomized expansion (Arm A 0.3 mg vs. Arm B

0.6 mg mezigdomide) stratified by IMWG Frailty Score, to further define optimal dosing and confirm efficacy.

OA-53

Phase II Trial of Fixed-Duration Consolidation With Elranatamab Post-Idecabtagene Vicleucel CAR-T (EPIC) to Deepen Responses and MRD-Negativity in Relapsed or Refractory Multiple Myeloma

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Introduction: Bispecific antibodies may improve outcomes as post-CAR-T consolidation by re-invigorating anti-myeloma T-cell responses. We report updated results of the EPIC trial, an ongoing phase 2 study of elranatamab (Elra) as a fixed-duration consolidation after idecabtagene vicleucel (ide-cel) CAR-T cell therapy (NCT06138275). **Methods:** Eligible pts had received ide-cel for relapsed or refractory multiple myeloma after ≥2 prior lines of therapy (LOTs) without PD after ide-cel. Pts received Elra consolidation for 6 cycles starting between Day +100 and +160 after ide-cel. Elra schedule included step-up dosing followed by weekly dosing for cycles 1 and 2, and then every other week dosing for cycle 3–6. The primary endpoint is PFS. Secondary endpoints include adverse events (AEs) and IMWG response. Data cutoff was April 15, 2026. **Results:** 25 pts had started Elra consolidation at a median of 3.8 months from ide-cel (range, 3.0–5.2 mo); 23 pts had completed at least one cycle. The median age was 67 (range, 48–82). Seven pts (28%) had high-risk cytogenetics [defined by t(4;14), t(14;16), or del(17p)] and 4 pts (16%) had a history of extramedullary disease. The median number of prior LOTs was 3 (range, 2–6). 13 pts (52%) received Elra step-up dosing as an outpatient. With a median follow-up of 9.8 months from Elra initiation (range, 1.8–22.6 mo), the median PFS has not yet been reached. 6 pts (26%) so far have had an ongoing response over 12 months. Only 1 patient has had PD with a cutaneous plasmacytoma not requiring systemic therapy. Of the pts who had completed at least one cycle of Elra, 61% (n = 14/23) started Elra with best response of ≤VGPR post-ide-cel (SD: n = 2, PR: n = 9, VGPR: n = 3, CR/sCR: n = 9). 100% of the pts with ≤VGPR post-ide-cel (n = 14/14) had deepening of their IMWG response. The best overall response after Elra among the 23 evaluable pts was CR/sCR in 83% (n = 19/23) and VGPR in 17% (n = 4/23). 11 pts had evaluable MRD samples at screening and after completing or stopping Elra consolidation. Five pts (45%) had conversion from MRD-positivity to MRD-negativity at 10-6 sensitivity and 5 pts (45%) remained MRD-negative from screening through Elra completion; one pt lost MRD-negativity after stopping Elra. CRS occurred in 11 pts (44%), predominately grade (Gr) 1 with 2 pts (8%) having Gr 2 CRS. No ICANS occurred. Gr 3 or 4 hematologic AEs occurred in 11 pts (44%; neutropenia: n = 10, 40%, anemia: n = 4, 16%, thrombocytopenia: n = 3, 12%). Gr 3 or 4 non-hematologic AEs occurred in 9 pts (36%). Infections occurred in 14 pts (56%) with Gr 3 or 4 infections in 5 pts (20%). CMV viremia occurred in 6 pts (24%), with only 1 pt requiring CMV-directed treatment while the other 5 pts had resolution of CMV viremia without intervention. All patients received IVIG. **Conclusions:** Fixed-duration consolidation after ide-cel with Elra led to deepening of disease responses and MRD-conversion with ongoing, durable responses observed. The EPIC trial is fully accrued and updated data will be presented.

OA-54

Plasma cfDNA Methylation Defines Progression-Associated Epigenetic States in Multiple Myeloma

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Introduction: Liquid biopsy approaches are increasingly explored for minimally invasive disease monitoring in multiple myeloma (MM). While circulating biomarkers such as serum soluble BCMA (sBCMA) primarily reflect tumor burden, it remains unclear whether plasma-derived cell-free DNA (cfDNA) methylation profiling captures epigenetic patterns associated with MM progression and aggressive disease states. We investigated whether cfDNA methylation identifies distinct MM states beyond conventional tumor burden assessment. **Methods:** All participants provided informed consent and the study was approved by the local institutional ethics committee. Peripheral blood samples from healthy donors (n = 20), Smoldering MM (SMM, n = 20), Newly Diagnosed MM (NDMM, n = 24), and Relapsed/Refractory MM (RRMM, n = 20) patients underwent cfDNA methylation profiling using the Avida Methyl 3400 DMR Cancer Panel (Agilent). Serum sBCMA was quantified using the multiplex ELLA platform (Bio-Techne). Differential methylation, Principal Component Analysis (PCA), correlation, genomic annotation, and gene set enrichment analyses were

performed in R using normalized DMR methylation matrices. Multiple testing correction was performed using the Benjamini–Hochberg false discovery rate (FDR) method. **Results:** Both methylation index and sBCMA progressively increased across disease stages despite only a moderate correlation (Spearman $\rho = 0.36$, $P = 0.0025$), indicating incomplete overlap between tumor burden and epigenetic remodeling. Global methylation analyses identified n = 102 differentially methylated regions (DMRs), including n = 78 monotonic DMRs, of which 77 showed progressive methylation gain from healthy donors to advanced MM states. PCA revealed a continuous methylation axis strongly associated with disease stage (Spearman $\rho = 0.79$, $P < 1 \times 10^{-16}$), supporting a continuous epigenetic progression model across MM evolution, with NDMM samples displaying marked epigenetic heterogeneity spanning relatively Healthy-like to advanced MM methylation configurations. DMRs localized predominantly within promoter regions (~75.6%) and converged on developmental and chromatin programs. Representative loci included NKX6–2, SIX1, DBX1, PAX6, SP8, and LHX1. Transcription factor enrichment analyses demonstrated recurrent enrichment for Polycomb chromatin regulators including EZH2, SUZ12, RNF2, EED, JARID2, BMI1, and CBX2. A reduced methylation signature of n = 29 DMRs identified NDMM epigenetic states associated with inferior overall survival (log-rank P = 0.0029), higher sBCMA levels (P = 0.0417), and increased frequency of high-risk cytogenetic abnormalities (P = 0.0397). **Conclusions:** Plasma cfDNA methylation profiling reveals progressive promoter-centered epigenetic remodeling across MM evolution and identifies clinically aggressive NDMM epigenetic states beyond conventional tumor burden assessment, supporting the use of cfDNA methylation for minimally invasive identification of aggressive MM progression states.

OA-55

Poor Outcomes Post Sequential BCMA and GPRC5D Exposed Myeloma Can Be Improved by Subsequent Targeted Agents Versus Conventional Therapy: An IMWG Immunotherapy Registry Analysis

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Introduction: BCMA- and GPRC5D-targeting agents, including CAR-T, bispecific antibodies (BsAb), and antibody-drug conjugates (ADCs), are approved for relapsed/refractory multiple myeloma (RRMM). An increasing number of patients are treated with BCMA- and GPRC5D-directed therapies (DEMM) sequentially and clinical outcomes remain undefined. We report outcomes from the largest-to-date international cohort of DEMM and heptaexposed MM [bortezomib, carfilzomib, lenalidomide, pomalidomide, CD38 Ab, BCMA, GPRC5D]. **Methods:** We report the outcomes of DEMM patient population, treated with both BCMA- and GPRC5D-targeted therapies (CAR-T, BsAb, or ADC) between November 2022 and April 2026 across 12 institutions in the United States, Europe, Asia, and Canada. The exposure to BCMA and GPRC5D targeting agents had to be sequential, not have been a bridging regimens and regimens between the exposures was allowed. The primary endpoint was PFS (index date of progression after the last dual exposure) and OS (index date of progression/death after the last dual exposure). **Results:** One hundred fifty-seven patients with BCMA and GPRC5D immunotherapy exposure were included. Median age at first immunotherapy was 63 years (range 35–85); 58% were male. High-risk cytogenetics were present in 43.3%, prior ASCT- 85.4%, 96.8% were triple class exposed and 61.8% had penta class exposed MM. Extramedullary disease (EMD) was present in 29.8% (true EMD 20.5%, paraskeletal/paramedullary 9.3%). The median follow-up was 6.6 months. Median OS was 9.4 months; 6-, 12-, and 24-month survival rates were 62%, 43%, and 32%, respectively. The presence of any paraskeletal/soft tissue EMD was the only factor independently associated with inferior OS (HR 1.57, p = 0.048) on multivariable analysis. High-risk cytogenetics and penta-drug exposed status did not significantly impact OS. Of the 157 patients, 41 patients died/received no subsequent therapy, and 116 patients received subsequent line of therapy. In the 116 patients, median PFS was 4.3 months; 3-, 6-, and 12-month EFS were 64%, 38%, and 17%, respectively. Patients who received subsequent therapy targeting BCMA, GPRC5D or FCRH5 after dual exposure had significantly improved PFS relative to non-immunotherapy salvage (7.4 vs. 3.9 months; p = 0.01). In the heptaexposed MM subgroup (N = 97), median OS was 11 months and median PFS was 3.8 months. **Conclusions:** In this largest international cohort of patients with dual BCMA/GPRC5D exposure, outcomes remain poor, with a median PFS of 4.3 months and a median OS of 9.4 months. Paraskeletal/soft tissue EMD was the only independent adverse prognostic factor for OS. Notably, BCMA- or GPRC5D or FCRH5-directed therapy after dual exposure was associated with superior outcomes compared to conventional salvage, Hence further studies are needed to understand mutational resistance and sequencing strategies to optimize

subsequent targeted treatment for DEMM. DEMM identifies a high-risk population in urgent need of novel therapeutic strategies.

OA-56

Predicting Cure in Myeloma: Sustained MRD Dynamics, Genomic Risk, and ISS Define Ultra-Low-Risk Subgroup With Favorable Outcomes After Stopping Therapy

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Introduction: Multiple myeloma has traditionally been considered incurable, but novel therapies and increasingly sensitive measurable residual disease (MRD) monitoring are challenging this paradigm. An IMS consensus meeting recently proposed a cure definition of persistent MRD negativity ≥5 years off therapy; however, prediction tools to identify curable patients and guide therapy discontinuation are limited. **Methods:** We reviewed patients at our center who achieved sustained MRD-negative, imaging-negative remission lasting ≥24 months (sMRD24). Relative survival was estimated using US population data matched by age, sex, and calendar year. Relapse risk was estimated with death as a competing event using Gray test and Fine-Gray hazard models. **Results:** 421 patients achieved sMRD24 with median follow-up of 75 months; MRD negativity was confirmed by NGS in 64% and by next-generation flow (NGF) in 36%. High-risk features were well-represented, including IMS/IMWG genomic high-risk in 20% and ISS stage 3 in 25%. 5-year OS landmarked from first MRD assessment was 98%, and 5-year relative survival was 1.08 (95% CI 1.07–1.10), suggesting superior survival for the sMRD24 cohort compared to age-matched actuarial survival in the general population. Risk factors for relapse after sMRD24 included MRD by NGF alone (aHR 7.54, $p < 0.001$), genomic high risk (aHR 3.43, $p = 0.001$), and ISS stage 3 (aHR 2.66, $p = 0.01$). Patients without these risk factors (n = 166, 39%) formed an ultra-low-risk subgroup with 8-year relapse incidence of 6.9%, compared to 21.2% and 57.3% with 1 and ≥2 risk factors. While high-risk patients had improved outcomes after longer sMRD duration, ultra-low-risk patients had similarly low relapse rates after 2- or 5-year sMRD. 280 patients stopped therapy at varying timepoints; 112 remain MRD-negative at ≥3 years and 56 are MRD-negative ≥5 years off treatment. After discontinuing therapy, 5-year relapse incidence was 17.2% but plateaued after that point (≤1.5% per year). Notably, ultra-low-risk patients off therapy had a 5-year relapse incidence of just 3.0%. After sMRD24, maintenance duration before stopping did not impact relapse risk (aHR 1.03 per year, $p = 0.67$). Finally, relapsed patients requiring reinitiation of systemic therapy (n = 29) had indolent courses: 28 remain in remission on their next line or subsequent T cell redirection at median 16-month follow-up, and 1 high-risk patient died of disease. Of those with MRD resurgence after stopping treatment (n = 66), 39% spontaneously reconverted to MRD-negative without therapy. **Conclusions:** Patients achieving sMRD24 had significantly longer survival than the age-matched general population. This included an ultra-low-risk subgroup (MRD by NGS, genomic standard risk, ISS 1–2) with rare progression after stopping therapy, marginal benefit from additional maintenance, and preserved treatment sensitivity among the minority who relapsed. We propose that low-risk patients with sMRD24 may be candidates for prospective de-escalation strategies aimed at cure.

OA-57

Predicting Progression in Smoldering Multiple Myeloma: A Dynamic AI Model That Learns From Each Clinical Visit

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Introduction: Current methods to identify smoldering multiple myeloma (SMM) patients at high risk (HR) of progression to active MM, including the Mayo 2/20/20 model, rely on tumor burden assessed at single time points. Newer models like PANGEA 2.0 incorporate additional datapoints at predefined timepoints. Neither exploit the dense, longitudinal data generated during SMM surveillance. Using 428 SMM patients from MSKCC and 1089 patients from the Danish Lymphoid Cancer Resource (DALY-CARE), we developed and validated CALM (Continuous Assessment of Longitudinal Myeloma), a novel AI model that updates individual progression risk with each new set of laboratory values at each clinical visit. CALM outperformed existing models and outputs an interactive clinician dashboard providing explainable-AI feature attributions. **Methods:** We retrospectively analyzed 428 SMM patients diagnosed at MSKCC between 2002 and 2020 (median follow-up 3.9 years; median 17 visits, 42% with progression). Results were validated on 1089 patients from the DNCR (median follow-up 2.5 years; median 18 visits, 29% with progression). The model used bone marrow biopsy results and all routine clinical laboratory data measured during

surveillance to determine the optimal set of input features to predict progression risk at 3-month intervals. To ensure explainability, per-visit, per-feature contributions to individualized risk were incorporated into a clinician- and patient-facing SMM dashboard. **Results:** CALM identified six highly predictive laboratory values, in addition to bone marrow biopsy results. This included M-protein levels, kappa and lambda light chains, total serum protein, hemoglobin, and albumin. CALM achieved a global c-index of 0.87, meaningfully outperforming both the Mayo (c = 0.73) and the newer PANGEA 2.0 (c = 0.71) models when applied to the MSKCC cohort and detected 81% of progressors. When trained and evaluated on the DALY-CARE cohort, the model had a global c-index of 0.91, compared to Mayo (c = 0.68), and PANGEA 2.0 (c = 0.70). To assess long-term predictive value, the model was further evaluated at 5 landmarks: 6, 12, 24, 36, and 48 months, using data available only up until the specified landmarks, a harder task than using all available data, yet CALM remained the top model, with a mean c-index of 0.74 (Mayo 0.70, PANGEA 2.0 0.70). We also evaluated the model's ability to predict progression in 2-year forward-looking windows across landmarks, with mean time dependent AUC of 0.79, again outperforming Mayo (0.76) and PANGEA 2.0 (0.75). **Conclusions:** CALM utilizes routinely collected serial data into a continuously updating, individualized risk estimate for SMM patients. This approach delivers materially better discrimination than all static and landmark-based models while making explicit which values drive risk. This approach supports more personalized surveillance using all available clinical data to power SMM risk predictions. Code and model weights will be available on GitHub.

OA-58

Projecting Functional Cure in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM) in the MajesTEC-3 Study of Teclistamab-Daratumumab (Tec-Dara) Using a Mixture Cure Model

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Introduction: In the phase 3 MajesTEC-3 study (NCT05083169), Tec-Dara significantly improved progression-free survival (PFS; HR 0.17; 95% CI 0.12–0.23) and overall survival (OS; HR 0.46; 95% CI 0.32–0.65) vs Dara plus dexamethasone with pomalidomide or bortezomib (DPd/DVd) in pts with RRMM and 1–3 prior lines of therapy (median follow-up 34.5 mo). The Tec-Dara OS and PFS survival curves plateau, suggesting that a fraction of pts potentially achieved functional cure, defined as no excess mortality beyond that of the general population with long-term remission. We estimated functional cure fractions for OS and PFS for Tec-Dara and DPd/DVd in MajesTEC-3, using a relative survival mixture cure model (MCM). **Methods:** We modeled OS and PFS using both traditional parametric relative survival models and relative survival MCM for Tec-Dara (N = 291) and DPd/DVd (N = 296) in MajesTEC-3 (ITT population). The relative survival MCM assumes a fraction of pts are cured and experience the same hazard as the general population, obtained from 2023 United Nations database life tables, matched to the age, gender, and country of each enrolled pt. The uncured fraction experiences excess RRMM-related hazard in addition to the general population mortality hazard. Survival analysis of the uncured fraction used 7 classical parametric models: exponential, Weibull, lognormal, loglogistic, Gompertz, gamma, generalized gamma. Best fit models were selected according to statistical goodness of fit criteria. Projected life expectancy was calculated as the area under the survival curve over a 40-yr time window. **Results:** For Tec-Dara pts, high cure fractions were estimated across models, with low uncertainty and consistency between estimated OS and PFS cure fractions (best fit model, exponential MCM for both; OS 86.6% [95% CI 81.3–90.8]; PFS 86.7% [95% CI 81.5–90.8]). For DPd/DVd pts, cure fractions with best fit models were 0% [95% CI: 0–100] for OS with exponential and 7.6% [95% CI: 0–43.7] for PFS with lognormal, and there was high uncertainty in cure fraction estimates across models for OS (95% CI widths, 61–100 percentage points) and PFS (95% CI widths, 18–100 percentage points), suggesting a cure model may not be relevant for DPd/DVd. Mean age in the study was 63 yrs. Projected remaining life expectancy was 18.6 yrs with Tec-Dara using the best fit relative survival MCM and 6.7 yrs with DPd/DVd using the best fit relative survival (exponential) model without cure, vs 21.5 yrs for the general population. **Conclusions:** Best fit models estimated >85% cure fractions for OS and PFS in Tec-Dara pts in MajesTEC-3. While functional cure does not imply biological/clinical cure, the analysis suggests that a substantial fraction of Tec-Dara-treated pts will experience a mortality risk and projected life expectancy similar to the general population. MajesTEC-3 is ongoing, and if continued follow-up confirms the model-based predictions, Tec-Dara may help redefine survival expectations in RRMM.

OA-59

Racial and Socioeconomic Drivers of Second Primary Malignancies in Multiple Myeloma: A Machine Learning Analysis

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Introduction: Improved survival rates in Multiple Myeloma (MM) have led to a rising incidence of second primary malignancies (SPMs). While racial disparities are known to affect primary MM

survival, their precise impact alongside socioeconomic status on the timing and specific types of secondary cancers remains largely unexplored. **Methods:** We analyzed 7,513 MM survivors from the SEER Research database (2000–2022) who developed a confirmed, invasive SPM (excluding non-melanoma skin cancers). To account for the shorter follow-up duration in the modern era, latency drivers were assessed using Fine- Gray competing risk models which adjust for censoring. Racial and socioeconomic differences were quantified using logistic regression adjusted for age, sex, and median household income. Random Survival Forests were used to identify predictors of SPM latency with variable importance (VIMP) indicating the contributor for each factor. **Results:** The mean time-to-SPM decreased from 5.18 years (2000–2010) to 2.61 years (2011–2022) ($p < 0.001$). Black patients developed SPMs earlier than White patients (Average Direct Effect: −0.33 years, $p < 0.001$) and at a younger mean age for secondary Prostate cancer (68.5 vs. 71.6 years, $p < 0.001$). In Random Survival Forest modeling, biological age (VIMP = 0.15) was the primary predictor of latency, followed by Stem Cell Transplant and Radiation utilization (VIMP = 0.03). Multivariable linear regression indicated that patients with low household income (< $60k) developed SPMs 0.34 years faster than wealthier peers ($p = 0.009$). Black patients had significantly lower odds of therapy-related hematologic malignancies (OR 0.62, 95% CI 0.49– 0.77; $p < 0.001$) but higher odds of solid tumors (OR 1.62, 95% CI 1.30–2.04; $p < 0.001$). This solid tumor disparity persisted after adjusting for age and income ($p = 0.27$) and was driven by Prostate (OR 1.79, 95% CI 1.54–2.09) and Breast cancer (OR 1.31, 95% CI 1.06–1.62). Post- SPM mortality hazard was higher in Black patients compared to White patients (HR 1.15, $p < 0.001$). **Conclusions:** Socioeconomic and racial factors independently drive the clinical presentation and timing of SPMs in MM survivors. Lower-income and Black patients develop secondary cancers earlier, with Black patients showing a marked predisposition for solid tumors like breast and prostate cancer. Addressing these unequal survivorship outcomes requires the immediate integration of tailored, early-intervention screening strategies for vulnerable subgroups.

OA-60

Rapid Renal & Hematologic Responses and Favorable Safety with IsaVCd Induction & IsaR Maintenance in NDMM Patients with Severe Renal Impairment: Phase 2 Study Final Results-Greek Myeloma Study Group

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Introduction: Isatuximab(Isa) has shown efficacy and improved renal recovery combined with pomalidomide/dexamethasone (d) in relapsed/refractory (RR) Multiple myeloma (MM). Isa with bortezomib(V), lenalidomide(R), and d (Isa-VRd) is approved for NDMM in both ASCT transplant-eligible (TE) and transplant-ineligible (TI) patients (pts). We evaluated the renal/hematologic efficacy and safety of Isa with V, cyclophosphamide(C), and d (Isa-VCd) followed by Isa and R maintenance in NDMM pts with severe RI. **Methods:** EAE116 (NCT05147493) is a phase 2, open-label, multicenter study of NDMM pts with severe RI (eGFR < 30 mL/min/1.73 m2 or requiring dialysis). Pts received six 28-day cycles of IsaVCd as induction treatment (Isa 10 mg/kg IV:C1 QW; C2–6: Q2W; V 1.3 mg/m2 SC:C1: D1, 4, 8, 11; C2–6: QW; C 300 mg/m2 IV C1: D1, 8, 15; C2–6: QW; d 40 mg [or 20 mg ≥75 years] PO/IV [C1: D1–4, D 9–12; C2–6: QW). From C7, Isa 10 mg/kg IV Q4W + R 10 mg PO daily (per renal function). Endpoints included renal response rate (RRR), ORR (≥PR), PFS, OS, time to response and safety. **Results:** In final analysis, 51 pts entered the study (median age: 70.0 years; male: 62.7%; ECOG PS ≤1: 64.7%; median involved FLC: 1,791.0 (7.9–52,900.0) mg/L); ISS stage III: 92.2% and R-ISS stage III: 47.1%; 60.8% pts completed treatment and 39.2% discontinued (death: 21.6%; PD: 7.8%; consent withdrawal: 5.9%; physician decision: 3.9%). Overall, 13.7% pts had high-risk cytogenetics and 11.8% had soft tissue plasmacytomas. Median treatment duration/follow-up was 17.6/22.3 months. Median Isa exposure was 23.2 and 10 mg/kg/28 days during induction and maintenance phases, respectively. AE-related dose skips:17.6% pts during induction; none in maintenance. The median isa dose administered was 100%. Among renal-response-evaluable pts (N = 49), 75.5% achieved ≥ MRR in a median time of 1.1 months. RRR (≥ renal PR) was observed in 38.8% pts; CRR: 32.7%; PRR: 6.1%), with a median time to best response of 2.4 months. Among 11 (21.6%) dialysis-dependent pts, 6 (54.5%) became independent. Hematologic ORR was 86.3% (sCR: 25.5%, CR: 11.8%, VGPR: 37.3%, PR: 11.8%), with a median time to first response of 1 month. Median PFS and TTP were not reached, with 17 PFS events: 4 PD and 13 deaths. 12- and 24-month PFS were 77.7% (95% CI 63.4–87.0) and 62.3% (95% CI 45.4–75.3); OS was 84.0% and 66.5% (95% CI 70.5–91.7 and 49.5–78.9, respectively), MRD negativity was 72% among evaluable patients (n = 25). TEAEs occurred in 88.2% (grade ≥3: 41.2%; grade 5: 21.6%; ≥1 serious TEAEs: 35.3%). **Conclusions:** IsaVCd induction treatment followed by IsaR maintenance elicits notable renal and hematologic responses and high MRD negativity rates in NDMM pts with severe RI. Responses were rapid, including high dialysis independence rates, with a safety profile consistent with known toxicities. These findings support IsaVCd as a

promising frontline option for MM pts with severe RI. Sanofi funded; no role in design or analysis.

OA-61

Recurrent Non-Coding Mutational Hotspots Reveal Regulatory Drivers in Multiple Myeloma

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Introduction: Multiple myeloma (MM) harbors complex genetic alterations that drive oncogenic activity and dysregulated cellular growth. However, most genomic analyses and therapeutic strategies focus on the ~2% of the genome that is protein-coding, potentially overlooking pathogenic non-coding regulatory alterations. We therefore aim to identify functionally relevant non-coding mutational hotspots that disrupt epigenetic regulation in MM. **Methods:** Whole-genome sequencing of 157 MM samples was used to identify recurrent hypermutated regions (mutational hotspots) in the MM genome. Detected hotspots were ranked using a negative binomial model accounting for hotspot length, mutation burden and background mutation rate, followed by genomic annotation enrichment analysis. Selected variants were functionally characterized using homology-directed repair–mediated CRISPR–Cas9 editing in MM cell lines, followed by correlative genomic analyses and functional assays. **Results:** We identified 1,284 hypermutated regions across the MM genome, with hotspots enriched in promoter (1.93-fold) and intergenic (1.60-fold) regions relative to expectation. Of these, 125 hotspots mapped to immunoglobulin loci undergoing somatic hypermutation and class-switch recombination and were excluded due to physiological B-cell mutagenesis events. The remaining 1,159 hotspots included known MM driver genes such as NRAS, KRAS, BRAF, TP53, and DIS3, along with additional candidate regulatory regions. Among the top 30 statistically significant hotspots, we identified an understudied hotspot within the 3′UTR of the BMP6/TXNDC5 loci (padj = 3.13×10^{-77}) that overlaps a super-enhancer. Among 40 altered samples, 25 harbored small mutations and 10 contained only translocations, suggesting that small variants may independently disrupt super-enhancer function. Introduction of four patient-derived variants into MM cell lines reduced TXNDC5 expression ($\log_2$FC = −0.72, P = 0.0025). Consistent with these findings, patient RNA-seq analysis demonstrated reduced TXNDC5 expression in mutated samples relative to non-mutated samples ($\log_2$FC = −0.20, P = 0.036), supporting transcriptional deregulation at the locus. Functionally, mutant clones exhibited ~35% reduced cellular proliferation at 120 hours compared with wild-type controls (P < 0.001). Furthermore, high-confidence differential H3K27ac peaks within the TXNDC5 topologically associating domain (MACS2 bdgdiff score ≥30) support mutation-driven disruption of local super-enhancer activity. **Conclusions:** Our study identifies widespread recurrent non-coding mutational hotspots in MM, particularly within regulatory genomic regions. Functional characterization of a recurrently mutated super-enhancer hotspot at the BMP6/TXNDC5 locus demonstrates that non-coding variants can disrupt gene regulation independently of structural rearrangements. Ongoing in vitro and PDX studies will further define regulatory and pathogenic significance of this super-enhancer hotspot in MM.

OA-62

Re-Defining Ultra-High-Risk Myeloma by Combining Genomic and Transcriptional Risk Assessment: An Exploratory Study of the UKMRA OPTIMUM/MUKnine Trial

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Introduction: Ultra-high-risk (UHiR) multiple myeloma (MM) characterized by 2+ high-risk cytogenetic abnormalities (HRCA) and/or high-risk gene expression profiling (GEP-HR) remains challenging due to high rates of early relapse (ER) and short PFS with current standard approaches, exemplified by recent sub-group analyses from GRIFFIN and MASTER. The OPTIMUM/MUKnine trial demonstrated for the first time marked improvement in UHiR NDMM with intensified risk-stratified treatment with Dara-CVRd before and after ASCT. However, outcomes were still heterogeneous. Here, we

performed an exploratory analysis integrating extended genetics with GEP-HR to further stratify UHiR patients and identify subgroups with continuing unmet need. **Methods:** We analysed 98 transplant-eligible UHiR MM (all carrying 2+HRCA and/or GEP-HR as per screening criteria) from the OPTIMUM trial with complete data on t(4;14), t(14;16), t(14;20), del(17p) ± TP53mut, del(1p) incl homozygous del(1p), gain(1q), and SKY92-based GEP-HR. To classify patients, we assigned points to each lesion in accordance with screening criteria (≥2 points required to enter OPTIMUM; each HRCA = 1, GEP-HR = 2 points). Biallelic del(17p) or del(1p) were assigned 2 points due to reported exceptional prognostic impact. Patients were grouped by total risk score (2, 3, 4, or ≥5 points). ER was defined as relapse within 24 months, PFS as time to progression or death from any cause, both calculated from treatment initiation. Outcomes were assessed by Kaplan-Meier estimates and log-rank methods. **Results:** Among 98 patients, 35 patients (35.7%) had 2 points, 28 (28.6%) 3 points, 26 (26.5%) 4 points, 8 (8.2%) 5 points, and 1 patient (1.0%) had 6 points. ER rates increased progressively with cumulative genomic burden, rising from 5.7% (2-point group) to 56% (≥5 point group; P < 0.001). Median PFS was not reached for patients scoring 2 or 3 points, compared to 54.3 months for 4 points and 16.6 months for ≥5 points. All patients with a 5-point risk score (n = 8) were GEP-HR and harboured either 2+ (n = 5) or 3+ HRCA (n = 3). The one patient with 6 points (GEP-HR, t(4;14), amp(1q), del(17p)/TP53mut) progressed at 3.4 months. Conversely, the 2-point risk group did extremely well with a 48-month PFS of 94.3% (95% CI: 86.9–100), comparable to all-comer 48 m PFS reported in PERSEUS (84.3%). This 2-point favourable risk group (n = 35) was genomically heterogeneous with respect to the underlying HR features, including t(4;14) & gain(1q) (n = 7), del(1p) & gain(1q) (n = 5), combinations incl. del(17p) (n = 4), t(14;20) (n = 2), t(14;16) (n = 1), and solely GEP-HR (n = 14). **Conclusions:** Our data reinforces risk-adapted OPTIMUM treatment for most UHiR subgroups. Integrating genetic and transcriptional HR features into a simple lesion-counting framework showed excellent outcomes for patients with 2 points only, regardless of the specific lesions. Conversely, patients with cumulative genomic burden had persistently poor outcomes despite intensified therapy and should be the focus for future trials.

OA-63

Refining Frailty Assessment in Transplant-Ineligible Multiple Myeloma: Geriatric Assessment in Hematology Enhances the Simplified Frailty Index for Benefit-Risk Evaluation of Quadruplet Therapy

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Introduction: Guidelines recommend tailoring treatment intensity in transplant-ineligible (TIE) multiple myeloma (MM) based on frailty, commonly via Simplified Frailty Index (SFI). However, SFI heavily relies mainly on age and ECOG, potentially overestimating frailty. In the GEM2017FIT trial, the Geriatric Assessment in Hematology (GAH) scale was used to identify TIE fit patients (GAH ≤42) up to 80 years. Patients were randomized to DKRd, KRd or VMP/Rd. Though all were considered fit, we have previously reported that GAH < 20 was associated with better tolerance and outcomes with quadruplets. Also, conventional survival analyses often censor unacceptable toxicity (UT) underestimating its impact. We hypothesized that the GAH provides a more accurate benefit-risk assessment than the SFI. **Methods:** Post-hoc analysis of the GEM2017FIT trial comparing the GAH and SFI (Fit vs. Frail) scales. GAH categorized patients as ultra-fit (< 20) or fit (20–42). UT—defined as treatment discontinuation due to toxicity or toxic death—and time to treatment failure (TTF)— defined as the time until progression, death, or UT—were compared across arms. **Results:** Based on SFI, 367 patients were fit (80%) and 94 frail (20%). Among SFI-fit patients, 57% were GAH-ultra-fit and 43% GAH-fit, balanced across arms. Concordance between both SFI-fit and GAH-ultra-fit status was found in 46% of the cohort, equally distributed. SFI-frailty was mainly driven by ECOG and age, corresponding to 36% GAH-ultra-fit and 64% GAH-fit. SFI-frail patients were distributed as follows: 27% in DKRd, numerically higher than KRd (19%) and significantly higher than VMP/Rd (15%; P = 0.011). Among SFI-frail patients, GAH< 20 was found in 29%, 33%, and 43% in the DKRd, KRd, and VMP/Rd arms, respectively. UT was reported in 12% of patients: 13% (n = 20) in DKRd, 12% (n = 19) in KRd and 10% (n = 16) in VMP/Rd. In the DKRd arm,

UT was higher in GAH-fit than in GAH-ultra-fit patients (19% vs. 7%; P = 0.044), and occurred earlier (P = 0.047), with 50% of events taking place within the first 3 months. Notably, in the DKRd arm, SFI classified 15 out these 20 patients as fit. No differences were observed in the remaining arms, and SFI failed to capture differences regarding UT and time to UT. At a median follow-up of 33 months, the overall 30-month TTF was 72%. DKRd and KRd showed a 30-month TTF of 75%, both superior to VMP/Rd (P = 0.022). GAH-ultra-fit patients treated with DKRd had 30-month TTF of 82%, outperforming KRd (69%, P = 0.049) and VMP/Rd (70%, P = 0.026). Conversely, SFI-fit patients treated with DKRd showed a comparable 30-month TTF to KRd (77% both) but higher than VMP/Rd (67%, P = 0.012). **Conclusions:** Within GEM2017FIT, SFI appears to overestimate frailty in a relevant proportion of TIE patients, potentially restricting access to quadruplet regimens. GAH offers greater granularity and may improve prediction of early UT and selection for intensive therapies, particularly for GAH < 20.

OA-64

Self Administration of Bortezomib in Multiple Myeloma and Amyloidosis: A Prospective Feasibility Study

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Introduction: Bortezomib is a proteasome inhibitor widely used in the treatment of plasma cell disorders in combination regimens, and requires a weekly subcutaneous (SC) injection in the hospital setting. Weekly visits for injection present a significant cost, time, and physical burden. Self/ Caregiver based administration of SC bortezomib has been demonstrated to be feasible in Western cohorts; however, no prospective data exist in the Indian subcontinent where health literacy, socioeconomic factors, caregiver dynamics, and biomedical waste infrastructure differ substantially. **Methods:** This is a prospective, single-arm feasibility study enrolling 50 patients with MM or AL amyloidosis planned to receive weekly SC bortezomib. Patients/ caregivers unable to understand instructions, unwilling to comply to protocol, skin conditions hampering SC administration, and those with bloodborne viral infections were excluded. Patients underwent weekly in-person training during Cycle 1; transitioned to home administration from Cycle 2 with once per cycle clinic reviews for routine follow up, adverse event (AEs) documentation, and biomedical waste disposal. Telephonic follow up was conducted on dosing days. After 4 cycles, patients transitioned to routine clinical care with the option to continue self administered SC bortezomib if feasible. The primary measure of protocol adherence was Relative Dose Intensity (RDI), defined as actual vs planned dose intensity expressed as percentage, with planned doses adjusted for early discontinuation unrelated to protocol. Key secondary end points included time saved, ORRs, AEs, and proportion of patients continuing home injections. **Results:** A total of 700 doses were planned and administered, representing 100% overall delivery. The mean RDI was 99.17% exceeding the preset feasibility threshold of 80%. Only 3 patients had an RDI < 100%, all due to a febrile episode needing a dose hold; no doses were missed and the delays were due to causes unrelated to home administration. Home injections were predominantly caregiver administered (46/50). No Grade ≥3 injection-related adverse events were recorded. Peripheral neuropathy occurred in 17 (34%) patients, all grade 1. Response assessment at 4 cycles was done in 43 patients, yeilding an ORR of 88.4%. Beyond the study period 86% (43/50) of patients continued home administration, with the remaining 7 discontinuations not attributable to home administration. Based on injection wait time, an average of 16.7 hours were saved per patient. Notably, 41 (82%) patients resided outside the city, representing substantial time and cost savings beyond those captured by institutional wait time alone. **Conclusions:** A caregiver/ self based home administration of Bortezomib is feasible and safe in a low resource setting, with ORRs and AE profiles similar to routine clinical practice, while offering significant time and cost savings - supporting broader clinical application and informing programmes in other LMIC settings.

OA-65

Single-Cell Analysis Reveals Stage-Specific γδ T-Cell Remodeling Across the Multiple Myeloma Continuum

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Introduction: γδ T cells bridge innate and adaptive immunity through MHC-independent tumor recognition and cytotoxic effector functions, highlighting their therapeutic potential in MM. However, their functional remodeling across the MM continuum remains incompletely understood due to small-scale studies. To study γδ T cell dynamics across precursors (MGUS, SMM) and myeloma stages (NDMM, RRMM, Post-CART), we performed a large-scale integrative analysis of our and publicly available single-cell data. **Methods:** We developed MYSCAPE, an integrated platform comprising healthy donors, MGUS, SMM, NDMM, RRMM, and post-CART samples. γδ T cells were identified using an entropy-based lineage annotation framework incorporating program contrast scoring and neighborhood belief propagation. Curated γδ T cell

programs representing anti-tumor immunity, bone marrow niche adaptation, and cellular fitness were quantified at single-cell resolution. Distributional shifts across disease stages were quantified using signed Wasserstein distance. Analyses were restricted to groups with ≥3 samples and ≥20 γδ T cells/sample. Differential Gene expression analysis was performed using the Wilcoxon rank-sum test (adjusted p-value < 0.05). **Results:** MySCAPE comprises 4.5 million single cells from 35+ studies, harmonized through standardized QC, normalization, and integration pipelines. Our annotation framework identified 16,125 γδ T cells, including 14,506 bone marrow γδ T cells spanning all disease stages. The most pronounced γδ T-cell transition occurred during SMM-to-NDMM progression, characterized by increased activation programs driven by DUSP1/FOS/NFKBIA, consistent with enhanced immune response at symptomatic onset. Increased CXCR4/RGS1/CD69 expression drove chemokine-trafficking and marrow-retention programs, suggesting TME adaptation. Reduced FCGR3A/PRF1/GNLY-associated ADCC activity accompanied symptomatic progression, potentially reflecting diminished antibody-dependent anti-tumor surveillance. NDMM-to-RRMM progression was associated with restoration of ADCC programs driven by FCGR3A/TYROBP/GNLY, suggesting re-emergence of NK-like effector functions. Following CAR-T therapy, γδ T cells adopted a distinct state with reduced activation, trafficking, and marrow-retention programs. Despite reduced ADCC activity from GNLY loss, FCGR3A/TYROBP expression remained preserved, indicating retention of core cytotoxic and antibody-recognition machinery. Concurrent enrichment of IL15/STAT5/IL2RG survival-fitness and KLRK1/NCR3/VAV1 innate tumor-recognition programs suggest T cells post-CAR-T may remain capable of MHC-independent tumor surveillance. **Conclusions:** γδ T cells undergo stage-specific functional reprogramming across the MM continuum, with the greatest remodeling at symptomatic MM onset and emergence of a distinct Post-CART state. These findings provide a framework for γδ T-cell biology in MM and support γδ T cell states as biomarkers of progression and treatment response.

OA-66

Single-Cell Antigen:TCR Mapping Reveals Tumor-Specific Effector T-Cell Responses in Multiple Myeloma

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Introduction: T cell immunity is recognized as a determinant of response across immunotherapeutic approaches in multiple myeloma (MM). Durable clinical benefit has been associated with expansion of endogenous effector T cells. The antigen specificity of these responses remains incompletely defined. We hypothesized that durable immune control of MM following immunotherapy is mediated by emergence and persistence of tumor-specific effector T cell clonotypes. **Methods:** We integrated single-cell immunoprofiling and antigen:TCR mapping in BMT CTN 1401, a phase II trial of lenalidomide maintenance with or without dendritic cell/MM fusion vaccination after autologous HCT. Single-cell gene expression and paired TCR sequencing were performed on 160 paired bone marrow (BM) and peripheral blood (PB) samples from 40 patients pre-/post-HCT. T-cell clonality, phenotype, BM-PB overlap, and clinical outcome were analyzed. To define T cell specificity, we developed an integrated in silico-experimental framework combining whole-exome seq, bulk RNA-seq, ribosome profiling, machine learning-based epitope prioritization, and DNA-barcoded dCODE MHC-I Dextramer profiling to identify antigen:TCR pairs and recover antigen-specific TCRs and transcriptional states at single-cell resolution in HLA-A*02:01-positive patients. **Results:** sCR/CR and VGPR correlated with activation and clonal expansion of effector-memory T-cell clonotypes consistent with an antigen-driven T cell response. Substantial TCR sharing was observed between BM and PB among highly expanded clonotypes. More than half of highly expanded BM clonotypes were detected in PB at enrollment, increasing to 64% by pre-cycle 9 of lenalidomide; ~30% of highly expanded PB clonotypes were detected in BM. Patients achieving sCR/CR had greater BM-PB TCR sharing, suggesting recirculation of tumor-associated T-cell clonotypes linked to deeper remission. To investigate the tumor-specificity of the expanded clonotypes, we applied antigen discovery/single-cell dCODE profiling. We prioritized >50 cancer-restricted epitopes, including non-canonical ORFs in plasma cell-associated genes such as BCMA and SLAMF7. In the first 2 patients analyzed, we identified >6,000 antigen:TCR pairs across viral and MM-associated antigens. MM antigen-reactive T cells were enriched in activated/effector-memory states, whereas viral-reactive T cells were memory-like. **Conclusions:** Deep clinical response after HCT in MM is associated with expansion of effector T clonotypes. Integration of TCR analysis and antigen discovery enabled identification of tumor-reactive clonotypes and functional states. We are extending this framework to additional patients and post-vaccination samples to define vaccine-induced anti-tumor T-cell immunity. In parallel, we are applying this approach to BCMA-directed bispecific T-cell engager cohorts to determine whether durable response is associated with the emergence of TCE-induced tumor-specific T-cell immunity.

OA-67

Targeting a New Metabolic-Epigenetic Axis Towards Improved CAR T Therapy in Multiple Myeloma

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Introduction: T cell therapies are rapidly becoming the cornerstone of multiple myeloma (MM) treatment, and their efficacy is highly dependent on T cell "fitness." Metabolic disorders that lead to hyperglycemia are associated with impaired T cell "fitness" as well. Epigenetic regulation is essential for T cell function, shaping activation, memory formation, and susceptibility to exhaustion, a major cause of immunotherapy failure. However, the drivers of exhaustion-associated epigenetic programs remain poorly defined. **Methods:** This study includes: 1. In vitro T cell assays - methylglyoxal (MGO) quantification, MGO based suppression of T cell function, western blot analysis of histone glycation and flow cytometry. 2. Samples from patients with MM - analyzed in vitro with bulk RNA sequencing and GSEA analyses. 3. Glycated histone antibody generation with CUT&TAG analysis. 4. In vivo and in vitro CAR T cell assays - Generation of CAR T cells (control, non-signaling and DJ-1 overexpressing). In vivo MM CAR T cell experiments utilized an NSG-MHC I/II DKO with OPM2 injection.5. Clinical MM patient data - with and without hyperglycemia receiving CAR T cells. **Results:** We identify histone glycation as a metabolically driven epigenetic modification that links cellular metabolism to T cell fate. Upon activation, T cells accumulate the glycolytic byproduct MGO, which selectively and non-enzymatically modifies histones, a process exacerbated by hyperglycemia. Histone glycation impairs T cell activation, restricts memory formation, and accelerates terminal differentiation. Integrated transcriptomic and chromatin analyses reveal that MGO-induced chromatin reprogramming enforces exhaustion-associated gene programs and that affected genes are enriched for histone glycation at transcription start sites. These signatures mirror those observed in patients with MM and diabetes and chronically stimulated mouse T cells, indicating a conserved metabolic-epigenetic mechanism. To track histone glycation in T cells we developed of a novel histone glycation antibody and find that histone glycation localizes to transcription start sites of key inflammatory genes. In 193 patients with relapsed MM who received CAR T cell therapy, patients with hyperglycemia within 90 days prior to infusion had worse progression free survival than patients without hyperglycemia ($p < 0.05$). Reducing MGO burden by overexpressing the MGO-detoxifying enzyme DJ-1 in Multiple Myeloma BCMA targeted CAR T cells promotes memory-like states ex vivo and enhances tumor control in vivo when exposed to MGO. Moreover, the diabetes drug metformin rescues T cell function by scavenging MGO, uncovering a previously unrecognized mode of action. **Conclusions:** Together, these findings establish histone glycation as a causal metabolic-epigenetic pathway driving T cell exhaustion and suggest metabolic intervention to improve immunotherapy efficacy in patients with MM.

OA-68

Teclistamab Plus Talquetamab Consolidation in Newly Diagnosed Myeloma Patients With Positive Measurable Residual Disease After DVRD Induction: Interim Analysis of the Phase 2 Study IFM 2022-01

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Introduction: Autologous-stem cell transplantation remains the standard of care after quadruplet regimen induction in transplant eligible (TE) newly diagnosed multiple myeloma (NDMM). Bispecific antibodies (BispAb) offer an attractive strategy to challenge the role of transplant in NDMM. Of note, the combination of teclistamab (tec) and talquetamab (tal) demonstrated high efficacy in relapsed refractory myeloma (Kumar et al. NEJM 2025). IFM 2022-01 is a phase 2 trial evaluating tec plus tal or tec plus lenalidomide consolidation in TE-NDMM patients according to measurable residual disease (MRD) after Daratumumab Bortezomib Lenalidomide Dexamethasone (D-VRd) induction. Here we present the interim analysis with safety and efficacy after the first 3

cycles of tec-tal. **Methods:** IFM 2022 (NCT06353022) is an open label, multicenter study wherein TE NDMM patients received D-VRd induction for 6 cycles. Patients with negative MRD (NGS, 10-5) after induction are planned to receive teclistamab plus lenalidomide (tec-len) combination for 2 years (cohort A). Patients with positive MRD (NGS, 10-5) after induction are planned to receive tec-tal combination for 2 years (cohort B). The primary endpoint is the rate of sustained MRD for cohort A and rate of MRD conversion for cohort B. The study is ongoing and this interim analysis aims to assess efficacy and safety of the 3 first cycles of tec-tal (cohort B). **Results:** One hundred and three patients with previously untreated NDMM were included from June 2024 to May 2025 in 19 IFM centers. Median age was 58 (range 49–62). Sixteen (17.2%) patients had high-risk cytogenetics based on IMS/IMWG 2025 definition. Five (5.2%) patients presented with extra-medullary disease. After 6 cycles of D-VRd, all patients reached at least a partial response and 56 (54.9%) patients had negative MRD (NGS, 10-5). Safety with DVRd induction was consistent with known profile. Patients with positive MRD after induction (n = 46) were enrolled in cohort B and received teclistamab (C1D1 = 0.06 mg/kg, C1D3 = 0.3 mg/kg, C1D8 and C1D15 = 1.5 mg/kg, C2 to C24 D1 : monthly dosing 3 mg/kg) and talquetamab (C1D1 = 0.01 mg/kg, C1D3 = 0.06 mg/kg, C1D8 = 0.4 mg/kg, C1D15 = 0.8 mg/kg; C2 to 24D1 = monthly dosing 0.8 mg/kg). After 3 cycles of tec-tal, all evaluable patients (n = 43) reached undetectable MRD (NGS, 10-5). Most common non-hematologic adverse events observed during the 3 first cycles of tec-tal were dysgeusia (63%), infections (34.8% including 2% grade 3–4), CRS (46%, all grade 1–2), skin rash (30.5%, including 4% grade 3–4), weight loss (21.7%, all grade 1–2), diarrhea (19.6%, all grade 1 or 2). **Conclusions:** The combination of tec+tal resulted in early and high undetectable MRD rates in NDMM patients with detectable MRD after D-VRD induction. These preliminary data showed no new safety signal was observed with tec+tal used in frontline.

OA-69

The Benefit of Daratumumab Plus Bortezomib, Lenalidomide, and Dexamethasone (DVRd) on Depth and Durability of Response in the Phase 3 CEPHEUS Trial: Updated Minimal Residual Disease Analysis

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Introduction: In the phase 3 CEPHEUS study, DVRd significantly increased depth of response, including rates of overall minimal residual disease negativity (MRDneg), complete response or better (≥CR), and sustained MRDneg, vs VRd at a median follow-up of 58.7 mo in patients (pts) with transplant-ineligible (TIE) or transplant-deferred NDMM. These deep responses translated into superior progression-free survival (PFS) vs VRd. This expanded analysis of MRD outcomes from CEPHEUS describes a longer median follow-up of over 6 years (76 mo). **Methods:** The primary endpoint was MRDneg rate by next-generation sequencing (NGS; 10^{-5} and ≥CR). Key secondary endpoints included investigator-assessed PFS and ≥CR rate; sustained MRDneg (confirmed MRDneg at ≥12 (±1 mo), 24, 36, 60, and 72 mo (±3 mo) apart without MRD positivity in between and ≥CR) was also assessed. The MRD-evaluable population was defined as pts with ≥CR, successful baseline calibration, and MRD samples at each specified time point; there were fewer MRD-evaluable pts at time points with longer follow-up. **Results:** 395 pts (DVRd, n = 197; VRd, n = 198) were enrolled; of these, 289 were TIE (DVRd, n = 144; VRd, n = 145). Outcomes are presented for the intent-to-treat (ITT), MRD-evaluable, and TIE populations. Overall MRDneg rates were significantly higher with DVRd vs VRd in the ITT (10^{-5}: 61.4% vs 39.9% [odds ratio (OR) 2.36; P < 0.0001) and MRD-evaluable populations (≥1 post-baseline MRD sample; 10^{-5}: 81.2% vs 68.7% [OR 1.91; P = 0.0209]; 10^{-6}: 63.1% vs 47.8% [OR 1.82; P = 0.0172]). Rates of sustained MRDneg for ≥24 mo were also higher with DVRd vs VRd in the MRD-evaluable population (≥1 post-baseline MRDneg sample; 10^{-5}: 91.8% vs 73.0% [OR 4.12; P = 0.0018]; 10^{-6}: 86.1% vs 71.4% [OR 2.36; P = 0.0836]), with continued benefit of sustained MRDneg observed with DVRd vs VRd for 60 mo in the MRD-evaluable population (10^{-5}: 87.5% vs 63.0% [OR 3.30; P = 0.0342]; 10^{-6}: 80.0% vs 40.0% [OR 5.42; P = 0.0413]). DVRd improved MRDneg rates at all prespecified assessment time points vs VRd in the MRD-evaluable population up to 72 mo (10^{-5}: 53/66 [80.3%] vs 27/45 [60.0%] [OR 2.28; P = 0.0303]; 10^{-6}: 40/66 [60.6%] vs 17/45 [37.8%][OR 2.32; P = 0.0213]). Median PFS improved with DVRd vs VRd in the ITT population overall (HR 0.59 [0.44–0.80]), in MRDneg (10^{-5}: HR 0.71 [0.44–1.16]), and in MRD-positive pts (10^{-5}: HR 0.74 [0.49–1.10]). Median PFS also improved with DVRd vs VRd in pts with 12-mo sustained MRDneg in the ITT

(10^{-5}: HR 0.65 [0.34–1.26]) and TIE populations (10^{-5}: HR 0.75 [0.35–1.60]). Additional endpoints will be presented. **Conclusions:** In this analysis of CEPHEUS, DVRd led to clinically meaningful, deep responses, with higher overall MRDneg rates, and reported for the first time, 60-mo sustained MRDneg rates vs VRd across all time points in the ITT, MRD-evaluable, and TIE populations, translating to improved survival outcomes. These data further demonstrate that continued treatment with DVRd improves and deepens responses over time vs VRd in pts with NDMM.

OA-70

Updated Safety and Efficacy of Ramantamig (Ram; JNJ-5322) at the Recommended Phase 2 Dose (RP2D), Demonstrating Feasibility of Outpatient Dosing (OPD) in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Ram, a readily available, T-cell–redirecting (TCR) trispecific antibody (Ab) targeting BCMA and GPRC5D, demonstrated a favorable clinical profile vs bispecific Abs (BsAbs) with robust efficacy and lower rates of cytokine release syndrome (CRS) and oral adverse events (AEs) in patients (pts) with triple-class exposed (TCE) RRMM at the RP2D (a single 5 mg step-up dose [SUD] followed by 100 mg subcutaneously every 4 weeks [Q4W]). Building on experience with BsAbs and promising early safety data, this first-in-human study (NCT05652335) proactively assessed Ram OPD feasibility at start of treatment (tx). We report updated safety, efficacy and OPD outcomes in an expanded RP2D cohort. **Methods:** In parts 1 and 2 of this phase 1 study, pts with TCE RRMM received Ram at the RP2D. Primary endpoint was safety. Additional endpoints included ORR, DOR, PFS, and measurable residual disease negativity (MRD–). The OPD cohort (subset of RP2D cohort) was to receive all doses outpatient, including SUD and tx dose 1; prophylactic tocilizumab (ppx toci) was recommended. **Results:** As of April 2026, 56 pts (median age, 68 y; median prior lines of tx, 3 [range, 1–11]; high-risk cytogenetics, 41.9%; triple-class refractory, 51.8%) received Ram at the RP2D (median follow-up [mFU], 16.4 mo), including 47 TCR-naive pts (mFU, 19.4 mo). The safety profile was consistent with previously presented data. Nonhematologic AEs included infections (80.4% [gr 3/4, 25.0%]), CRS (39.3% [gr 1, 30.4%; gr 2, 7.1%; gr 3, 1 pt (1.8%) at tx dose 2 (pt was a nonresponder with progressive disease)]); no ICANS was reported. One pt had a dose-limiting toxicity (neutropenia). One pt discontinued tx due to AEs (pruritis/maculopapular rash); no deaths reported due to tx-related AEs. In the OPD cohort (n = 30), among those receiving tx, 93.3% received SUD and 79.3% received tx dose 1 outpatient (reasons OPD not completed: SUD [pt concern n = 1, disease burden n = 1]; tx dose 1 [power outage n = 1; disease burden n = 2; AEs n = 3 [neutropenia, noncardiac chest and tumor pain]). With 96.6% receiving ppx toci, CRS at SUD (10.0%) and tx dose 1 (6.7%) was all gr 1. Within 2 days of OPD at SUD or tx dose 1, 4 pts required hospitalization and 2 required out-of-home care (reasons: CRS n = 3; pain n = 3 [tumor; bone; noncardiac chest]). In TCR-naive pts, ORR was 93.6% (≥CR, 76.6%); 100% of evaluable pts were MRD– (10^{-5} NGS). 18-mo DOR and PFS rates (95% CI) were 90.7% (73.1–97.0) and 84.6% (68.1–93.0); (median DOR/PFS, not reached). In 27 TCR-naive pts in part 1 (mFU, 23.5 mo), 24-mo PFS rate was 81.9% (95% CI, 56.9–93.2). **Conclusions:** Longer follow-up of Ram monotherapy at the RP2D continues to demonstrate deep, durable responses in TCE RRMM with no new safety signals. OPD at start of tx was feasible with low-gr, manageable CRS using ppx toci. The safety profile and convenient schedule (single SUD dose, fixed Q4W dosing) support use of this novel dual myeloma-antigen targeting Ab across practice settings.

POSTER PRESENTATIONS

PA-001

A Collagen-Hydroxyapatite 3D Bone Marrow Model Recapitulates Microenvironment-Mediated Drug Resistance in Multiple Myeloma

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Introduction: The bone marrow microenvironment (BMME) is a central player in multiple myeloma onset, progression and response to treatment. As the BMME architecture, cellular components and paracrine signalling are not adequately reproduced in conventional two-dimensional (2D) cultures, there is growing interest in preclinical models reproducing MM cell-extrinsic mechanisms. Here we present a collagen-hydroxyapatite three-dimensional BM scaffold (BM3D) and evaluate its structural and functional properties in the context of MM preclinical applications. **Methods:** Coll-HA scaffolds were prepared from type I collagen and hydroxyapatite (30:70 ratio), cross-linked using 1,4-butanediol diglycidyl ether and freeze-dried in a 3D-printed mold (4.5 mm diameter × 2 mm thickness, 24-well format). Scanning electron microscopy and compression testing defined scaffold porosity and mechanical properties. A tri-culture system was built by seeding HS-5 stromal cells and HUVECs on Day 0 (5 × 105/each), followed by MM cell lines (1 × 106, NCI-H929 or JJN3) on Day 3. Primary BMMCs were isolated from patient BM aspirates and seeded at 1 × 106/scaffold. Cytokines (IL-2, IFN-γ, TNF-α, IL-6, IL-10, GM-CSF) were measured using the multiplex ELLA platform. A multiparameter cytometry protocol was used for MM detection (CD38/CD138/CD319, Live/Dead, Annexin V). Drug sensitivity was evaluated by IC50 calculation. **Results:** BM3Ds showed reproducible porous architecture with a mean surface porosity of 39.3% ± 8.7% and median Feret diameter of 55.9 ± 7.4 µm supporting scaffold colonization. Young's modulus was 7.8 ± 2.5 kPa, consistent with the reported range of perivascular BM stiffness. H&E and immunohistochemistry analyses confirmed extensive scaffold colonization by stromal and endothelial cells, while MM cells localized within multicellular regions inside scaffold pores. Cell viability remained >80% for up to 7 days for MM cell lines and 72 h for BMMCs. Compared with MM monocultures, BM3D tri-cultures showed increased cytokine secretion, with cytokine profiles partially overlapping primary RRMM BM plasma. Drug sensitivity assays showed higher MM resistance in 3D versus 2D cultures. Specifically, in NCI-H929 cells, IC50 increased from 1.86 nM to 3.51 nM for bortezomib, from 4.98 nM to 19.20 nM for carfilzomib, from 0.06 µM to 24.73 µM for lenalidomide, from 0.30 µM to 0.92 µM for pomalidomide, and from 2.14 µM to 4.90 µM for melphalan. **Conclusions:** BM3Ds reproduce structural and biomechanical features of the BM niche while supporting stromal, endothelial, and MM cell interactions in a physiologically relevant three-dimensional context. The consistent increase in drug resistance observed across multiple therapeutic classes suggests that BM3Ds capture micro-environment-mediated protection mechanisms not observed in standard 2D cultures. This scalable platform supports primary patient-derived samples and provides a preclinical platform for ex vivo drug testing in MM.

PA-002

A Machine Learning Pipeline to Distinguish Myeloma-Reactive from Bystander T Cells in the Bone Marrow

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Introduction: Identifying tumor-reactive T cells in the bone marrow (BM) remains a critical challenge in multiple myeloma (MM). Tumor-reactive T cells are rare, particularly in newly diagnosed patients, and lack the distinctive phenotypic features that characterize reactive T cells in solid tumors. While recent studies have combined measures of TCR clonality with gene expression profiling, the rarity of MM-reactive clones means this still provides insufficient resolution to separate tumor-reactive cells from bystander populations. A machine learning framework that jointly integrates TCR sequence features and transcriptomic profiles represents a logical next step toward finer discrimination. **Methods:** We assessed whether phenotypic signatures alone could distinguish MM-reactive from bystander T cells using published single-cell datasets. We then applied a multimodal machine learning framework, developed by the Zhang Laboratory at UCSF, that integrates TCR sequence embeddings and transcriptomic profiles to generate joint T cell representations. The pipeline was benchmarked against wet-lab validated myeloma-reactive TCR clones from the Friedrich group (DKFZ). We subsequently applied this approach to a cohort of newly diagnosed MM (NDMM) patients from Shasha et al. (Blood, 2025), which includes matched BM and peripheral blood (PB) samples and longitudinal outcomes, including response to autologous stem cell transplantation (ASCT). **Results:** Phenotypic signatures were insufficient to reliably distinguish myeloma-reactive from bystander T cells. Our integrated pipeline successfully separated wet-lab validated myeloma-reactive clones from bystander populations with similar phenotypes. In the NDMM cohort, our approach identified distinct T cell clusters; however, assigning tumor reactivity required further refinement. Using matched PB and a database of TCRs with known bystander reactivity as filters, we identified candidate myeloma-reactive clusters, though wet-lab validation remains necessary to confirm definitive reactivity. The frequency of these putative tumor-reactive cells within CD8T cells predicted ASCT response in the small Fred Hutch cohort, independently of cytogenetic risk or disease stage. Notably, putative tumor-reactive clones identified pre-ASCT were expanded post-ASCT in complete responders. **Conclusions:** Integrating TCR sequence features and gene expression through machine learning improves discrimination of MM-reactive T cells beyond current approaches. Filtering against matched PB and databases of known bystander TCR specificities provides further refinement, yielding candidate populations that associate with response to ASCT. While wet-lab validation remains an important next step, these findings

suggest that multimodal integration of TCR and transcriptomic data offers a tractable path toward reliably identifying endogenous anti-tumor T cell immunity in MM, with potential implications for patient stratification and the rational design of T cell-based immunotherapies.

PA-003

A Model for Outpatient Cilta-cel Administration and Cytokine Release Syndrome (CRS) Management without a 24-hour Clinic: Clinical Protocol and Early Results

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Introduction: Cilta-cel can safely be given outpatient (OP), yet hospital admission is common for CRS management due to lack of 24-hour clinic availability. Unlike previously described OP protocols that rely on early tocilizumab (toci) in a 24-hour clinic, we describe a protocol that integrates remote patient (pt) monitoring (RPM) and after-hour intervention with dexamethasone (dex) for grade 1 CRS to bridge pts safely to next-day clinic evaluation and early toci. **Methods:** Pts receiving OP cilta-cel were seen daily in a dedicated OP transplant and cellular therapy (TCT) unit for 14 days post-infusion and had a continuous caregiver and local lodging within 30 minutes. Hospital at Home (HAH) provided pts with a thermometer, blood pressure cuff, and pulse oximeter as part of the RPM kit, plus 24-hour phone access to a HAH nurse for triage of issues arising outside of the OP TCT unit. During business hours (7A-5P), pts with fever (temperature ≥100.4 ∘F) were seen in the OP TCT unit and received toci 8 mg/kg with return to their local lodging after defervescence and observed clinical stability. Pts with fever after hours (5P-7A) were instructed to call the HAH nurse, prompting a complete set of vitals and ICANS assessment. Those with confirmed grade 1 CRS were instructed to take acetaminophen (975–1000 mg) and dex 10 mg by mouth, and to check vital signs every 30 minutes. The HAH nurse contacted the pt within 1 hour to ensure that fever was resolving, and the pt remained in their local lodging with instructions to return to the OP TCT unit at 7:30 AM the next day for evaluation and preemptive tocilizumab. The protocol directed admission for grade ≥2 CRS after-hours, grade 1 CRS that did not resolve with initial intervention, and any ICANS after-hours. We retrospectively reviewed clinical outcomes for the first 21 consecutive pts treated with this OP protocol. **Results:** The first 21 pts (median age 69 years and ECOG performance status 1) had received a median of 3 prior lines of therapy. Bridging therapy was given to 86% of pts with stable disease or better for all. CRS was seen 13 (62%) pts (52% grade 1, 10% grade 2) with median onset of 7 days and median duration of 1 day. All 13 pts with CRS received toci per protocol. Ten (48%) pts had CRS managed OP after hours with acetaminophen ± dexamethasone per protocol and none required admission overnight for persistent or worsening CRS. One pt had grade 1 ICANS that did not require admission. Only 3 pts (14%) required admission within 30 days of cilta-cel (none for CRS/ICANS management), resulting in zero median inpatient days and a mean of 0.9 hospital days per pt. With median follow-up of 130 days, the best overall response rate to cilta-cel was 100% (67% ≥ CR) without any progression or death events. **Conclusions:** After implementation of an OP CRS management protocol utilizing acetaminophen plus dex for grade 1 CRS after hours, early tocilizumab, and RPM, 86% of pts did not require any hospitalization within 30 days of cilta-cel infusion.

PA-004

A Modular AI Framework Generates Interpretable, Multi-modal Analysis Pipelines to Support Translational Research for Multiple Myeloma

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Introduction: Oncology increasingly relies on large, heterogeneous datasets spanning genomics, clinical records, imaging, and treatment history. Large language models (LLMs) show promise for synthesizing such information, yet currently suffer from limited transparency, hallucination risk, and poor alignment with real-world clinical reasoning. There is a critical need for AI systems that can integrate multimodal data while preserving interpretability, traceability, and clinician control. **Methods:** We developed a modular AI decision-support system to assist oncologists in complex clinical reasoning tasks. Unlike monolithic LLM approaches, it decomposes clinical questions into atomic sub-tasks that are executed through structured, auditable pipelines, while integrating curated clinical data (EHR, genomics, pathology), external knowledge bases, and computational analyses via a function-oriented architecture. Each step is independently validated, logged, and audited to ensure correctness.

It uses a hybrid local/cloud architecture and was evaluated on real-world oncology use cases in Moffitt Cancer Center's Multiple Myeloma (MM) cohort, which contains three data modalities: clinical, molecular, and pre-clinical. Clinical data resides in a PHI-compliant Snowflake data warehouse (Moffitt Cancer Analytics Platform, MCAP), including longitudinally-resolved treatment and outcome information from clinical notes, labs, pathology and

radiology reports. CD138-enriched bone marrow samples from 1,260 MM patients were molecularly profiled using RNA-seq (n = 1,376 biopsies) and whole exome sequencing (WES, n = 1,427), whereas 549 tumor samples from MM patients were tested for ex vivo drug sensitivity. **Results:** This system successfully decomposed complex clinical questions into atomic sub-questions and generated appropriate database queries and software tool calls to retrieve relevant information across heterogeneous data sources. Independently, the system integrated clinical data—including physician notes, pathology reports, laboratory values and pharmacy records—to reconstruct longitudinal patient histories achieving 80% concordance with expert manual abstraction, while reducing case synthesis time from hours to minutes. Importantly, the system preserved transparency by explicitly exposing intermediate reasoning steps and highlighting missing or ambiguous data requiring clinician judgment. **Conclusions:** We propose a shift from generative AI toward structured, interpretable clinical reasoning systems. By emphasizing modularity, auditability, and human-in-the-loop design, we offer a scalable path toward trustworthy AI deployment in oncology. This framework supports precision medicine not by replacing clinical judgment, but by amplifying it—providing clinicians with transparent, reproducible, and context-aware decision support.

PA-005

A multicenter real-world study: efficacy and outcomes of selinexor combined with pomalidomide and dexamethasone (XPd) in the treatment of multiple myeloma with central nervous system involvement

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Introduction: Central nervous system involvement in multiple myeloma (CNS-MM) is rare and associated with a dismal prognosis. This study aimed to evaluate the efficacy and safety of selinexor (an XPO1 inhibitor) in combination with pomalidomide and dexamethasone (XPd regimen) in patients with CNS-MM. **Methods:** This is a multicenter, prospective and observational study, including CNS-MM patients treated with the XPd regimen. Baseline characteristics, prior treatment, CNS involvement, XPd treatment details, efficacy and survival outcomes were collected. Descriptive statistics were used to analyze the efficacy and survival outcomes. **Results:** A preliminary analysis included 10 patients, 9 of whom had relapsed/refractory MM (RRMM).Among these, 4 patients had high-risk cytogenetic features (defined as at least one of t(4;14), t(14;16), t (14;20), 17p deletion or 1q21 gain). CNS involvement patterns mainly comprised adjacent bone invasion with brain parenchymal involvement, brain parenchymal involvement and meningeal involvement. Prior to XPd treatment, 4 patients (40%) had been exposed to bortezomib, lenalidomide/pomalidomide, and anti-CD38 monoclonal antibody (daratumumab), and 2 patients (20%) had undergone autologous stem cell transplantation (ASCT). Following XPd treatment, the overall response rate (ORR) was 44.4%. The median progression-free survival (PFS) was 10 months (95% CI: 1–20). Three patients died after disease progression. The main adverse reactions of cerenisol were nausea, vomiting and ≥ grade 3 cytopenia (including thrombocytopenia, neutropenia and anemia). **Conclusions:** The XPd regimen demonstrated improved outcomes compared with historical controls in patients with CNS-MM, providing a therapeutic option, although it is not curative. More effective treatment strategies are warranted, including combination approaches with BCMA-targeted therapies and novel immunotherapies, to achieve deeper and more durable responses.

PA-006

A New Prognostic Model Based on Age and LDH Which is More Suitable for Prognostic Stratification of MM with Extramedullary Bone Involvement

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Introduction: To evaluate the applicability of existing staging systems (ISS, R-ISS, R2-ISS) in multiple myeloma (MM) patients with extramedullary bone involvement (EMB), and to establish and validate a novel prognostic model specifically for this subgroup. **Methods:** A total of 80 newly diagnosed EMB patients from December 2011 to December 2021 were retrospectively analyzed. The discriminatory ability of ISS, R-ISS, and R2-ISS was assessed by survival analysis and C-index. Prognostic factors were identified using Cox regression. A novel prognostic model was constructed and internally validated by C-index, time-dependent ROC, decision curve analysis (DCA), and calibration curves, with bootstrap resampling (1000 times). **Results:** None of the ISS, R-ISS, or R2-ISS staging systems effectively stratified EMB patients by prognosis. Multivariate analysis identified age ≥60 years (HR = 2.592) and LDH ≥240 U/L (HR = 2.445) as independent risk factors, while transplantation was a protective factor (HR = 0.443). A three-tier prognostic model based on age and LDH (low-risk: age< 60 and LDH< 240; intermediate-risk: age≥60 or LDH≥240; high-risk: age≥60 and LDH≥240) significantly stratified EMB patients (P < 0.001). The model achieved a C-index of 0.630, with 12-, 36-, and 60-month AUCs of 0.698, 0.654, and 0.688, respectively. DCA and calibration curves demonstrated good clinical net benefit and predictive accuracy, and bootstrap confirmed model stability. **Conclusions:** The ISS, R-ISS, and R2-ISS staging systems are not applicable for EMB patients. The

newly developed age- and LDH-based prognostic model is simple, effective, and exhibits good discrimination, calibration, and clinical utility, making it a practical tool for individualized prognostic assessment and treatment decision-making in EMB patients.

PA-007

A Novel CD138 CAR-T Cell Therapy is Safe and Can Induce Response in Relapsed/Refractory Multiple Myeloma though Efficacy is Limited by Soluble CD138

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Introduction: BCMA-directed CAR-T cell therapy has revolutionized the treatment of Relapsed/Refractory Multiple Myeloma (RRMM), yet patients still experience relapse. A need to identify additional targets remains. CD138, which promotes myeloma cell survival, emerged as an intriguing target. We manufactured a novel CD138 CAR-T, which significantly prolonged survival in preclinical models, prompting clinical application. **Methods:** We conducted a non-randomized, open label, single site, phase 1 clinical trial with 3+3 dose escalation, ranging from 5 × 106 to 2 × 108 CAR-T cells/m2 for patients with ≥3 prior lines of therapy. The primary endpoint was to establish a safe CAR-T dose, with secondary objectives to determine overall survival (OS), progression free survival (PFS), overall response rate (ORR), and duration of response (DOR). **Results:** Twenty-five patients enrolled between 2018–2024, 64% were female and 24% Black, with median age 59 (43–76), 4.4 years from diagnosis (1.4–15.8), 6 prior lines (3–12), 40% with high-risk cytogenetics, 48% with extramedullary disease, and 8% prior T-cell directed therapy. Sixteen patients received CD138 CAR-T infusion. Drop out was due to manufacturing failure, electing alternate therapy (BCMA CAR-T, once FDA approved), disease progression, and organ failure. Bridging therapy was with cytotoxic chemotherapy due to highly refractory disease and lack of contemporary bispecific approval. The study met its primary endpoint for safety; no dose limiting toxicities were observed and maximum tolerated dose was not reached. Rate of CRS was low (29%), all grade 1–2. No ICANS was observed. Cytopenias were universal. Intent to treat median OS was 11.6 months. Median OS and PFS of treated patients were 11.2 months and 49.5 days post-infusion, respectively. ORR was 12.5%; one patient each achieved a CR, VGPR and MR and seven achieved at least stable disease. Mean DOR was 122 days (65–188). While no significant correlation was observed between dose and response, responders were treated with at least 2.5 × 107 CAR+ cells/m2, suggesting a minimum effective dose. We hypothesized that CD138 CAR-T efficacy was limited by target and T-cell-mediated factors. This heavily pre-treated population manufactured a highly terminally differentiated CAR-T product, which has been associated with inferior outcomes. Furthermore, similarly to BCMA extracellular domain shedding which limits BCMA CAR-T efficacy, CD138 also undergoes shedding, released as soluble "sCD138." We measured low sCD138 in responders and PFS inversely correlated with pre- and post-infusion sCD138 levels ($p = 0.04$). This suggests that T-cell terminal differentiation and elevated sCD138 limit CAR-T efficacy. **Conclusions:** CD138 CAR-T cell therapy is safe in the treatment of RRMM, but a terminally differentiated CAR-T product and CD138 shedding limit efficacy. Modulation of these limitations may enhance application of CD138 CAR-T cell therapy, expanding the repertoire of therapeutic targets.

PA-008

A Phase 1/2, Open-Label, Platform Study to Evaluate the Safety and Efficacy of Etentamig Monotherapy or Combination Therapy in Patients with Multiple Myeloma

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Introduction: Many patients (pts) with multiple myeloma (MM) face unmet needs for innovative treatments or novel combinations that provide robust efficacy with a manageable safety profile. B-cell maturation antigen (BCMA) is emerging as a key target in MM for its highly selective expression in malignant plasma cells. Etentamig (etenta) is being developed as a patient-centric, next-generation BCMA × CD3 bispecific T-cell engager composed of a bivalent BCMA-binding domain with high-avidity, low-affinity CD3-binding domain potentially reducing cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life enabling convenient monthly (Q4W) dosing from the start. In a Phase 1 study, etenta monotherapy showed encouraging efficacy and was well tolerated in pts with relapsed/refractory (RR) MM, with ≥3 prior lines of therapy. This platform study will determine the recommended dose of etenta—as a monotherapy or in combination with standard of care (SoC) or investigational agents—evaluating safety, tolerability, preliminary anti-MM activity, pharmacokinetics (PK), and immunogenicity. **Methods:** This is a Phase 1/2, open-label, multicenter, dose selection and optimization platform study (NCT06892522) using a master protocol to evaluate etenta as monotherapy or in combination with other agents. Etenta regimens will be evaluated in separate substudies

which may include a dose-escalation phase (Phase 1) and/or a dose-expansion and selection phase (Phase 2). Eligible pts will be ≥18 years of age with an ECOG-PS of ≤1, with either newly diagnosed (ND) or RRMM, depending on substudy. Different substudies will enroll pts with transplant-ineligible NDMM (TI NDMM), transplant-eligible NDMM (TE NDMM) post autologous stem cell transplant, or RRMM pts with 1–3 prior lines of therapy. Treatments are based on a 28-day cycle (C). Etenta will be administered at the cohort-designated dose starting from C1 Day (D) 4 onwards after one 2 mg step-up dose on C1D1. If combined with daratumumab, etenta will be initiated as from C1D8, while lenalidomide and carfilzomib will be initiated from C2D1. Etenta may be administered in an outpatient setting per institutional guidelines; otherwise, pts are hospitalized 24 hrs to monitor for cytokine release syndrome after etenta on C1D1 and C1D4. Primary endpoint is to determine dose-limiting toxicities (DLTs) of etenta monotherapy or in combinations. Secondary endpoints include treatment response assessed by IMWG 2016 criteria. Additional endpoints include safety, PK, and immunogenicity. **Results:** The platform design of this study enables evaluation of etenta dosing, safety, and efficacy as monotherapy or in combination with current SoC across multiple pt populations to inform future research. Dose level 1 has been cleared for the first 3 substudies. **Conclusions:** This trial in progress highlights ongoing efforts to develop novel therapies for MM to improve pt outcomes.

PA-009

A Pilot Study of Romosozumab in Postmenopausal Women with Myeloma-related Bone Disease and Osteoporosis

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Introduction: Myeloma-related bone disease (MBD) affects up to 80% of patients with newly diagnosed multiple myeloma (NDMM). Although antiresorptive agents for MM inhibit bone resorption, they do not increase bone formation. Sclerostin is an osteocyte product that inhibits osteoblast maturation, impairs bone mineralization, and induces osteoblast apoptosis. Romosozumab (romo) is an anti-sclerostin monoclonal antibody approved in osteoporosis that causes rapid and marked increase in bone formation then moderate but sustained decrease in bone resorption, reflected in Procollagen Type 1 N-telopeptide (P1NP) and Type 1 collagen C-telopeptide (b-CTX) levels, respectively. We report results from a pilot study evaluating the efficacy (based on bone turnover marker levels; BTM) and safety of romo in MM patients (pts) with MBD. **Methods:** Postmenopausal women with MBD and osteoporosis received romo 210 mg SC monthly for 12 months with standard MM therapy. Primary endpoint was percent change in P1NP level after 1 month (mo) of romo compared to baseline. Key secondary endpoints include percent change in other BTMs (osteocalcin, bone alkaline phosphatase [BAP], b-CTX), evidence of bone remineralization on 6- and 12-mo imaging, and change in bone mineral density (BMD) at 12 and 24 mos. **Results:** Ten pts completed 12 mos of romo with the following characteristics: 60% with NDMM, median age 69 (range 62–81), and 50% with high-risk cytogenetics per the IMS/IMWG definition. During romo therapy, 4 were on maintenance therapy, 5 on daratumumab-based regimens with 2 proceeding to CART, and 1 on observation. While on romo, 9 pts maintained or had deepening of their responses (7 ≥CR, 2 VGPR); 1 had stable disease and then had progressive disease. All pts had prior zoledronic acid (ZA) with median time from last dose of ZA to romo start of 22 (range 4–58) mos. Median baseline P1NP level of 27 mcg/L (IQR 24–56) increased to 116 (IQR 67–144) after 1 mo of romo with median percent change of 160% (IQR 104%–304%) (P = 0.002). Median osteocalcin level was 13 ng/mL (IQR 11–23) at baseline and 46 ng/mL (23–58) at mo 1 with median percent change of 149% (IQR 109%–185%) (P = 0.002). Median BAP at baseline was 10.1 mcg/L (IQR 8–12) and increased to 19.5 mcg/L (16–25) at mo 1 with median percent change of 96% (67%–109%) (P = 0.002). Median b-CTX at baseline was 202 pg/mL (IQR 132–378) and mo 1 was 201 pg/mL (134–402) with median percent change of 1% (−17%–35%) (P = 0.8). No remineralization of target lytic lesions was seen on PET/CT. At 12 mos, mean percent changes in BMD at the lumbar spine and total hip was 6.73% and 4.46%, respectively. The safety profile was consistent with known romo adverse events with no major adverse cardiac events reported. **Conclusions:** In our study, romo was well-tolerated and resulted in significant early increases in bone formation markers (P1NP, osteocalcin, BAP) compared to baseline. Our findings suggest that romo has positive anabolic effects in MM pts without negatively impacting anti-MM therapy.

PA-010

A Pre-Diagnostic Plasma Proteomic Signature Linked Immune-Ageing Clock Anchored to BCMA/TACI Signalling Axis Predicts Risk of Progression to Multiple Myeloma

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Introduction: As various immunotherapies move treatment toward earlier in Multiple Myeloma - including an approved therapy for Smouldering Multiple Myeloma (SMM) - and raise the

prospect of curative or preventive intervention, there is now an important research gap due the limitations of current genomic and clinical models to separate progressive from stable MGUS. Affinity-based plasma proteomics enable the development of proteomic "clocks" - models that predict biological age from protein levels, so that deviation from chronological age flags risk (Oh et al. Nat Med 2025). As age is one of the strongest predictors of MM, we sought to identify a compact MM-specific plasma signature, distil it into an immune-ageing clock, and evaluated it's utility for tracking progression risk. **Methods:** We extended our previously used method to identified plasma protein biomarkers associated with incident MM in the UK Biobank (Fieggen et al. Blood Adv 2025). Specificity to myeloma was tested against five other age-related haematological malignancies, and findings were validated in an external cohort. We characterised the signature using single-cell bone-marrow transcriptomics with shift-share decomposition, network analysis, and germline variants. We then trained age-residualised LASSO proteomic clocks from the signature and benchmarked them against tissue- and lineage-specific immune-ageing clocks. **Results:** An 11-protein high-confidence signature was identified, led by TNFRSF17 (BCMA), TNFRSF13B (TACI), and SLAMF7. It was highly specific to MM, deviated from healthy baseline more than a decade before diagnosis, and replicated in EPIC-Norfolk (per-protein hazard ratios R = 0.81). The signature converged on the BCMA/TACI-non-canonical NF-kB survival axis; single-cell decomposition showed the cell of origin and circulating rise of these proteins was driven predominantly by clonal plasma-cell expansion rather than altered per-cell expression. Germline gain- and loss-of-function variants at TNFRSF13B produced mirror-image effects on the signature and concordant effects on MM risk, anchoring it mechanistically. Distilled into an age-residualised proteomic clock, the signature was the strongest predictor of incident MM across all cohorts: individuals with accelerated ageing (age-gap z >1.5) reached (>6 fold enrichment). The clock scaled monotonically across the MGUS-MM continuum, rising progressively from incident MGUS to MM diagnosed within two years, and outperformed B2-microglobulin, globulin fraction, and CRAB-associated biochemical measures. **Conclusions:** A compact, mechanistically grounded plasma protein signature can mark plasma-cell clonal expansion in bone marrow years before overt disease and provide a continuous, biologically anchored marker of progression along the MGUS-MM trajectory, with implications for risk stratification, monitoring and early interception.

PA-011

A Production-Scale Data Commons for Multiple Myeloma: Unifying Longitudinal Clinical and Multi-Omic Data for Translational Discovery

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Introduction: Large-scale clinico-genomic datasets are critical for understanding disease biology and informing therapeutic development; however, their translational impact is frequently constrained by data fragmentation, limited accessibility, and lack of interoperable analytical infrastructure. These challenges are particularly pressing in multiple myeloma, where the disease remains largely incurable and improved understanding of disease progression, therapeutic response, and resistance depends upon systematic integration of longitudinal multi-modal molecular datasets across studies and institutions. **Methods:** We developed the MMRF Virtual Lab (virtuallab.themmrf.org), a cloud-native myeloma data commons enabling governed access, analysis, visualization, and download of longitudinal clinical and multi-omic datasets. Built on the open-source Gen3 framework and deployed on AWS, the platform integrates harmonized whole genome and exome sequencing, bulk and single-cell transcriptomic, and methylation datasets with longitudinal clinical, therapeutic, demographic, and outcome-linked annotations. The Virtual Lab ecosystem incorporates scalable governed data access, cohort-centric exploration, and integrated analytical interfaces enabling dynamic interrogation of molecular and clinical attributes within a governed and reproducible analytical environment. **Results:** The platform currently supports integrated interrogation of >1,500 patients across multiple longitudinal myeloma studies and molecular profiling initiatives, including CoMMpass, representing >250 TB of harmonized molecular and clinical data, and supports a growing international community with >200 registered users spanning academic, clinical, and translational settings. Integrated capabilities enable cohort-based molecular and clinical interrogation of multi-omic and single-cell features linked to longitudinal therapeutic exposure and clinical outcomes. Representative analyses reproduced established associations between high-risk genomic alterations, including TP53 disruption, 1q gain, and t(4;14), and inferior progression-free and overall survival in multiple myeloma, while enabling integrated exploration of associated progression-related transcriptional and immune programs across longitudinally profiled patient cohorts. These capabilities facilitate biomarker discovery, retrospective therapeutic response analyses, translational hypothesis generation, and reproducible multi-omic investigation within a collaborative multi-institutional research ecosystem. **Conclusions:** The MMRF Virtual Lab establishes a production-scale framework for collaborative precision hematology research by unifying longitudinal

clinical and multi-omic data within a scalable and governed analytical infrastructure. This platform enables systematic translational investigation of disease biology and therapeutic response in multiple myeloma, accelerating collaborative data sharing, biomarker discovery, and translational research across the precision hematology community.

PA-012

A Protocolised Multidisciplinary Workflow for Early Myeloma Directed Therapy in Suspected Light Chain Cast Nephropathy: Outcomes from a Multi-Hospital Network

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Introduction: Acute kidney injury caused by light chain cast nephropathy (LCCN) is a major complication of multiple myeloma, which can result in long-term renal replacement therapy (RRT). Rapid free light chain (FLC) reduction is associated with renal recovery, with earlier achievement yielding superior outcomes. Delays in referral, diagnostics, FLC turnaround, and inter-hospital transfer impede timely treatment. We report a pilot analysis of a protocolised workflow to enable earlier myeloma directed therapy (MDT) in suspected LCCN. **Methods:** Patients (age >18) with AKI and clinical suspicion of LCCN eligible for chemotherapy were prospectively captured from July 2024 across two regional hospitals and one tertiary centre, where myeloma directed therapy is exclusively administered. Eligibility: AKI with creatinine ≥150 µmol/L (1.7 mg/dL) (or doubling of baseline for CKD) with anaemia, hypercalcaemia, fractures, or biopsy-confirmed cast nephropathy. The workflow triggered on suspicion, defining time-bound responsibilities: (1) Renal Medicine: same-day myeloma screening, expedited FLC testing, urgent haematology activation; (2) Haematology: bone marrow studies on day of referral, clonal therapy same or next working day; (3) Laboratory Medicine: FLC on next available run with same-day release, reducing turnaround from 1 to 2 weeks to 4 days or less; (4) Inter-hospital transfer: P1 priority protocol from regional to tertiary centre within 24 hours of suspected LCCN. **Results:** From July 2024 to September 2025, 8 eligible patients were managed under the new workflow. Median follow up was 5.5 months (3–18 months). Median age was 65 years old (57–78 years). All patients had estimated glomerular filtration rate (eGFR) < 60 on diagnosis, with 2 patients having an eGFR < 15. Of these 8 patients, 2 were commenced on RRT at diagnosis.

MDT was initiated within 7 days in 7/8 patients (87.5%) compared to a historical rate of 50%. All patients received bortezomib based therapy and 75% (6/8) received daratumumab containing therapy, One patient had delayed initiation of chemotherapy for 42 days due to multiple infective complications.

By Day 21–30, 6/8 patients (75%) achieved involved FLC reduction by 60%, compared to historical rate of 66.6%. At the end of follow up treatment, 1 patient had demised. The remaining patients achieved good renal recovery with none requiring long term RRT. **Conclusions:** A protocolised multi-hospital workflow, triggered on clinical suspicion of LCCN, achieves 87.5% early initiation of MDT and translates into meaningful patient benefit, with none requiring long-term RRT. Rapid FLC reduction through early treatment can prevent long-term dialysis dependence. This is an ongoing initiative; planned expansion to Orthopaedics, General Medicine, and Geriatrics aims to capture suspected LCCN across all inpatient specialties.

PA-013

A Real-World Staging System for Multiple Myeloma integrating Age, Performance Status, Renal Function, and the new High-Risk IMS/IMWG System outperforms existing models: a Machine Learning analysis

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Introduction: Prognostication in multiple myeloma (MM) has improved with biologically driven models like the Revised International Staging System (R-ISS), R2-ISS and the recently proposed IMS/IMWG Consensus Genomic Staging (CGS) for High-risk (HR) MM. However, these systems often underrepresent elderly patients or patients with comorbidities (i.e. renal impairment), thereby limiting their applicability and generalizability to real-world (RW) clinical practice.

We aimed to develop a pragmatic diagnosis-time RW staging system (RWSS), compare it with the established R2-ISS and use RSF survival modelling as a machine-learning benchmark of prognostic signal.

Methods: We analyzed 1,538 patients with newly diagnosed MM included in a large multicenter registry between 2003 and 2024; a RWSS was developed by assigning one point to each of the strongest baseline predictors of overall survival (OS) and progression-free survival (PFS): age ≥75 years, ECOG performance status ≥2, eGFR < 40 mL/min/1.73 m^2, and CGS-defined high-risk cytogenetics. To validate the RWSS and estimate the predictive ceiling of our dataset, we applied Random Survival Forests (RSF) across 10 repeated seed runs (70/30 train/test splits). Two ML models were predefined: (1) a strict baseline model (RSF_10_Pred) using only diagnosis-available predictors to avoid immortal time bias; and (2) a treatment-adjusted explanatory model (RSF_16_Exp) integrating clinically relevant markers, biology, and treatment/response dynamics. **Results:** The cohort's median age was 66 years (range 33–91) [M/F: 773/765; IgG: 923, IgA: 399, Light Chain: 188, IgD: 11, non-secretory: 15, IgM: 2)]. Overall, 88% received novel agents, 38% lenalidomide plus PI or daratumumab-based regimens, and 32% underwent autologous transplantation (ASCT). Over a median follow-up of 64 months, 694 (45%) patients died; median PFS and OS were 31 and 79 months, respectively. The proposed RWSS identified four distinct risk groups: low, low-intermediate, intermediate-high, and high (0, 1, 2 and 3 points, respectively). Compared to the established R2-ISS (OS C-index: 0.643 ± 0.018; PFS: 0.589 ± 0.015), the 4-point RWSS displayed significantly superior discrimination (OS C-index: 0.701 ± 0.013; PFS: 0.631 ± 0.020; OS AUC-12m/60m: 0.777/0.726). The baseline ML model (RSF_10_Pred) yielded an OS C-index of 0.720 ± 0.016, confirming that the simple RWSS captures most of the prognostic signal at diagnosis. The explanatory model (RSF_16_Exp) achieved the absolute highest performance (OS C-index: 0.745 ± 0.015; OS AUC-12/36/60m: 0.804/0.776/0.771), highlighting the added predictive value of treatment and response. **Conclusions:** Integrating CGS-defined cytogenetics with clinically relevant markers enables the development of a pragmatic staging system (RWSS) that significantly outperforms existing models in RW settings. Validated using advanced ML, the RWSS represents a robust, ready-to-implement tool for individualized risk stratification.

PA-014

A Scoring Model Based on 3D Telomere Profiling of Circulating Tumor Cells in the Peripheral Blood Predicts Relapse in Newly Diagnosed Multiple Myeloma Patients

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Introduction: Minimal residual disease (MRD) has emerged as one of the strongest predictors of progression-free survival (PFS) and overall survival (OS) in newly diagnosed MM (NDMM). However, currently, there are no established scoring models that integrate biological risk stratification to predict relapse beyond conventional tumor burden assessment.

We have shown that genomic instability, a hallmark of cancer progression, is driven by telomere dysfunction. Three-dimensional (3D) telomere profiling using TeloView technology enables quantification of telomere dysfunction and has previously demonstrated prognostic value in several malignancies, including MM. We previously established a workflow for isolating circulating tumor cells (CTCs) from peripheral blood. In the present study, we evaluated a cohort of 50 MM patients treated with Dara-VRD and followed for 3 years to determine whether 3D telomere profiling of peripheral blood CTCs could identify signals associated with relapse risk beyond conventional MRD assessment. **Methods:** CTCs were isolated from viably frozen peripheral blood mononuclear cells (PBMCs) using the ScreenCell device. Three-dimensional telomere profiles of individual CTCs were analyzed using TeloView for six key telomere parameters. Interim non-parametric analyses were performed using case-level summary statistics derived from cell-level features, including median, first quartile (Q1), third quartile (Q3), and interquartile range (IQR). Group comparisons between relapse and non-relapse cases were evaluated using the Wilcoxon rank-sum test, with effect sizes assessed using Cliff's delta and rank-biserial correlation. ROC curve analyses were subsequently performed for the strongest predictors. **Results:** We identified Average Distance to Nuclear Center as the strongest predictor of relapse. Relapse cases demonstrated significantly higher values for Q3 (3925.03 vs 3431.41, p = 0.002, AUC = 0.85), median (3428.68 vs 3151.97, p = 0.005, AUC = 0.83), and Q1 (3069.71 vs 2799.58, p = 0.011, AUC = 0.79) compared with non-relapse cases. Increased variability of this feature (IQR) also demonstrated an association with relapse (947.92 vs 627.33, p = 0.057, AUC = 0.72). **Conclusions:** Our findings suggest that 3D telomere profiling of peripheral blood CTCs may identify spatial and nuclear morphology-related signals associated with relapse risk in MM, potentially complementing existing MRD methodologies by providing biologically relevant risk stratification beyond tumor burden assessment alone. This represents an interim relapse risk scoring model that requires validation in larger cohorts. Ongoing studies will expand the cohort size and evaluate additional telomere parameters to further improve predictive performance.

PA-015

Access and uptake of Bispecific Antibodies in the UK

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Introduction: The treatment of multiply relapsed myeloma has transformed in recent years with the introduction of novel

immunotherapies such as bispecific antibodies. Elranatamab and teclistamab were the first bispecific antibodies approved in the UK and have been available to patients in England and Wales since July 2024 and in Scotland and Northern Ireland since September 2024. Due to their superior efficacy, these drugs should be the preferred option for patients with relapsed myeloma who have had at least three prior treatments, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory drug. However, due to the innovative nature of these treatments, there were concerns that uptake in the UK was fragmented and lower and slower than hoped. In this mixed-method study, we gathered qualitative and quantitative data on bispecific use across the UK to identify areas of poor uptake. **Methods:** Between April 2025 and March 2026, Myeloma UK submitted freedom of information (FOI) requests to NHS health boards and/or trusts across the UK to assess the use of elranatamab and teclistamab and identify any areas of inequality in accessing bispecific antibodies. We received responses from 14/14 health boards in Scotland, 7/7 health boards in Wales, 5/5 Health and Social Care Trusts in Northern Ireland and 172/180 trusts in England. We also analysed data from NHS England's Systemic Anti-Cancer Treatment database and interviewed regional myeloma specialists to aid analysis and interpretation of the FOI responses. **Results:** The responses indicated that 34% (73/218) of the hospitals treating myeloma patients were not routinely using bispecific antibodies. Of these hospitals, 66% (48/73) either had low patient numbers (< 10) or indicated that patients had access via another hospital. 34% (25/73) appeared to have no access. Also, uptake appeared low in 18% (26/145) of hospitals routinely giving bispecific antibodies. Regions with the lowest uptake of elranatamab and teclistamab were the Midlands and the South East, with the most varied access in the East of England, London, North East and Yorkshire, and Wales. More data will be presented at the meeting. **Conclusions:** Uptake of bispecific antibodies in UK clinical practice has been lower and more unequal than expected. More needs to be done to quickly identify barriers to the rollout of newly approved treatments and reduce inequalities in access.

PA-016

Accurate Assessment of Treatment Response in AL Amyloidosis Using Mass Spectrometry

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Introduction: Depth of hematologic response is critical in AL amyloidosis, where persistent monoclonal light chain production may contribute to ongoing organ damage despite apparent conventional remission. Response assessment relies on serum free light chains (FLC), serum protein electrophoresis (SPEP), and immunofixation electrophoresis (IFE). Mass spectrometry-based assays such as EXENT™ Immunoglobulin Isotypes (GAM) may provide improved sensitivity and discrimination of therapeutic antibodies from residual disease-associated monoclonal proteins.

A 74-year-old male was diagnosed with renal AL amyloidosis in December 2024. Initial investigations demonstrated an IgG λ paraprotein of 5.5 g/L with elevated λ free light chains (108 mg/L) and abnormal κ/λ ratio (0.17). Renal biopsy in February 2025 confirmed amyloidosis (Congo red positive) with λ and IgG restriction. Bone marrow aspirate and trephine showed no increase in plasma cells and Congo red staining was negative, suggesting no marrow involvement.

Baseline findings included proteinuria (urine protein 2.4 g/L; urine albumin 1523 mg/L) and impaired renal function. Cardiac evaluation showed no cardiac amyloidosis. The patient was classified as stage I renal disease. **Methods n/a Results:** Dara-VCD treatment started on 21 February 2025, followed by daratumumab maintenance until December 2026. After 6 cycles, serum FLC normalised (κ 9.9 mg/L, λ 12 mg/L, κ/λ ratio within normal range), suggesting complete hematologic response by conventional criteria.

SPEP in April and May 2025 demonstrated an unquantifiable IgG λ paraprotein, while EXENT™ GAM analysis identified and quantified both daratumumab (1.27–1.24 g/L) and persistent disease-associated IgG λ protein, decreasing from 1.16 g/L to 0.518 g/L between 11 April and 09 May 2025. **Conclusions:** This case highlights limitations of conventional response assessment. Despite normalisation of dFLC and absence of quantifiable paraprotein by SPEP, EXENT™ GAM analysis showed residual monoclonal protein, indicating that complete response had not been achieved. Importantly, EXENT™ GAM analysis discriminated therapeutic daratumumab from the pathogenic IgG λ clone without requiring reflex testing including IFE.

Persistent low-level monoclonal protein production may drive end-organ injury and increase the risk of renal deterioration, relapse, and dialysis dependence. The patient remained at risk of renal impairment with eGFR 38 mL/min/1.73m^2 despite conventional hematologic remission.

Mass spectrometry-based monitoring provided clinically actionable information not detected by SPEP or serum FLC alone. The EXENT™ analyser enabled discrimination and quantification of residual pathogenic monoclonal protein in the presence of daratumumab, demonstrating that complete response had not been achieved despite normalised dFLC. These findings support the role of mass spectrometry in refining response assessment in AL amyloidosis and may identify patients who could benefit from earlier intervention to prevent organ damage.

PA-017

Adrenergic stimulation remodels bone marrow immunity and impacts immunotherapy response in multiple myeloma

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Introduction: Adrenergic signaling is a key component of the neuroendocrine–immune axis regulating immune homeostasis, but its role in hematologic malignancies remains poorly understood. Multiple myeloma (MM) develops within the bone marrow (BM), a highly specialized niche integrating neural, immune, and stromal interactions. Whether adrenergic stimulation modulates BM immunity and influences MM progression and therapeutic response remains unclear. **Methods:** To investigate the impact of adrenergic stimulation on MM immune profile, we used the immunocompetent 5T33MM murine model. Sustained sympathetic activation was induced through chronic restraint stress (CRS), while selective β-adrenergic stimulation was achieved using isoprenaline. BM and splenic immune landscapes were profiled by multi-parameter flow cytometry, and systemic inflammatory responses were evaluated through serum IFN-γ quantification. β2-adrenergic receptor expression was examined at both protein and transcript level using primary murine samples and publicly available single-cell RNA sequencing datasets. In parallel, murine and patient-derived BM cultures were exposed to β-adrenergic stimulation alone or in combination with MM immunotherapies to assess effects on tumor cell survival and therapeutic activity. **Results:** Physiological adrenergic activation through CRS induced alterations within the BM immune microenvironment of MM-bearing mice, including expansion of neutrophil, NK-cell, and NKT-cell populations, accompanied by a reduction in B cells and increased circulating IFN-γ levels. These alterations correlated with decreased MM infiltration in the BM, whereas markers of systemic disease, including splenic involvement and serum M-protein, were unaffected. Similar immune remodeling was observed in non–tumor-bearing mice subjected to CRS, although the magnitude of these effects increased in the MM setting. Transcriptomic analyses identified mature BM neutrophils as a prominent β2-adrenergic receptor expressing population. Pharmacologic β-adrenergic stimulation partially reproduced the CRS-associated immune phenotype and resulted in a temporary reduction in BM tumor burden in vivo. In contrast, ex vivo exposure to isoprenaline did not directly influence MM cell viability but consistently diminished the anti-myeloma activity of multiple immunotherapeutic agents in both murine and patient-derived BM cultures. **Conclusions:** Adrenergic activation modulates the BM immune niche in MM and induces divergent effects depending on biological context. While sustained adrenergic signaling in vivo was associated with innate immune activation and reduced BM tumor burden, direct β-adrenergic stimulation ex vivo impaired immunotherapy efficacy. Together, these data support the existence of a BM neuroendocrine–immune axis with potential relevance for therapeutic responses in MM.

PA-018

Age Gauge: A Transformative Platform to Increase Older Adult Myeloma Clinical Trial Enrollment

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Introduction: Background: We created a Clinical Trial (CT) Dashboard which is a novel interactive platform that transforms CT enrollment monitoring by delivering critical accrual data as trials progress- giving investigators unprecedented visibility into participation patterns. The Dashboard collates enrollments into clinical trials and reports demographic data in aggregate. It visualizes Multiple Myeloma (MM) patient enrollment by age, gender, race, ethnicity, and geographic location (metropolitan vs. rural, Appalachian vs. non-Appalachian) and overtime. The primary objective was to determine if clinical trials with age–friendly eligibility criteria and endpoints (Age-Gauge) are associated with increased enrollment of older adults. The secondary objective was to evaluate the usage and acceptability of the clinical trial dashboard. **Methods:** Methods: The Age Gauge defines the age-friendliness of each therapeutic trial using a scoring rubric, a higher score indicates a study more inclusive for older adults, with a maximum score of 13. Accrual is uploaded daily to the dashboard from Oncore, a web-based clinical trial management system that collects data on trial participants and is integrated with electronic medical record. The dashboard displays aggregated patient data (no protected health information) and is disseminated to physician investigators to promote real-time feedback in trial accrual. **Results:** Results: At a single institution, from 2016 to 2026 patients with MM were enrolled into therapeutic clinical trials, were mostly 65 years and older (69%), predominately female (59%), 84% White, 12% Black/African American, 3.3% other. 61 patients were from rural (non-metropolitan) areas and 32 patients from Appalachian counties. Using the Age-Gauge rubric, 25 MM clinical trials were included (n = 5 Phase I, n = 4 Phase II, n = 10 phase I/II, n = 6 Phase III). The median total score of the Age-Gauge was 6 (range 4–9), eligibility score was 3 (range 2–5), endpoint score was 2 (range 1–5). The feasibility of the CT dashboard was examined among clinician participants (n = 12) with system usability scores ranging from good to average (50–77.5. **Conclusions:** Conclusion: Older adult enrollment into MM therapeutic CT is a major gap: the dashboard empowers physicians and research teams to identify enrollment gaps

immediately rather than retrospectively. The Age-Gauge rubric is being developed as a predictive tool to support the selection of age-inclusive, age-friendly MM clinical trials.

PA-019

AI Doctor-in-the-Loop Abstraction: Enhancing Completeness in Flow Cytometry Data Abstraction for Multiple Myeloma Genomic and Immune Profiling

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Introduction: Flow cytometry is valuable for analyzing tumor microenvironment, and immune profiling in Multiple Myeloma (MM). However, systematic data extraction often faces issues such as collection errors and inconsistent capture of relevant features. To address this, we created a dual-interface abstraction tool with a manual option and an AI-assisted 'Doctor-in-the-Loop' (DITL) workflow. By consolidating phenotyping metrics into a unified entry, this instrument streamlines data validation. Initial evaluations showed that the AI-DITL workflow recovered missing information in 65% of reports overlooked during manual abstraction. **Methods:** We conducted a randomized crossover study to assess data omission rates in 144 entries within 35 flow cytometry reports from MM patients. Seven expert clinical data abstractors processed each report using either the manual or the AI-DITL workflow driven by Gemini 3.1 Pro via Google Cloud Vertex AI. This study aimed to evaluate the completeness and precision of the AI-DITL method versus the manual, quantify omitted data, and identify differences in capture rates, assessing areas prone to human oversight. In this tool, an entry is defined as a collection of aggregated data points representing an entire cell population, including Parent Gate, Identification Gate, Cell Population, Cell Behavior, % Cells Analyzed, and all Phenotype Markers (marker, result, brightness) present or not. **Results:** In 35 reports with 144 entries assessed, 47.2% of manual extractions were incomplete (23.6% were entirely omitted; 23.6% were partially completed). An evaluation of the entries 222 data points showed AI-DITL precision at 97.2% (173/178; $p < 0.0001$), significantly higher than manual precision at 84.1% (37/44; $p < 0.0001$). Significant asymmetry in data capture was observed ($\chi^2 = 86.79$, $p < 0.0001$), with manual extractors missing 4.7 times as many data points. Wilcoxon signed-rank testing confirmed AI's superiority in completeness ($W = 2655$, $p < 0.0001$). Field-level analysis revealed that the most striking manual recall failures were in Cell Behavior, Cell Population (McNemar $p < 0.0001$), and Marker data (McNemar $p = 0.001$). Brightness qualifiers had the most pronounced precision failure: manual precision was 42.9% ($p = 0.773$), and AI-DITL precision was 85.7%, making it the only field in which manual recording was unreliable. **Conclusions:** These findings have crucial implications for the management of MM patients undergoing T-cell therapy. Accurate data capture for immune profiling is vital for therapeutic decision-making, assessing the tumor immune microenvironment, and monitoring T-cell efficacy. Omissions in data can impede the evaluation of treatment failure and introduce gaps into real-world data registries and studies. The completeness of AI-DITL extraction may reduce errors, enhance consistency in immunophenotypic profiling, and enhance registry evidence integrity. Further validation in larger, multicentre cohorts is necessary to confirm these results.

PA-020

ALDOA promotes invasive phenotypes associated with extramedullary involvement in multiple myeloma by regulating metabolic adaptation

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Introduction: Extramedullary multiple myeloma (EMM) is an aggressive disease phenotype associated with poor clinical outcomes. Adaptation to hypoxic and metabolically stressful microenvironments is considered an important biological feature underlying extramedullary dissemination; however, the metabolic regulators involved in this process remain incompletely characterized. In single-cell transcriptomic profiles from five paired bone marrow and extramedullary lesions, ALDOA was preferentially expressed in extramedullary plasma cells and enriched in stress-response and EMT-related plasma-cell states. This study aimed to define the role of ALDOA in metabolic adaptation and invasive phenotypes in EMM. **Methods:** Patient-derived single-cell RNA sequence and public myeloma transcriptomic datasets were integrated to assess the clinical and biological relevance of ALDOA in extramedullary disease. An ALDOA-overexpressing RPMI8226 cell model was generated for functional characterization of proliferation, migration and metabolic remodeling. RNA sequencing, qRT-PCR validation, and untargeted metabolomics were performed to identify ALDOA-associated molecular and metabolic alterations. **Results:** ALDOA was highly expressed in extramedullary plasma cells and associated with hypoxia-, stress-response-, and EMT-related programs. Patient and public transcriptomic analyses further showed increased ALDOA expression in CD138+ plasma cells from patients with extramedullary involvement, progressive upregulation during myeloma progression, and an association with survival. Functionally, ALDOA overexpression enhanced RPMI8226 cell growth under nutrient deprivation and promoted migration. Although glucose uptake was reduced in

ALDOA-overexpressing cells compared with controls (2.92% vs. 4.41%), extracellular lactate increased by approximately 23.7%, whereas intracellular lactate decreased, suggesting lactate redistribution and enhanced efflux. JC-1 staining showed increased green fluorescence, consistent with mitochondrial membrane potential loss. CFSE and cell-cycle analyses showed increased cumulative division with G1 accumulation and reduced S-phase fraction. Multi-omics analyses revealed coordinated remodeling of carbon and mitochondrial energy metabolism, nucleotide and membrane lipid metabolism, phosphoinositide signaling, cytoskeletal organization, and stress-adaptation pathways. **Conclusions:** ALDOA is enriched in extramedullary, hypoxic, stress-responsive, and EMT-like myeloma plasma cells and is linked to extramedullary involvement, disease progression, and adverse outcome. Functional and multi-omics analyses indicate that ALDOA supports nutrient-stress tolerance and invasive behavior by rewiring lactate metabolism, mitochondrial homeostasis, membrane lipid metabolism, and cytoskeleton-related programs, identifying ALDOA as a potential regulator of metabolic adaptation and invasive progression in EMM.

PA-021

ALKBH5-Mediated Regulation of XBP1 Impairs Plasma Cell Maturation and Confers Proteasome Inhibitor Resistance in Multiple Myeloma

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Introduction: Despite substantial advances in targeted and immunotherapeutic strategies, multiple myeloma (MM) remains an incurable hematological malignancy. Proteasome inhibitors (PIs) are the cornerstone of frontline therapy for most MM patients; however, acquired resistance arises in nearly all cases, and the molecular mechanisms driving this process remain incompletely elucidated. N^6-methyladenosine (m^6A), the most abundant internal mRNA modification, has emerged as a regulator of therapeutic resistance across cancers. Nonetheless, the role of m^6A modification, particularly its demethylase ALKBH5, in modulating PI resistance in MM remains largely uncharacterized. **Methods:** We analyzed the association between ALKBH5 expression and clinical response to bortezomib in MM patient cohorts and primary clinical specimens. ALKBH5 was genetically silenced via short hairpin RNA or overexpressed (wild-type or catalytically inactive H204A mutant) in human MM cell lines. PI sensitivity was assessed using in vitro cell viability assays and in vivo xenograft tumor models. To identify ALKBH5 targets, we performed integrated multi-omics analysis combining m^6A-seq, RNA-seq, and Ribo-seq. Key findings were validated by m^6A-IP-qPCR, RIP-qPCR, and RNAscope in situ hybridization. Western blotting quantified unfolded protein response (UPR) effectors, including CHOP, ATF4, and GADD34. Plasma cell differentiation was evaluated by flow cytometry based on CD38 and CD138 expression, while immunoglobulin secretion was measured via ELISA. **Results:** Low ALKBH5 expression correlated with inferior bortezomib responses in MM patients. Genetic depletion of ALKBH5 induced resistance to both bortezomib and carfilzomib, two clinically relevant PIs. Conversely, restoration of wild-type ALKBH5, but not the H204A mutant, re-sensitized MM cells to PI treatment in vitro and in xenograft models. Mechanistically, transcriptome-wide m^6A profiling identified XBP1 mRNA as a critical target of ALKBH5-mediated demethylation. In ALKBH5-deficient cells, XBP1 transcripts displayed elevated m^6A methylation, reducing spliced XBP1 (XBP1s) levels. This attenuated UPR signaling, as evidenced by decreased CHOP, ATF4, and GADD34 expression. ALKBH5 loss impaired plasma cell maturation, with reduced CD38/CD138 expression and lower immunoglobulin secretion. Consequently, ALKBH5-deficient MM cells failed to undergo terminal endoplasmic reticulum (ER) stress-induced cell death, acquiring PI resistance. **Conclusions:** These findings demonstrate that ALKBH5 governs PI sensitivity in MM by maintaining XBP1 expression and promoting plasma cell differentiation. ALKBH5 loss locks MM cells in an immature, differentiation-arrested state with intrinsic PI resistance. This study establishes m^6A modification as an unrecognized regulator of PI resistance in MM, offering mechanistic insights and highlighting therapeutic vulnerabilities to overcome drug resistance in myeloma.

PA-022

Alternative Promoter–Driven Protein Structural Programs in NDMM: Distinguishing Poor and Non-Poor Responders

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Introduction: RNA expression analyses reveal transcriptional programs shaping disease biology and outcomes, yet gene-level summaries obscure key regulatory layers such as alternative promoter (Alt P) usage. Analyses of newly diagnosed multiple myeloma (NDMM) patients in the CoMMpass cohort identify distinct survival groups based on RNA expression, but standard RNA-Seq captures only gene-level expression and overlooks Alt P usage. Although present in RNA-seq data, Alt P activity is rarely analyzed, limiting biological stratification and risk prediction. Alt P–driven transcript (XS) isoforms can encode functionally distinct protein isoforms hidden within overall gene expression signal—complexity missed by conventional approaches. To address this, we developed RSA-PIP (RNA Seq Assisted-Protein Isoform Prediction), an AI-driven framework integrating Alt P XS usage, AlphaFold-based structural modeling, and protein domain annotation. **Methods:** Alt P activity was quantitated using RNA-Seq data (ProActiv) from NDMM CoMMpass patients, comparing poor responders (PR, n = 51) to Non-PR (n = 663). A RSA-PIP pipeline mapped Alt XS, predicted primary amino acid sequences, and generated reference and alternative

protein structure models using AlphaFold. Reference and Alt protein structures were analyzed at the domain level with structural and sequence annotation tools. Isoforms were prioritized based on predicted structural disruption, impact on protein interaction networks, and clinical association. Pathway differences between PR and Non-PR Alt P-driven genes were assessed using g:Profiler. **Results:** We identified 560 differentially regulated Alt-P events driving 943 XS, 43% of which encode proteins with altered amino acid sequences relative to reference (MANE) protein. 78% of these Alt P events occur in genes with < 2-fold expression differences between PR and non-PR patients, a threshold typically used to contrast gene expression across two populations, suggesting that the biological influence of these Alt P–driven protein isoforms may have been previously missed. Alt XS encode Alt proteins with divergent domain architectures, potentially altering function, interactions, and signaling pathways. Ongoing analyses are aimed at prioritizing isoforms affecting oncogenic and regulatory proteins, including those influenced by alternative splicing. Strikingly, genes bearing increased Alt P activity in PR patients exhibit an enrichment of transcription factor binding sites when compared to Non-PR patients. **Conclusions:** Alt P driven XS and protein isoforms represent an underexplored layer of molecular diversity in MM. By linking transcript variation to predicted protein structure, RSA-PIP enables identification of biologically meaningful alterations not captured by conventional coding-region (exome) analyses. These isoforms represent a novel class of biomarkers and candidate therapeutic targets, with potential to improve risk stratification and inform precision medicine strategies.

PA-023

ALTITUDE - ALTernating Induction Therapies to achieve Undetectable Disease Endpoints: Ph 1/2 Dara-RVd/Teclistamab-RVd in Transplant Eligible Standard-Risk Newly Diagnosed Multiple Myeloma

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Introduction: The treatment for transplant-eligible, newly diagnosed multiple myeloma (TE NDMM) has seen significant advances driven by deeper responses with PERSEUS demonstrating MRD negativity (MRD-neg) (10-5) of 57.5% for Dara-VRd after consolidation. Teclistamab (tec), a BCMA × CD3 bispecific antibody, demonstrated 100% MRD-neg (10-5) in TE-NDMM patients (pts) receiving 6 cycles of tec-based induction in MajesTEC-5. Given the clonal heterogeneity of MM, sequencing Tec-RVd after Dara-RVd may offer a rational biological strategy to target resistant subclones and mitigate overlapping toxicities of concurrent dosing. Here we report the phase (Ph) 1 safety run-in of ALTITUDE. **Methods:** ALTITUDE is a Ph 1/2 single-arm study for standard-risk TE-NDMM pts (N = 59–65) defined by 2025 IMW-IMWG CGS criteria. The Ph 1 run-in (n = 6) evaluates safety and DLT of Tec-RVd following 3 cycles of Dara-RVd, with the DLT period defined as 4 weeks from the first Tec-RVd dose. Induction consists of Dara-RVd × 3 cycles, stem cell collection (SCC), followed by Tec-RVd × 3 cycles (tec step-up dosing: 0.06, 0.3, 1.5 mg/kg on days −3, −1, 1 and 8 of cycle (C) 4, then 3.0 mg/kg SC on day 1 of C5 and C6; bort 1.3 mg/m2 SC days 1, 8, 15; len 25 mg days 8–21 of C4 and days 1–21 of C5 and C6), and ASCT. Pts then receive 2 years of Tec-Dara maintenance (dara 1800mg SC q4 weeks; tec 3.0 mg/kg SC q8 weeks). Use of prophylactic tocilizumab (toci) was permitted. The Ph 2 primary endpoint is MRD-neg rate (10-5) after 6 induction cycles. Secondary endpoints include safety and tolerability, sCR/CR rate and ORR, sustained MRD negativity, PFS, EFS, OS, and HRQoL. **Results:** From September 2025, six pts enrolled onto Ph 1 of ALTITUDE study, including 5 male and 1 female with a median age of 63 years (43–73). Pts enrolled included 1 R-ISS stage I and 5 R-ISS stage II. Current median follow-up is 224 days. No DLTs were observed. Grade 3/4 treatment related adverse events (TRAEs) were 6/6 (100) lymphopenia, 4/6 (67) neutropenia, and 1/6 (17) thrombocytopenia. Grade 3/4 non-hematologic TRAEs included 1/6 (17) febrile neutropenia. Related SAEs included 2 episodes of febrile neutropenia (occurred in 1 pt; prior to Tec-RVd). AESIs included 2/6 (33) Grade 2 CRS resolved with toci, no grade 3/4 CRS, no ICANS (any grade), and no grade 3/4 infections with 3/6 (50) pts receiving IVIG. One pt is completing induction. Following Tec-RVd (end of C6), overall response rate in 5 evaluable patients is 5/5 (100). Among MRD-evaluable pts, all four evaluable pts are 4/4 (100) MRD-neg at 10-5 and 10-6; one pt is MRD unevaluable. All 6 pts completed SCC (median CD34 yield of 5.7 × 106 (3.7–11.3)) and remain on protocol with planned ASCT. **Conclusions:** Ph 1 run-in of ALTITUDE demonstrates tolerability with no additional safety DLTs with the incorporation of Tec-RVd to frontline therapy. Following Ph 1, Ph 2 launched on March 25, 2026, with an additional 7 patients enrolled to date. Updated results to be presented at meeting.

PA-024

Amyloidogenic Casts in Plasma Cell Dyscrasias: Rare manifestation of Monoclonal Light Chain Associated Renal Injury

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Introduction: Renal involvement in plasma cell dyscrasias is protean, with cast nephropathy, amyloidosis and monoclonal immunoglobulin deposition disease, being the commonest lesions. Rarely, amyloidogenic light chain casts occur within renal tubules and may represent an early localized form of systemic amyloidosis. We evaluated the clinicopathological and ultrastructural features of amyloidogenic cast nephropathy and explored mechanisms of intratubular amyloidogenesis. **Methods:** This retrospective study included 8 renal biopsies and 1 medical autopsy case. Tissue was processed for light microscopy, immunofluorescence, Congo red staining and electron microscopy. Histological assessment included cast morphology, peripheral crystallization, giant cell reaction, tubular epithelial injury, intracytoplasmic crystals and vascular/interstitial changes. Detailed ultrastructural study of amyloidogenic casts were done. **Results:** Over 20 years, among renal biopsies and 16 medical autopsies of multiple myeloma patients; 9 cases of amyloidogenic cast nephropathy were identified out of 369 cases of monoclonal renal lesions (prevalence 2%). There were 229/12092 cases (18%) of renal amyloidosis, of which 3% showed presence of amyloidogenic casts. 9 of 58 cases (15%) of light chain cast nephropathy (LCCN) were amyloidogenic. Patients showed female predominance (55.6%) and a relatively older age at presentation (mean 53 years), than LCCN. All presented with renal dysfunction and elevated serum creatinine (2.1–8.6 mg/dL). All cases showed central lamellated PAS-negative casts with peripheral radiating spicules. Tubular injury and dilatation were universal, while giant cell reaction and fibroinflammatory response were frequent. Tubulopathy was identified in 66.7% cases and intracytoplasmic crystalline inclusions in tubular epithelium in 22.2%. IF demonstrated monoclonal-light-chain restriction, predominantly lambda (77.8%) and CR positivity. EM demonstrated randomly arranged nonbranching 8–12 nm fibrils within casts. The autopsy case showed persistence of the characteristic amyloidogenic cast morphology, unlike conventional light-chain casts that often lose their rigid structure following therapy. **Conclusions:** Amyloidogenic cast nephropathy represents a distinct rare form of monoclonal light chain–associated renal injury. The absence of significant glomerular or systemic amyloid deposition in most cases suggests that amyloidogenesis may begin within the tubular lumen/tubular epithelial microenvironment. Ultrastructural demonstration of amyloid fibrils within casts supports true intratubular amyloid formation rather than degenerative change. We propose altered tubular physicochemical conditions, including luminal pH, tubular stasis, interaction with Tamm–Horsfall protein promote conformational transformation of filtered light chains into amyloid. Persistence of amyloidogenic casts at autopsy suggests limited structural resolution after therapy, likely because these casts exist in a fixed fibrillar configuration.

PA-025

An Engineered Lysosomal Protease Inhibitor Improves CAR-T Cell Therapy in Multiple Myeloma by Preventing CAR Downmodulation and Inducing the Formation of Memory CAR-T Cells

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Introduction: We have found that high cystatin E/M (CST6) expression is associated with the absence of bone lytic lesions in human multiple myeloma (MM) patients, and CST6 suppresses the formation of osteolytic lesions by blocking osteoclast differentiation and function in MM. Wild-type CST6 (CST6WT) protein secreted by MM cells is an N-linked glycosylated form. We have engineered BCMA-CAR-T cells to secrete CST6WT proteins, and these BCMA/CST6WT-CAR-T cells lysed MM cells and suppressed osteolytic lesions in MM mouse models. Through mutagenesis of CST6, we further identified that the N-linked glycosylation mutant (i.e., N137D) form of CST6 (CST6N137D) does not influence CST6′s ability to inhibit osteoclast differentiation. However, unlike CST6WT, CST6N137D does not induce M2 macrophage polarization or suppress T cell proliferation. The objective of this study is to establish CST6N137D as a biological agent to improve CAR-T cell therapy in MM and other cancers. **Methods:** The BCMA/CST6N137D CAR vector contained the BCMA-scFv and mutant CST6N137D. A P2A self-cleaving peptide was inserted between the CAR and CST6N137D sequences. Cytotoxicity assays were performed to assess the cytotoxic activity of CAR-T cells against MM cells in vitro. Flow cytometry was used to analyze the percentage and phenotype of CAR-T cells and myeloma cells. Human MM cell line xenograft mouse models were employed to evaluate CAR-T cell therapeutic effects in vivo. RNA sequencing and proteomics were performed to determine the mechanisms by which CST6N137D improves CAR-T cell therapy. **Results:** We constructed BCMA/CST6WT-CAR-T and BCMA/CST6N137D-CAR-T cells. The percentages of CAR-T transduction in T cell subtypes were analyzed and showed that both types of CAR-T cells elicited similar effects. Both BCMA/CST6WT-CAR-T and BCMA/CST6N137D-CAR-T cells released high levels of CST6 in culture media. Importantly, BCMA/CST6N137D-CAR-T cells, compared to BCMA-CAR-T and BCMA/CST6WT-CAR-T cells, showed increased cytolytic activity toward two human MM cell lines (MM1S and ARP1) xenografted in immunodeficient mice. Flow cytometry demonstrated that BCMA/CST6N137D-CAR-T cells exhibited increased

activation, with high levels of cell-surface CD69, and also produced increased levels of the cytokines IL-2 and IFN-γ in culture media. We also found that CST6N137D prevents CAR downmodulation in CAR-T cells in vitro and CAR-T cell persistence in vivo, extends the lifespan of CAR-T cells, and enhances their ability to kill MM cells in vivo. We identified c-Fos as playing a major role in mediating CST6N137D's enhancement of CAR-T cell cytotoxicity against MM cells. **Conclusions:** BCMA/CST6N137D-CAR-T cells show improved tumor clearance compared to BCMA-CAR-T cells and BCMA/CST6WT-CAR-T cells both in vitro and in vivo. Our findings provide a promising strategy to enhance the antitumor efficacy of CAR-T cell therapy.

PA-026

An Integrated High-Sensitivity Flow Cytometry Platform Revealing Dissemination-Associated Phenotypes and Therapeutic Target Heterogeneity in Multiple Myeloma: The MMulticolors Panel

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Introduction: Multiple myeloma (MM) is a heterogeneous plasma cells (PCs) malignancy characterized by complex interactions between neoplastic PCs and the bone marrow (BM) microenvironment (ME). Despite major therapeutic advances, including BCMA- and GPRC5D-targeted immunotherapies, disease progression, clonal evolution, and dissemination remain major clinical challenges. Current diagnostic flow cytometry (FC) approaches mainly focus on PCs and provide limited information on therapeutic target expression, PC maturation states, dissemination biology, and BM/peripheral blood (PB) ME interactions. To address these unmet needs, we developed the MMulticolors multiparametric FC (MFC) platform, integrating MM and ME characterization. **Methods:** Four novel 8-color MFC tubes were combined with two standard diagnostic tubes to comprehensively analyze BM and PB samples, enabling simultaneous evaluation of tumor burden, circulating PCs (CPCs), therapeutic targets (e.g., BCMA), PC maturity/stemness features, and immune-related pathways. Thirty-two MM patients (pts) [15 newly diagnosed (NDMM) and 17 relapsed MM (RMM)] were analyzed, including 30 paired BM/PB samples. High-sensitivity acquisition protocols achieved a limit of detection of 10-5, allowing reliable identification of rare CPCs. Paired analyses were performed using Wilcoxon signed-rank testing with FDR correction. **Results:** NDMM pts showed significantly higher BM-PCs infiltration than RMM pts (median 15.3% vs 3.58%, FDR = 0.01). Similarly, CPCs levels were higher in NDMM than RMM (median 0.109% vs 0.044%), although not significantly. Paired BM/PB analyses identified stable compartment-specific phenotypic differences. Across 15 evaluable MM pairs, CD200 and SLAMF7 expression were significantly higher in BM-PCs, whereas CD44 expression was enriched in CPCs (FDR = 0.034 for all comparisons). Substantial inter-patient heterogeneity was observed for BCMA, GPRC5D, and CD24 expression. BCMA expression did not strongly correlate with either GPRC5D or SLAMF7, suggesting non-redundant therapeutic landscapes and potential complementarity. In contrast, CD24 positively correlated with CXCR4 (R = 0.72, FDR = 0.004) and may reflect a BM-retentive PC state characterized by preserved stromal interactions and reduced dissemination potential, while SLAMF7 inversely correlated with CD44 (R = -0.54, FDR = 0.02). This, together with the enrichment of SLAMF7 and CD200 in BM-PCs and CD44 in CPCs, suggests a phenotypic transition from BM-associated to dissemination-associated PCs states. **Conclusions:** In conclusion, the MMulticolors platform enables highly sensitive and integrated characterization of PC across BM and PB compartments. Our results identify reproducible dissemination-associated phenotypic shifts, while also revealing marked inter-patient heterogeneity in clinically relevant therapeutic targets. These findings support the utility of advanced MFC for biological stratification and optimization of target-directed therapies in MM. ACK: AMO LA VITA ODV, PNRR-TR1-2023-12378246.

PA-027

An Omics-Guided Cytokine Culture Platform Sustains Primary Multiple Myeloma Cells Ex Vivo and Enables Functional Manipulation

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Introduction: Ex vivo culture of primary multiple myeloma (MM) cells is limited by rapid loss of viability and phenotypic fidelity outside the bone marrow (BM) niche, restricting functional interrogation and translational applications. We sought to develop a biologically informed cytokine-supported culture system to sustain primary MM cells ex vivo. **Methods:** Candidate cytokines were prioritized using MMRF CoMMpass RNA-seq data (n = 770) by associating cytokine and receptor expression with clinical outcomes. Primary MM patient samples from 70 unique donors informed the study; however, limited availability of high-yield samples determined final assay sizes. Thirteen cytokines were screened in 2- and 3-

cytokine combinations (n = 364) using CD138$^+$-selected MM patient samples (n = 3). Top-performing combinations were evaluated longitudinally (up to 14 days; n = 3 donors) by flow cytometry to assess viability and CD138$^+$ cell maintenance. Fold changes were normalized to RPMI + 10% FBS, with statistical comparisons performed against matched no-cytokine media controls. Functional performance was further assessed in whole bone marrow samples (n = 3) through CD138 recovery following cryopreservation and preservation of cellular morphology, and in lentiviral transduction assays (n = 1) to evaluate compatibility with genetic manipulation. **Results:** Combinatorial cytokine signaling consistently outperformed single-factor conditions and identified a three-cytokine cocktail (provisional patent filed) as a robust cytokine backbone for ex vivo MM maintenance. Relative to matched no-cytokine controls, this condition significantly improved viability and CD138$^+$ MM cell counts through day 10 (fold change viability: 3.631 vs 1.422, p = 0.032; CD138$^+$ cell counts: 3.921 vs 1.267, p = 0.041). Cytokine-supported conditions accelerated recovery of CD138 expression in cryopreserved samples within 24 hours post-thaw and preserved cellular morphology, consistent with improved phenotypic stability. Cytokine-supported culture also improved the functional tractability of primary MM cells during lentiviral engineering. Although transduction efficiencies were comparable to no-cytokine controls, cytokine-supported conditions preserved post-transduction viability near baseline upon infection at days 1 and 7 in culture. In no-cytokine media, viability decreased to 0.7-fold and 0.4-fold relative to untreated controls at days 1 and 7, respectively, whereas cytokine-supported conditions maintained viability at 1.1-fold and 0.8-fold, enabling functional manipulation. **Conclusions:** We describe a patient-derived, omics-guided cytokine culture platform that enhances survival, phenotypic stability, and experimental accessibility of primary MM cells ex vivo. This cytokine cocktail supports downstream applications and provides a scalable framework for patient-specific functional modeling. Specific cytokine identities are withheld pending ongoing intellectual property considerations and will be disclosed upon resolution.

PA-028

An Unsupervised Inflammation Score (dMIS) Independently Predicts Progression-Free Survival in Newly Diagnosed Myeloma in the Current Treatment Era

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Introduction: Since 2021, CD38 antibodies have become standard first-line therapy for NDMM in China, reducing the generalizability of supervised prognostic models. Additionally, current stratifications including RISS poorly capture immune-inflammatory heterogeneity. We therefore developed an unsupervised, denoised Mahalanobis distance-based Inflammation Score (dMIS) and validated it through independent temporal cohorts. **Methods:** Consecutive NDMM patients per IMWG 2014 criteria were enrolled into a training cohort (Jan 2015–Aug 2021, n = 319) and a temporally independent validation cohort (Sep 2021–Sep 2025, n = 176). Exclusion criteria: primary plasma cell leukemia, concurrent second malignancies requiring treatment, or missing baseline/follow-up data. Twenty-four baseline inflammatory-immune parameters were collected: cytokines (IL2, IL4, IL6, IL10, TNF-α, IFN-γ, IL-17A), lymphocyte subsets (CD3%, CD4%, CD8%, CD4/CD8, NK %), immunoglobulins (IgA, IgG, IgM), C3, C4, D-dimer, Ferritin, CRP, and blood count absolute counts (WBC, LYM, MON, NEU). After ULN correction and log transformation, dMIS (0–1) was constructed using a fully unsupervised strategy with random matrix theory denoising. Multivariable models included ISS, FISH-defined high-risk cytogenetics (del17p, 1q21 gain/amp, 1p del, t(4;14), t(14;16)), and EMD. PFS was analyzed by Cox/Firth regression. Model performance was evaluated by C-index, LRT, IDI, and cfNRI. Key drivers were identified by Spearman correlation. In 161 patients with 4-cycle MRD data (EuroFlow 10^{-5}), we assessed dMIS-MRD association and potential mediation effect. **Results:** Dichotomized at the training cohort median (0.153), high dMIS independently predicted worse PFS in both cohorts: validation (multivariable HR 1.834, 95%CI 1.011–3.327, P = 0.045) and training (HR 1.429, 95%CI 1.07–1.91, P = 0.015). Adding dMIS to the base model (ISS, high-risk cytogenetics, EMD) improved discrimination (C-index 0.778 vs 0.724, P = 0.054), fit (LRT χ^2 = 16.05, P < 0.0001) and reclassification (IDI 0.092, P = 0.016; cfNRI 0.614), with good calibration (slope 0.936). Importantly, dMIS effectively re-stratified high-risk cytogenetic patients: combined high-risk cytogenetics and high dMIS had HR 3.82 (95%CI 1.27–11.51, P = 0.010), while either factor alone was non-significant. dMIS was primarily driven by IL6, IL10, TNF-α, CRP, and lymphopenia. High dMIS correlated with lower 4-cycle MRD negativity (OR 0.033, P = 0.014), but its prognostic effect persisted after MRD adjustment, indicating it acts independently of MRD eradication. **Conclusions:** Reflecting the evolving treatment landscape, CD38 antibody exposure increased from 4.4% to 25.6% across the two cohorts. Built on 24 laboratory indicators, the unsupervised dMIS independently predicted PFS with favorable discrimination and calibration. Notably, it effectively restratified patients with high-risk cytogenetics. Its components are

routinely available, offering a practical risk tool for modern NDMM management. Prospective risk-adapted studies are warranted.

PA-029

Analysis of Autologous Stem Cell Storage Strategies in Multiple Myeloma From a Clinical and Economic Perspective: Is Stem Cell Collection for Two Transplants Necessary or a Waste of Resources?

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Introduction: Collecting sufficient peripheral blood stem cells for two transplantations prior to the initial autologous stem cell transplantation (ASCT) is a standard practice in multiple myeloma (MM) and aims to secure a backup product for salvage transplantation in the relapse setting. However, with the introduction of novel agents, the actual utilization of these "backup" cells is questionable. We analyze here the utilization rates of stored stem cells at our center. **Methods:** A retrospective analysis was conducted on 99 MM patients who underwent ASCT and were followed up at our institution. There were two cohorts: Cohort 1 comprised 46 patients of whom stem cells were collected for two transplants prior to the initial ASCT. Cohort 2 included 43 patients who underwent stem cell mobilization for salvage ASCT at relapse. For Cohort 1, total cryopreservation bag counts, dimethyl sulfoxide (DMSO) volumes, subsequent transplantation statuses, and timing of relapse (early: < 3 months; late: 18–36 months) were recorded. **Results:** In Cohort 1 (n = 46), the backup stem cells have remained unutilized in 43 patients (93.5%), with an actual second transplantation rate of merely 6.5% (n = 3). A total of 378 cellular products were harvested (median collection duration: 2 days, range: 1–5), of which 162 bags (43%) remain idle in long-term storage. Due to suboptimal initial yields, 13 patients required a second mobilization session. Within the non-transplanted subgroup of Cohort 1, 20% (n = 9) experienced aggressive disease relapse rendering their stored cells obsolete. Cumulatively, approximately 632.4 mL of DMSO remains stored within these unutilized bags.
In Cohort 2 (n = 43), mobilization failure occurred in only two patients. Remarkably, 11 of successfully mobilized patients had been on long-term (22–146 months) lenalidomide maintenance. The median interval between the first and second transplantations was 53 months (range: 21–172). **Conclusions:** Our institutional data reveal a stem cell utilization rate significantly below the 15–25% threshold reported in the literature, confirming that routine, upfront "two-transplant" collection has lost its clinical relevance in the era of modern MM therapies. The role of the salvage ASCT is altered in the current era. The risk of cell obsolescence is particularly pronounced in patients experiencing early relapse or progression within 36 months under lenalidomide maintenance. Furthermore, upfront dual-collection frequently extends apheresis protocols up to 5 days. Conversely successful mobilization could be safely performed at the time of relapse even after prolonged exposure to lenalidomide and daratumumab. Prolonged storage of unutilized cells inflicts a severe economic burden and creates significant laboratory workload. While utilizing these idle products in cellular therapy settings is important we conclude that stem cell collection goals must be strictly individualized based on patient risks and the available treatment options.

PA-030

Analysis of Cell Free DNA in Monoclonal Gammopathy of Renal Significance Reveals Rare Somatic Variants and Candidate Driver Mutations

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Introduction: In most cases of monoclonal gammopathy of renal significance (MGRS), bone marrow sampling is morphologically normal. The genomic underpinnings of MGRS are therefore largely unexplored. In this pilot study, we present an initial characterization of somatic mutations via whole exome sequencing (WES) of cell free DNA (cfDNA) in this rare disease. **Methods:** A total of 100GB of cfDNA across 10 peripheral blood samples taken at the time of diagnosis was used for WES. Pooled libraries were sequenced to an average depth > 100x. Somatic single-nucleotide variants (SNVs) and short insertions/deletions (indels) were called using GATK Mutect2. Genotype calls were retained only if total read depth (DP) $\geq$ 5, alternate-allele supporting reads > 3, and clonal variant allele fraction (VAF) $\geq$ 0.05. Each variant was assigned a population rarity tier based on its maximum AF across all annotation sources. A stringent ultra-rare tier (AF < 1 × 10-5) was used to identify novel candidate driver mutations, which have a probability of recurring in two unrelated individuals on the order of 10-9. Gene ontology (GO) analysis was undertaken and a panel of 62 MGRS-relevant genes assembled from GO, KEGG, and reactome pathway to explore possible relevance to known pathogenic processes. **Results:** Proliferative GN with monoclonal immune deposits was the most common presenting histology (6/10) and five pts (50%) harbored monoclonal protein in the serum. Detailed clinical data will be presented. WES identified 153 mutations with a population allele frequency between 0.001–0.01%. The majority (94%) represented missense mutations, with the remaining mutations representing stop gained mutations. Among these rare variants, 24 were present in the cfDNA of greater than one patient with 17 projected to carry either high or moderate impact on protein function.

The most commonly shared rare mutations among MGRS pts included SPANXB1 (50%), KRTAP10-4 (40%), FMO2 (30%), DUSP5 (30%), ANKRD35 (30%), and FDXR (30%). A full list of SNV and indels in our analysis will be presented. Gene ontogeny analysis against a top common gene set and a full gene set revealed enrichment in cellular components including the Golgi lumen ($p < 0.001$), luminal components of other luminal organelles ($p < 0.001$), and neuron projection ($p < 0.01$) among several others. Analysis across 62 genes involved in known MGRS related pathways including the B-cell/plasma cell clonal identity, the complement pathway, and podocyte function revealed SNVs in NPH52, TP53, LMX1B (2 pts), C9, and CST3. Germline sequencing, CNV analysis, mutational signatures, sequencing of renal cell DNA, as we all as further analysis of genomic feature distribution are underway. **Conclusions:** The results of this analysis suggest that rare somatic variants may cluster in higher than expected rates in MGRS patients and may play a significant role in disease pathogenesis. Mutations in genes relevant to know pathogenic processes in MGRS are detectable and may aid in future biomarker development.

PA-031

Analysis of Subsequent T-Cell–Redirecting Therapies (TCRTs) After Treatment with Belantamab Mafodotin in DREAMM-7 (D7) and DREAMM-8 (D8)

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Introduction: Targeting BCMA has transformed the relapsed/refractory multiple myeloma (RRMM) treatment landscape, raising questions about optimal treatment sequencing. Resistance mechanisms (eg, antigen loss, T-cell exhaustion) may limit effectiveness of sequential anti-BCMA agents such as bispecific antibodies and chimeric antigen receptor T-cell therapies. Belantamab mafodotin (belamaf), a BCMA-directed antibody-drug conjugate, does not rely on continuous T-cell engagement and exhibits minimal immunosuppressive effects. In translational studies of patients (pts) treated with belamaf, soluble BCMA levels returned to near baseline at time of progression, with no evidence of T-cell exhaustion or impact on the binding epitope observed, supporting sequencing TCRTs after belamaf. Belamaf combinations in pts with RRMM after ≥1 prior line of therapy demonstrated significant progression-free survival (D7: NCT04246047; D8: NCT04484623) and overall survival benefits (D7) vs standard of care, including an anti-CD38 regimen in D7. This analysis aims to evaluate efficacy of TCRTs after belamaf in D7 and D8. **Methods:** Pts in D7/D8 who received belamaf and ≥1 subsequent TCRT at data cutoff (D7: Jan 9, 2026; D8: July 7, 2025) are included in this post hoc analysis. Time from end of belamaf to start of subsequent TCRT; time from TCRT initiation to progression or death on TCRT treatment line, or until initiation of a subsequent therapy; and investigator-reported best response were assessed. Descriptive statistics were used to summarize results. **Results:** A total of 21 pts (D7, n = 9; D8, n = 12) received subsequent TCRTs at any point after belamaf. Median time from end of belamaf to start of first subsequent TCRT was 84.1 wk (range, 14.4–144.0) in D7 and 88.7 wk (range, 32.7–168.1) in D8 (pooled, 84.1 wk [range, 14.4–168.1]). Median time to disease progression or death in pts who received subsequent TCRT was not reached (NR) in D7 and 6.6 mo in D8 (95% CI, 1.5-NR). Although sample size was limited, deep responses occurred in pts who received TCRTs post belamaf, including those who received TCRTs directly after belamaf. Among pts with available data at data cutoff (D7, n = 8; D8, n = 5), nearly all responded to subsequent TCRTs (12/13 pts [92%]; 8/8 pts in D7 and 4/5 pts in D8). Very good partial response or better (≥ VGPR) was seen in 7/8 and 2/5 pts, and a complete response or better in 4/8 and 2/5 pts, respectively. Among evaluable pts, 4/8 in D7 and 1/5 in D8 progressed on belamaf; all responded to subsequent TCRT: D7, 1 partial response (PR) and 3 ≥ VGPR; D8, 1 PR. Four pts (2 per study) received TCRT immediately after belamaf; all of the evaluable patients (n = 3) responded, including 2 with deep responses. At data cutoff, 5/9 pts in D7 and 6/12 pts in D8 remained on TCRTs. **Conclusions:** Pts who received TCRTs after belamaf achieved deep responses, supporting sequencing belamaf ahead of TCRTs. Ongoing follow-up will allow analysis of longer-term clinical outcomes. **Sponsorship:** GSK (study IDs 207503, 207499).

PA-032

Anti CD38 Re-Treatment Is Effective After an Adequate Wash-Out Period. Updated Data on the DART4MM Phase 2 Trial on Relapsed Patients

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Introduction: The DART4MM trial is a multicenter phase 2 study in which Daratumumab single agent was used up to 24 months (December 2018–March 2022) in a selected population of 50 MM patients already in >VGPR but MRD positive with NGF measured at 10-6. MRD negativity was achieved in 30% of patients and maintained after 24 months of Daratumumab for a median of 45 months. Data are scarce on anti CD38 retreatment after initial use and some suggest that a wash out period (6 to 12 months) could be essential to achieve response again. We present here data on 11 patients who relapsed in the DART4MM study and were treated with Daratumumab again after a wash out period. **Methods:** Data were collected at diagnosis, during the study and at follow up for all patients treated in the DART4MM. Clinical data and genetic data were already available (Date of birth, date of diagnosis, Stage, Immunochemical MM type, FISH on selected plasmacells. Date of first and last Daratumumab in the DART4MM were registered as well as date of relapse, PFS1, new treatment schedule, PFS2 after a new treatment, best response and second relapse date, wash out period was also calculated from last Daratumumab dose and the new anti CD38 treatment. NGF according to Euroflow protocol was evaluated during the DART4MM study and available at relapse. CD38 espression was also available during all study at time 0,6,12,18,24 months and at relapse. **Results:** 11 patients (6M/5F) relapsed and were followed. Median age at relapse was 70 (range 62–76). Immunotype was IgG/k (7) IIgG lambda (1), IgA /lambda (1), K (1) Lambda(1) Relapse was registered after a median of 33 (18–57) months from last daratumumab dose (wash out period). 10/11 patients were treated with DAraRd, 1 patient received IsaKd. All patients except for one achieved a CR (11 CR, 1 MR). 2/11 patients had a second relapse at 3 and 30 months. Median PFS2 is not reached at 9 months median follow up (3–40). Longitudinal NGF will be reported with CD38 espression on plasmacells to correlate espression with new response or relapse. **Conclusions:** Anti CD38 retreatment is feasible and responses seem of high quality after a wash out period. These data could be informative in real life since maintanance treatment with Daratumumab is approved and it could be stopped after 24 months if the patient achieve MRD negativity as per Perseus protocol. Patient could stop the treatment and be eventually retreated at relapse (or MRD relapse) with the same drug, saving toxicity and money for the community. More work is needed to determine if CD38 espression has a role in determining a new response to anti CD38 retreatment.

PA-033

Anti–B-Cell Maturation Antigen Dual-Epitope Chimeric Antigen Receptor Marrow-Infiltrating Lymphocytes for Multiple Myeloma

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Introduction: BCMA-directed CAR-T therapy has shown substantial clinical activity in relapsed or refractory multiple myeloma (RRMM), but limited durability and relapse due to antigen loss or downregulation remain major challenges. Marrow-infiltrating lymphocytes (MILs), bone marrow–derived T cells enriched for central memory phenotypes and intrinsic myeloma reactivity, may provide an alternative cellular platform. We generated dual-epitope camelid single-domain antibody–based BCMA CAR-MILs. **Methods:** BCMA CAR-MILs were engineered from autologous MILs and evaluated for phenotype, antimyeloma activity, tissue trafficking, persistence, and safety. In vitro cytotoxicity was tested against BCMA-expressing MM cell lines, including RPMI8226 and U266, and autologous primary CD138-positive myeloma cells. In vivo efficacy was assessed in multiple MM xenograft models and compared with conventional BCMA CAR-T cells. Dose-escalation safety was evaluated in a systemic MM.1S model. **Results:** BCMA CAR-MILs were enriched for CD8-positive central memory T cells and showed potent antimyeloma activity in vitro, eliminating BCMA-positive MM cell lines and autologous CD138-positive myeloma cells. These findings suggest tumor killing through both CAR-dependent BCMA recognition and endogenous T-cell receptor–mediated recognition of myeloma-associated antigens. In xenograft models, BCMA CAR-MILs demonstrated superior antitumor efficacy compared with conventional BCMA CAR-T cells, with enhanced tumor control, broad tissue trafficking, sustained persistence, and preservation of memory-associated functions. BCMA CAR-positive CD8 T cells preferentially expanded or differentiated at sites of myeloma involvement. In dose-escalation studies, BCMA CAR-MILs were generally well tolerated from 0.1 to 5.0×10^6 cells/mouse, with no significant bodyweight loss, paralysis, or overt toxicity. **Conclusions:** Dual-epitope BCMA CAR-MILs combine BCMA-specific CAR activity with the memory-rich and tumor-reactive properties of marrow-derived T cells. This strategy may improve persistence, broaden antitumor recognition, and reduce vulnerability to antigen escape, supporting further clinical-enabling development toward first-in-human investigation.

PA-034

Anti-BCMA Immunotherapies Deplete Plasmacytoid Dendritic Cells and Impair Antiviral Immunity in Multiple Myeloma

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Introduction: Infections remain a crucial toxicity of anti-BCMA therapies in MM. Many infections are viral, and breakthrough infections remain common despite prophylaxis, highlighting the role of mechanisms beyond B cell depletion potentially contributing to viral susceptibility. **Methods:** BCMA mRNA and protein expression were assessed in healthy donor (HD) scRNAseq data (Broad Institute, N = 8; Erasmus MC, N = 5) and MM bone marrow (BM) samples (N = 15) using spectral cytometry. pDCs, mDCs, and B cells were assessed by spectral cytometry in 373 PB and BM samples from 57 MM patients treated with anti-BCMA/GPRC5D bsAbs - teclistamab (tec), elranatamab (elra), talquetamab (tal) (N = 44), or cilta-cel (N = 13). PB samples were analyzed longitudinally at D0, 7, 14, 21, 30, 60, 90, 180, 270, and 360. BM samples were evaluated at baseline and at MRD timepoint. For validation a functional in vitro assay was performed; IFN-α, IFNγ, and TNF-α levels were measured by ELISA in PBMC culture supernatants from MM patients (N = 13) treated with tec or tal following CpG-A stimulation mimicking viral encounter. **Results:** BCMA gene expression was detected in pDCs from HDs at levels comparable to B cells, whereas BCMA in mDCs and GPRC5D in both pDCs and mDCs was negligible. Spectral cytometry confirmed BCMA expression on pDCs in MM patients. Next, effect of anti-BCMA bsAbs on DC subsets was analyzed in 257 PB samples from 44 MM patients treated with bsAbs (tec/elra vs tal). pDC levels declined rapidly at D7 in the BCMA vs GPRC5D group ($p = 0.011$), followed by complete depletion at D14 persisting till D360 ($p < 0.001$–0.008). In contrast, analysis of CD1c+ mDCs showed no reduction at any timepoint (all $p > 0.112$). B cell kinetics was identical to pDCs. To assess whether pDC depletion is a shared feature of anti-BCMA therapies, 100 PB samples from 13 MM patients treated with cilta-cel CAR-T product were analyzed. pDC decreased at D7 ($p = 0.039$), and became undetectable up to D30. Recovery was observed from D60 ($p = 0.009$), becoming more evident at D90 ($p = 0.001$). mDCs were not depleted at any timepoint. B-cell kinetics followed pDC pattern. Furthermore, analysis of BM samples from patients treated with tec vs tal demonstrated pDC depletion in patients treated with tec (in contrast to tal) also in BM at MRD, while mDCs remained detectable in both groups. As a validation, levels of IFN-α, and IFN-γ, TNF-α (controls) were measured in supernatants following in vitro culture of mononuclear cells of 13 MM patients treated with tec and tal, with or without (control) CpG-A oligonucleotide, a potent TLR9 agonist. Stimulation led to a robust IFN-α production in GPRC5D group, whereas production was lacking in BCMA ($p = 0.016$). Levels of IFN-γ and TNF-α were unchanged between groups and stimulation conditions. **Conclusions:** This study describes pDC depletion and associated IFN-α production impairment as a mechanism potentially contributing to impaired antiviral immunity in patients treated with anti-BCMA therapy. **Introduction:** Infections remain a crucial toxicity of anti-BCMA therapies in MM. Many infections are viral, and breakthrough infections remain common despite prophylaxis, highlighting the role of mechanisms beyond B cell depletion potentially contributing to viral susceptibility. **Methods:** BCMA mRNA and protein expression were assessed in healthy donor (HD) scRNAseq data (Broad Institute, N = 8; Erasmus MC, N = 5) and MM bone marrow (BM) samples (N = 15) using spectral cytometry. pDCs, mDCs, and B cells were assessed by spectral cytometry in 373 PB and BM samples from 57 MM patients treated with anti-BCMA/GPRC5D bsAbs - teclistamab (tec), elranatamab (elra), talquetamab (tal) (N = 44), or cilta-cel (N = 13). PB samples were analyzed longitudinally at D0, 7, 14, 21, 30, 60, 90, 180, 270, and 360. BM samples were evaluated at baseline and at MRD timepoint. For validation a functional in vitro assay was performed; IFN-α, IFNγ, and TNF-α levels were measured by ELISA in PBMC culture supernatants from MM patients (N = 13) treated with tec or tal following CpG-A stimulation mimicking viral encounter. **Results:** BCMA gene expression was detected in pDCs from HDs at levels comparable to B cells, whereas BCMA in mDCs and GPRC5D in both pDCs and mDCs was negligible. Spectral cytometry confirmed BCMA expression on pDCs in MM patients.

PA-035

APOBEC3B Promotes Mitochondrial and Inflammatory Adaptation Underlying Proteasome Inhibitor Resistance in Multiple Myeloma

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Introduction: Multiple myeloma (MM) remains incurable despite significant therapeutic advances. Relapsed and refractory disease continues to represent a major clinical challenge, highlighting the need to identify mechanisms that promote disease progression and treatment failure. APOBEC3B (A3B), a cytidine deaminase associated with genomic instability and poor-risk MM biology, may have functions beyond mutagenesis. Because proteasome inhibition imposes substantial proteotoxic and energetic stress, we hypothesized that A3B promotes mitochondrial fitness and metabolic adaptation during bortezomib (BTZ) treatment. We therefore investigated the role of A3B in regulating mitochondrial metabolism, stress tolerance, and therapeutic response in MM. **Methods:** A3B KO and OE models were established in NCI-H929 and OPM2 MM cell lines. Functional studies assessed mitochondrial metabolism, DNA damage signaling, genomic instability, therapeutic response, and drug synergy using Seahorse analysis, immunoblotting, qRT-PCR, viability assays, and Bliss synergy analysis. Clinical associations were evaluated in the MMRF CoMMpass cohort (RNA-seq, n = 921; WGS, n = 700). A3B expression was correlated with overall survival using Kaplan–Meier and Cox regression analyses in bortezomib-treated patients, including those with follow-up BM_CD138pos samples (visit 2/3).

Results: Under bortezomib treatment, A3B-high cells showed increased mitochondrial respiration, including 1.7-fold higher basal respiration, 1.9-fold higher maximal respiration, and 1.2-fold higher spare respiratory capacity compared with A3B-low cells (all $p < 0.05$), consistent with enhanced OXPHOS adaptation. A3B loss enhanced sensitivity to BTZ/metformin, which was included as a mechanistic probe of mitochondrial metabolism, increasing Bliss synergy scores from 3.31 in parental cells to 6.78 in A3B-KO cells. However, APOBEC3B status did not substantially alter bortezomib IC50 values. A3B overexpression increased basal and BTZ-induced γH2AX signaling ($p < 0.05$) in MM cell lines and altered expression of metabolic and stress-associated genes, including APOBEC3A, FGFR3, CCND2, PPARGC1A, and TNFRSF10D ($P < 0.05$). A3B loss did not significantly alter canonical CNV-filtered sister chromatid exchange burden ($p = 0.29$) in MM cells. Consistent with patient transcriptomic findings, A3B depletion reduced IL-10 ($P < 0.05$), intracellular IL-6 ($P < 0.05$), and MIP-1α/CCL3 ($P < 0.01$) levels in MM cells. Among bortezomib-treated patients with available follow-up BM_CD138pos samples (visit 2/3; n = 40), high A3B expression was associated with significantly inferior overall survival (HR = 2.57, 95% CI 1.03–6.38, $p = 0.042$), supporting a role for A3B in therapeutic resistance. **Conclusions:** A3B promotes BTZ resistance through mitochondrial metabolic adaptation rather than increased sister chromatid exchange. These findings identify a novel role for APOBEC3B in MM and suggest that A3B-high disease may be vulnerable to OXPHOS-targeting therapies, including metformin-based combinations.

PA-036

Aponermin Combined with Carfilzomib, Pomalidomide, and Dexamethasone in RRMM Patients Relapsing After CAR-T or BiTE Therapy: A Subgroup Analysis of a Prospective, Single-Arm, Multicenter Trial

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Introduction: CAR-T and BiTE therapies are major breakthroughs for relapsed/refractory multiple myeloma (RRMM), but many patients still relapse. Salvage options after CAR-T failure typically yield an overall response rate (ORR) below 50% or are associated with severe toxicity. Aponermin (Apo), a recombinant circularly permuted human TRAIL, is a first-in-class death receptor 4/5 agonist approved for RRMM. This subgroup analysis of a prospective, single-arm, multicenter trial (ChiCTR2500107812) evaluated the efficacy and safety of Apo plus carfilzomib(K), pomalidomide(P), and dexamethasone(d) (Apo+KPd) in RRMM patients who relapsed after prior CAR-T or BiTE therapy. **Methods:** Eligible pts had received at least 3 prior lines of therapy or were triple-class exposed (PIs, IMIDs, and CD38), with measurable disease and adequate organ function. The regimen consisted of 28-day cycles: Apo 10 mg/kg on days 1–5,K 20 mg/m^2 on days 1–2 of cycle 1, then 27 mg/m^2 on days 1–2, 8–9, and 15–16,P 4 mg daily on days 1–21, and d 20 mg on days 1–2, 8–9, and 15–16. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was ORR per IMWG criteria. This analysis included pts who had relapsed after prior CAR-T or BiTE therapy. **Results:** Thirteen pts were included in this subgroup analysis. Among them, 83.3% (11/13) were aged ≥60 years, with a median disease duration of 5.2 years (range, 1.4–11.4). Durie-Salmon stage III disease was present in at least 69.2% (9/13, 3 missing data), and high-risk cytogenetics in at least 53.8% (7/13, 2 missing data), p53 deletion/mutation was observed in 30.8% (4/13), and double-hit or triple-hit abnormalities (involving 1q21 gain/1p32 deletion, p53 deletion/mutation, and/or del[13q]) in 30.8% (4/13). Extramedullary disease was noted in 84.6% (11/13): extraosseous in 7 pts, paraosseous in 4. Median prior lines of therapy was 4 (range, 3–7). Triple-class exposure was documented in 92.3% (12/13), 11 pts had prior exposure to K and/or P, 7 pts had received at least two prior CAR-T therapies, and 4 had received prior BiTE therapy. As of May 17, 2026, the median number of treatment cycles was 4 (range, 1–21). Among the 12 evaluable pts, the ORR was 69.3% (9/12), and median PFS was 4.3 months. In pts with extraosseous extramedullary disease, ORR was 71.4% (5/7), in those with paraosseous only, ORR was 75.0% (3/4). Among pts previously exposed to K and/or P, ORR was 72.7% (8/11). Any-grade adverse events(AE) occurred in 69.2% (9/13), and grade 3–4 AE in 23.1% (3/13), including hypertension, leukopenia, thrombocytopenia, neutropenia, respiratory viral infection, and tumor lysis syndrome. All events resolved with supportive care. **Conclusions:** The Apo+KPd regimen demonstrated substantial efficacy (ORR 69.3%) with a manageable safety profile in this subgroup who relapsed after CAR-T or BiTE therapy. These results support Apo+KPd as an effective salvage option for immunotherapy refractory relapses, warranting further validation.

PA-037

Aponermin+KT-DECP, a Good Bridging Regimen for Relapsed/Refractory Multiple Myeloma with Extramedullary Disease

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Introduction: Background and Aims : The survival of Relapsed/refractory multiple myeloma (RRMM) with Extramedullary Disease (EMD) was still poor (3-year OS: 58%), causing of bad efficacy of EMD. Aponermin (Apo), the first approved DR4/DR5 agonist, triggers the extrinsic apoptotic pathway through caspase cascade activation, showed some objective response rate(ORR) in patients (pts) with EMD. This study was to evaluate the efficacy and safety of Apo+KT-DECP* regimen in pts of RRMM and EMD. **Methods:** Methods: This multicenter, single-arm, phase 2 study (NCT05013190) aimed to enroll 31 pts with EMD-confirmed RRMM according to IMWG criteria. Patients received Apo-KT-DECP regimen*at least 4–6 cycles; and adding radiotherapy when efficacy less than complete remission (CR). The primary endpoint was overall response rate (ORR) after two cycles treatment. Key secondary endpoints including CR, very good partial remission (VGPR), Time to response (TOR), Progression-Free Survival (PFS) and safety. Clinical trial information: NCT05013190 *Apo-KT-DECP: Apo 10 mg/kg, days 1–3 and 15–18; carfilzomib: 27 mg/m^2, days 1–2, 8–9, 15–16; thalidomide: 100 mg, days 1–10 and 15–24; cisplatin, etoposide, cyclophosphamide, and dexamethasone at protocol-specified doses. **Results:** Results: 31 pts have been enrolled in this study, median age was 60 years, male was 41.9%, median prior lines of therapy was 2(range:1–9), 29.0% of pts with EMD≥3(1–7), 32.3% of pts with bone-independent and paraskeletal mass together, 25.8% of pts with big EMD(diameter≥5 cm), high-risk cytogenetics was 29.0%, EMD of 3 pts with blast-type plasma cell, 2 pts with malignant pleural effusion, 3 triple-class refractory (TCR) was 38.7%, and no BCMA exposure pts. By the data cutoff, 67.7%(21/31) of pts entered to maintenance. Median follow-up of 8 months, median PFS were not reached, 6-month and 12-month PFS rate was 75.9% and 45.0%, respectively. ORR of 2-cycle was 86.2% (25/29), much better than the efficacy of DECP in 20 pts with EMD(ORR 55%) that published in 2014(National Medical Journal of China). The best response included 25% of pts achieving ≥VGPR (20.4% achieving ≥CR, 2 pts with radiotherapy). In this study, 71.0% (22/31) of patients experienced adverse events (AEs) of any grade. The most common AEs were anemia (71.0%), thrombocytopenia (67.7%), infection (61.3%), and leukopenia (61.3%). The most frequent Grade 3/4 adverse events were leukopenia (35.4%), infection (35.4%), and thrombocytopenia (32.3%). **Conclusions:** Conclusion : Our study demonstrates that PFS prolonged obviously with less toxicity in RRMM with EMD. ORR of 2-cycle was 86.2%, could be a good choice as bridging regimen.

PA-038

Assessing the Prognostic Relevance of Hematologic Response for Outcomes in Patients with Newly Diagnosed AL Amyloidosis: Analysis from a Retrospective Study Conducted at a Tertiary Cancer Center

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Introduction: Light Chain (AL) amyloidosis is the most common form of systemic amyloidosis, characterized by the deposition of misfolded monoclonal light chains or their fragments in tissues, leading to progressive organ dysfunction. Multiple cohort studies and meta-analyses showed that patients who attain VGPR/CR (and especially deep rapid responses) have higher rates of subsequent cardiac and renal organ responses and longer survival. **Methods:** We conducted a retrospective observational study of patients diagnosed with AL amyloidosis at our institution between January 2013 and April 2025. Demographic details, clinical features, treatment regimens, and outcomes were extracted from electronic medical records and analysed. We specifically analyzed the relationship between hematologic response and survival outcomes in our cohort of patients with AL amyloidosis. **Results:** A total of 93 patients were included. The median age at diagnosis was 60 years (range: 29–85), with 68.8% (n = 64) being male. Renal involvement was the most common (71%), followed by cardiac involvement (63.4%). VCD-based induction therapy was administered to 53.8% (n = 50) of patients; only 2.1% (n = 2) received Daratumumab-VCD, and ASCT was performed in 6.4% (n = 6). Haematological outcomes available in post-induction were observed in 89.6%, with complete response (CR) in 24.1%, very good partial response (VGPR) in 41.4%, and partial response (PR) in 24.1%. At a median follow-up of 18 months (range: 4–145), the 24-month progression-free survival (PFS) was 58% (95% CI: 45%–71%), while the 24-month and 60-month overall survival (OS) rates were 72% (95% CI: 62%–82%) and 59% (95% CI: 48%–70%), respectively. Data for hematological response were available in 49 (52.68%) patients. Median PFS was not reached for patients having response (PR, VGPR, CR) post induction whereas it is 6 months (Range 1–18 months, 95% CI) (P value 0.001). Median overall survival was not reached for patients who have at least some response post induction (PR, VGPR, CR) whereas median overall survival was 31 months (95% CI, 14.6–47.3 months) for patients who did not have a response (P value 0.013). On univariate and

multivariate analyses, renal involvement (HR: 3.85; 95% CI: 1.14–12.93; P = 0.029) and lack of haematological response post-induction (HR: 4.2; 95% CI: 1.2–14.92; P = 0.022) were associated with inferior outcomes for survival. **Conclusions:** In this study hematologic response emerged as a strong and independent predictor of survival outcomes. Patients achieving post-induction hematologic response (PR, VGPR, or CR) demonstrated significantly superior progression-free and overall survival compared with non-responders. These findings reinforce the prognostic relevance of early and deep hematologic response in AL amyloidosis and underscore the importance of optimizing treatment strategies to achieve rapid light chain suppression.

PA-039

Association Between Progression-Free Survival (PFS) and Overall Survival (OS) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Receiving 2–4 Lines of Therapy: A Real-World Perspective

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Introduction: Advances in MM therapies have improved OS; however, mature OS data are often unavailable at early trial readouts, making PFS a key early indicator of treatment efficacy for regulatory approvals. While previous research has examined the relationship between PFS and OS in patients (pts) with RRMM using data from clinical trials, this relationship has not been evaluated by line of therapy (LOT) or prior therapy exposure. This study aims to evaluate the quantitative relationship between PFS and OS in pts with RRMM across 2–4 LOT, utilizing real-world (RW) data. **Methods:** This retrospective study used two databases: (1) the US-based Flatiron Health electronic health record database (January 1, 2011–December 31, 2025) and (2) the multinational PREAMBLE registry (US, Canada, EU; January 1, 2012–September 30, 2025). Analyses were conducted separately within each database. MM pts receiving 2–4 LOT were included, with the initiation date of each LOT as index. PFS was defined as time from index date to disease progression, start of a subsequent LOT, or death, whichever occurred first. Kaplan-Meier analyses estimated median PFS and OS. PFS-OS associations within each LOT were evaluated using Spearman's rank correlation coefficient (ρ) and a weighted least squares (WLS) regression. Landmark analysis with Cox regression assessed the relationship between progression and OS at 3, 6, 9, and 12 months (mo). Both WLS regression and landmark analysis were adjusted for baseline covariates. Subgroup analyses were conducted among (1) anti-CD38 naive, and (2) lenalidomide (len)-exposed pts. Statistical significance was defined as a p-value < 0.05. **Results:** In the Flatiron database, 3,198 second-line (2L), 2,746 third-line (3L), and 1,668 fourth-line (4L) pts were included. Median age was 72 years across all three cohorts. Median PFS/OS was 10.6/47.7 mo for 2L, 7.8/36.5 mo for 3L, and 6.5/29.1 mo for 4L.

Spearman's ρ between PFS and OS were 0.55 for 2L and 0.57 for both 3L and 4L (all P < 0.0001). The WLS regression weighted R^2 values were 0.90 (2L), 0.91 (3L), and 0.93 (4L) (all P < 0.0001). Across LOT, landmark analyses showed statistically significant associations between progression and OS at 3, 6, 9, and 12 mo (adjusted hazard ratios: 1.65–1.92). Subgroup analyses among pts who were anti-CD38-naive or len-exposed showed consistent PFS-OS associations across LOT.

Similar findings were observed in the PREAMBLE registry (1,173 [2L], 1,009 [3L], and 661 [4L] pts) across LOT and by subgroups. Across LOT, the Spearman's ρ of 0.52 (2L), 0.63 (3L), and 0.58 (4L) (all P < 0.0001) and the WLS regression weighted R^2 values of 0.69 (2L), 0.94 (3L), and 0.85 (4L) (all P < 0.0001). **Conclusions:** Consistent findings across two independent RW databases confirm the association between PFS and OS in pts with RRMM receiving 2–4 LOT. In the absence of mature OS data, PFS serves as a reliable early indicator of treatment efficacy to inform healthcare policy and decision-making.

PA-040

Association Between Statin Use and Survival in Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: Multiple myeloma (MM) remains an incurable plasma cell malignancy despite major therapeutic advances, with most patients eventually relapsing. Identifying safe, widely available adjunctive strategies that may improve survival is therefore clinically important. Statins inhibit the mevalonate pathway and downstream protein prenylation required for oncogenic Ras signaling and NF-κB activation, mechanisms implicated in myeloma proliferation and therapeutic resistance. Several population-based studies have suggested improved outcomes among statin users with MM, but the magnitude and consistency of this association remain uncertain. **Methods:** A PRISMA-compliant systematic review and meta-analysis of observational cohorts was performed. Adjusted hazard ratios (HRs) were pooled using a random-effects inverse-variance model. Primary outcome was all-cause mortality; secondary outcome was MM-specific mortality. **Results:** Four population-based cohorts comprising 21,129 patients were included. Statin exposure was associated with significantly improved overall survival (pooled HR 0.82, 95%

CI 0.76–0.89; $I^2 = 72.3\%$), corresponding to an 17% relative reduction in mortality. Two studies reporting MM-specific mortality demonstrated a consistent 25% relative reduction (HR 0.75, 95% CI 0.68–0.84; $I^2 = 0\%$). Sensitivity analyses restricted to time-varying exposure models demonstrated consistent findings pooled hazard ratio of 0.85 (95% CI 0.74–0.98; $p = 0.023$; $I^2 = 84.7\%$), supporting robustness of the observed association with directionally concordant effects across diverse healthcare systems. **Conclusions:** Across large population-based cohorts, statin exposure was consistently associated with improved overall and disease-specific survival in MM. Given their favorable safety profile, affordability, and mechanistic relevance to myeloma biology, statins represent a promising adjunctive strategy in MM management. Prospective studies are warranted to determine whether this association reflects a true disease-modifying effect.

PA-041

Atrial Fibrillation in Multiple Myeloma: High Prevalence, Incidence and Impact on Survival. A Population-Based Study on 8,672 Patients Diagnosed 2008–2021 from the Swedish Myeloma Registry

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Introduction: Multiple myeloma (MM) is a hematological malignancy among adults with a median age at diagnosis of 72 years in the Swedish Myeloma Registry (SMR). Consequently, cardiovascular comorbidity among MM patients is a concern. Current data on real-world MM patients' baseline cardiovascular disease (CVD) comorbidity are scarce. Using Swedish population-based registries, we aim to study CVD, especially atrial fibrillation (AF), at time of MM diagnosis, at 2 years follow-up and risk of death, in comparison with matched controls. **Methods:** All symptomatic MM patients in the SMR diagnosed 2008–2021 were included in the study. The controls were identified through the Swedish Total Population Registry, matched on sex, year of birth and county of residence. Data on CVD was collected using the International Classification of Diseases (ICD)-10 codes I00-I99 for all individuals, using the Swedish Patient Registry and the Cause of Death Registry. Differences in incidence between patients and controls were evaluated with chi-square tests. Differences in mortality were evaluated with Cox regression. Ethical consent was obtained from the Swedish Ethical Review Board. **Results:** Median age at time of MM diagnosis was 72 years, 57% were male. The patients were divided according to age at time of MM diagnosis; < 65 years: n = 2 273, 65–80 years: n = 4 590 and >80 years: n = 1 809. Median follow-up for patients was 3.1 years and 5.7 for controls. Within 5 years prior to MM diagnosis, 45.8% of the MM patients had a history of CVD compared to 35.7% of the controls ($p < 0.0001$). Following hypertension, the most frequent CVD was AF among both patients and controls, 11.1% vs 9.1%, $p < 0.0001$. Among patients >80 years, 64.7% presented with a CVD and 22% with AF at time of MM diagnosis. The highest incidence of AF, among MM patients, was seen within 3-month prior to and following MM diagnosis. During two first years of follow-up, 17.7% among patients vs 8.5% among controls, $p < 0.0001$, had an AF diagnosis. The occurrence of AF in patients >80 years was substantial, 30.1%, vs 17.7%, $p < 0.0001$. The risk of mortality was increased for patients diagnosed with AF within 2 years following MM diagnosis vs patients without AF, HR 1.18 (95% CI 1.03–1.35, $p < 0.05$). **Conclusions:** In the era of combination therapy with steroids, proteasome inhibitors and/or lenalidomide; 11% of MM patients had a history of AF at time of MM diagnosis, with a steep increase the adjacent 3 months prior and following MM diagnosis vs controls. Among patients >80 years, 30% had a registered AF diagnosis at 2 years follow-up. Notably, patients alive at 2 years follow-up with AF, demonstrated inferior survival vs patients without an AF diagnosis. Future real-world data on AF and CVD following modern MM therapies are warranted to improve outcome in these patients.

PA-042

Automated Identification of Extramedullary Multiple Myeloma from PET/CT Reports Using Large Language Models

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Introduction: True extramedullary myeloma (EMM), defined as myeloma infiltration of tissues or organs anatomically separate from bone, is an aggressive disease manifestation associated with poor prognosis. Large-scale identification of EMM from radiology archives is challenging because it requires review of unstructured free-text reports. **Methods:** We developed an LLM-based pipeline to classify Hebrew free-text 18F-FDG PET/CT reports from patients with active multiple myeloma at a single academic center. Five prompt strategies were tested on a 93-report consensus-labeled development set. The selected pipeline was applied to 2,687 reports from 709 patients from 2013 to 2025. All predicted-positive reports were clinician-reviewed; a random sample of predicted-negative reports was reviewed to estimate recall. Performance was reported with 95% Wilson confidence intervals. **Results:** The pipeline classified 283 reports as EMM-positive. Expert review initially flagged 47 predicted-positive reports as discordant; joint re-review reclassified 14 as true

positives, leaving 250 true positives and 33 false positives. Precision was 88% (95% CI, 84 to 92%). Among 248 reviewed predicted-negative reports, 8 false negatives were identified, yielding estimated recall of 76% (95% CI, 63 to 86%). Estimated report-level prevalence of true EMM was 12.2%. Concurrent second malignancy was the dominant false-positive source, accounting for 19 of 33 confirmed errors. **Conclusions:** An LLM pipeline identified true EMM from a 12-year Hebrew PET/CT archive with 88% precision and 76% estimated recall. By identifying initially discordant cases in which joint expert review changed the reference label, the pipeline supports human-in-the-loop cohort construction rather than standalone automation in non-English clinical settings.

PA-043

Baseline CMV Viremia Predicts CMV Reactivation During CAR-T Cell and Bispecific Antibody Therapy in Multiple Myeloma

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Introduction: Cytomegalovirus reactivation (CMVr) is increasingly recognized during T-cell redirecting therapy for relapsed/refractory multiple myeloma (MM), but real-world data across CAR-T cells and bispecific antibodies (BsAbs) remain limited. We evaluated CMVr incidence, predictors, and outcomes in RRMM treated with CAR-T cells or BsAbs. **Methods:** We conducted a single-center retrospective study in 193 patients with multiple myeloma treated with CAR T-cells or BsAbs between 2018 and 2025. As some patients received more than one qualifying immunotherapy, 220 treatment lines were analyzed, with treatment line as the unit of analysis. Immunotherapy type (IT type) was defined as CAR-T cells or BsAbs. CMVr was defined as persistent/rising viremia in 2 consecutive samples during follow-up, and CMV disease as documented tissue involvement. Baseline CMV status was classified as no prior, negative/non-detectable, positive serology, or detectable baseline viremia; the latter was not counted as an endpoint unless it met criteria for CMVr/disease or prompted antiviral treatment. Associations were assessed using logistic regression with patient-level cluster-robust standard errors. Sensitivity analyses included restriction to the first immunotherapy line per patient, broader adjusted, and a binary baseline viremia model. **Results:** Median age was 63 years (38–88), and 54.4% were male, and median number of prior lines were 4 (RIQ3–5). Regarding IT type, 59.5% of treatment lines involved BsAbs and 40.5% CAR T-cells. CMVr occurred in 31/220 treatment lines (14.1%; 95% CI, 10.1–19.3) and in 30/193 patients (15.5%; 95% CI, 11.1–21.3). Median time to CMV viremia was 25 days (IQR, 9–56.5). CMV disease developed in 9/31 reactivating treatment lines (29.0%). IT type was not associated with CMVr (adjusted OR, 1.04; 95% CI, 0.37–2.88; p = 0.941), nor was BCMA targeting (adjusted OR, 1.46; 95% CI, 0.45–4.73; p = 0.524). Compared with tocilizumab/anakinra, steroid-containing treatment was not associated with CMVr (OR, 1.04; 95% CI, 0.39–2.79; p = 0.931), whereas no treatment/paracetamol was associated with lower odds (OR, 0.34; 95% CI, 0.12–0.94; p = 0.038). Detectable baseline viremia was the strongest predictor of CMVr (60.0% vs 10.7%; p < 0.001) and remained independently associated after adjustment for age and IT type (adjusted OR, 8.08; 95% CI, 2.33–28.02; p = 0.001). Sensitivity analyses were consistent: in first-line patient-level analysis, 29/193 developed CMVr (15.0%; 95% CI, 10.3–20.9); associations remained similar in first-line (aOR, 7.67; 95% CI, 1.97–29.83; p = 0.003), broader adjusted (aOR, 6.55; 95% CI, 1.93–22.21; p = 0.003), and binary baseline viremia models (aOR, 11.38; 95% CI, 3.80–34.06; p < 0.001). **Conclusions:** In MM treated with CAR-T cells or BsAbs, CMV reactivation is frequent, with nearly one-third of reactivating treatment lines developing CMV disease. Detectable baseline viremia identifies a high-risk subgroup and may guide surveillance and pre-emptive management.

PA-044

Baseline Immune Fitness Defines a Transcriptional Subtype of Multiple Myeloma with Exceptional Response to Daratumumab-Based Regimens in the GEM2017FIT Trial

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Introduction: Multiple myeloma (MM) is a heterogeneous plasma cell malignancy. Within the phase 3 GEM2017FIT trial, patients non-eligible for transplant were randomized to VMP+Rd or KRd ± Daratumumab as treatment regimens (Mateos MV et al, Lancet Haematol 2025 Aug;12(8):e588–e598). An integrative multiomics study was performed to elucidate new biomarkers at diagnosis as a primary objective. **Methods:** We analyzed CD138+ isolated cells from 109 baseline bone marrow aspirates from newly diagnosed MM patients for bulk RNASeq and Whole-Exome Sequencing (WES). 5 distinct transcriptional groups (A–E) were identified by non-negative matrix factorization (NMF) and characterized at genomic and functional levels. Clinical outcomes, including progression-free survival (PFS) and overall survival (OS), were evaluated. Findings were validated in an independent cohort (MMRF-CoMMpass, IA24) incorporating tumor microenvironment information. **Results:** The 5 transcriptional groups exhibited distinct molecular characteristics at functional and genomic level. Groups were characterized by specific mutations and cytogenetic alterations well-established in MM. Notably, patients in Group E (n = 18) treated with D-KRd achieved 100% PFS, suggesting a high sensitivity of those patients to Daratumumab-based regimens. Biologically, Group E was characterized by the upregulation of the protein translation machinery and energy-related pathways, alongside a significant downregulation of cytokine/chemokines signaling and immune activation pathways. To further explore this scenario and the potential link between these alterations and the favorable response to Daratumumab-based treatment, we recapitulated previously defined transcriptional groups in an independent cohort. The MMRF-CoMMpass (IA24) cohort (n = 258) confirmed these alterations not only in plasma cells but across the immune microenvironment cells. Specifically, Group E displayed significant downregulation in IFN-alpha and IFN-beta signaling in CD8+ T-cells. Together, these findings characterize Group E by a quiescent, stem-like immune profile— a known predictor of sustained efficacy in CAR-T therapy —which effectively bypasses the basal overactivation that typically drives premature T-cell exhaustion in other clinical contexts. These results suggest that Group E's superior response to Daratumumab is driven by a preserved "immune fitness" capable of triggering a robust and long-lasting anti-tumor response. **Conclusions:** We identified a transcriptional subtype of MM characterized by metabolic activation and protein translation machinery coupled with a downregulation of immune-related signaling in both plasma cells and the bone marrow microenvironment. Data from two independent cohorts suggest that this quiescent immune profile provides a unique therapeutic window, enabling a sustained anti-tumor response when treated with Daratumumab. These findings highlight the importance of baseline 'immune fitness' as a critical determinant of long-term success in Daratumumab-based regimens.

PA-045

BCMA Bispecific Antibodies in Relapsed AL Amyloidosis: A Retrospective Cohort Study

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Introduction: BCMA is overexpressed on the surface of clonal plasma cells in AL amyloidosis which yields a promising target for immunotherapy. Despite the significant progress in the treatment of AL amyloidosis with the introduction of Daratumumab to first-line therapy, relapsed or refractory disease remains an unmet medical need. Patients with this disease were excluded from the pivotal myeloma trials with BCMA bispecific antibodies (BSAbs) Teclistamab and Elranatamab, necessitating dedicated studies in this population. **Methods:** This was a dual-center, retrospective cohort study to evaluate the safety and efficacy of Teclistamab and Elranatamab in relapsed and refractory AL amyloidosis. Our database combines two quaternary health care systems that identified 20 patients who met the study inclusion parameters. The European modified Mayo 2004 staging system was used to characterize the disease stage of each patient. Adverse events were graded with the NCI CTCAE v5.0 except for CRS that was graded according to the 2019 ASTCT consensus criteria. **Results:** Twenty patients were evaluated in this study with 11 patients receiving Teclistamab and 9 receiving Elranatamab. All patients were previously exposed to anti-CD38 mAb with 7/20 receiving autologous SCT. The median duration of treatment was 5.6 months (0.0–30.9) with a median duration of response of 15.2 months (0.3–31.0). All patients achieved hematological complete response (hCR) with median times to first hematologic response and to hCR being 0.5 (0.2–0.9) and 0.7 (0.2–1.9) months, respectively. Five patients experienced over a year continued response after discontinuation of BCMA therapy. Fourteen patients in the cohort had cardiac amyloid involvement, with 9/14 having stage IIIA/B involvement. Out of the 14, 13 patients were able to have organ response assessed with 12/13 achieving response. The breakdown of cardiac response was 3 complete responses (CR), 5 very good partial responses (VGPR), and 4 partial responses (PR). Of the 8 patients with assessable renal responses, 7 experienced responses (1

CR, 2 VGPR, 4 PR). Median time to cardiac and renal response were 5 and 2 months, respectively. Five patients in the cohort were assessed for minimal residual disease (MRD) with 4 being MRD negative. Five patients experienced disease progression or death. Cytokine release syndrome was seen in 10/20 patients with the majority being grade 1 and 7/10 requiring tocilizumab. There were two reports of grade 3 neutropenia and 1 patient experienced grade 3 thrombocytopenia. Patients were given monthly IVIG prophylaxis. **Conclusions:** In this retrospective study of patients with relapsed AL amyloidosis receiving BCMA BSAb we demonstrate early and deep response with 100% hCR rate. Organ response was observed in most patients within a short time course which is a critical determinant of long-term survival. Prospective studies are currently enrolling to further investigate the use of this therapeutic class in the relapsed setting.

PA-046

BCMA–Targeting Bispecific Antibody, as a Efficacy and Safety Bridging Therapy Before Anti-BCMA CAR-T Cell Therapy in Multiple Myeloma

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Introduction: Equecabtagene Autoleucel (eque-cel) and Zevorcabtagene Autoleucel (zevor-cel), 2 B-cell maturation antigen (BCMA)–directed chimeric antigen receptor T-cell (CAR-T) therapies, have transformed outcomes for relapsed/refractory multiple myeloma(RRMM); however, the 6 to 8 weeks manufacturing time risks disease progression or death in up to 10% of patients. Teclistamab and Elranatamab,2 BCMA–targeting bispecific antibody, represents a promising option. this study aimed to evaluate the safety and efficacy of a short course of teclistamab and elranatamab as bridging therapy prior to standard-of-care eque-cel or zevor-cel in patients with RRMM. **Methods:** This single-center retrospective cohort study enrolled 8 RRMM patients treated at the First Affiliated Hospital of Sun Yat-sen University between June 2025 and May 2026. A low-dose, ultra-short-duration dual-antibody bridging regimen was adopted. Patients aged over 18 years with an ECOG performance status score ≤1 and no prior exposure to BCMA-targeted agents were enrolled. All subjects received low-dose BCMA bispecific antibody following a standard stepwise dosing protocol, followed by 1 to 2 therapeutic doses adjusted according to disease conditions. **Results:** Three patients received teclistamab and five received elranatamab. The incidence rate of cytokine release syndrome (CRS) was 75% among the 8 enrolled cases, all classified as grade 1, and no immune effector cell-associated neurotoxicity syndrome (ICANS) was observed. The overall response rate (ORR) was 50% in patients treated with bispecific antibodies. Subsequently, seven patients underwent CAR-T cell infusion, while one patient failed to receive the infusion due to pulmonary infection. All seven infused patients developed CRS, including 2 cases of grade 3 CRS and the remaining cases of grade 1 CRS. No ICANS occurred throughout the observation period. Parkinson syndrome, peripheral neuropathy and Guillain-Barré syndrome were not detected in this study. With a median follow-up of 3.6 months after CAR-T infusion, the ORR reached 85.7%. (One patient has not been evaluated yet), and all evaluable patients achieved complete remission (CR). Neither progression-free survival (PFS) nor overall survival (OS) had been attained. **Conclusions:** Teclistamab and Elranatamab bridging appears safe, enabling the majority of difficult-to-treat patients to successfully proceed to BCMA CAR-T therapy and does not affect the efficacy of CAR-T therapy.

PA-047

Belantamab Mafodotin Plus Vd in Relapsed/Refractory Multiple Myeloma – An Optimized Regimen Mitigates Ocular Adverse Events Without Compromising Clinical Efficacy: A Czech Multicenter Phase 2 Study

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Introduction: Within the anti-myeloma therapeutic armamentarium, belantamab mafodotin (belamaf)–containing regimens have demonstrated marked therapeutic benefit and a favorable risk–benefit ratio. However, ocular adverse events represent a known risk. We designed an optimization study (EudraCT 2022-002515-34) to reduce grade (gr.) ≥3 ocular findings by at least 75% while preserving efficacy, defined as maintaining ≥80% of the ORR observed in DREAMM-6 study. The aim was to evaluate whether a lower dose of belamaf (1.9 mg/kg) administered less frequently (Q8W) in combination with bortezomib and dexamethasone in patients (pts) with multiple myeloma in their second or higher line of therapy could achieve comparable efficacy with decreased toxicity compared with the standard belamaf dosing (2.5 mg/kg Q3W). **Methods:** Treatment consisted of eight 28-day cycles of bortezomib (1.3 mg/m^2 SC days 1, 8, 15, and 22) and dexamethasone (20 mg PO days 1, 2, 8, 9, 15, 16, 22, and 23), plus belamaf (1.9 mg/kg IV Q8W) until disease progression or unacceptable toxicity. The inclusion/exclusion criteria mirrored DREAMM-7 study. The data cut-off was May 1, 2026. **Results:** Fourty-five pts after a median of 3 (range 1–7) prior lines of therapy (LOT) started the treatment. Median age was 71 (range 44–89). High-risk cytogenetics [t(4;14), t(14;16), del(17p)] was found in

35% (15/43) of pts; 9% (4/45) and 31% (14/45) of pts were double and triple-class refractory, respectively. Response was evaluable in 41 pts who reached 2nd cycle: ORR 68% (28/41), including CR in 22% (9/41), VGPR in 24% (10/41), and PR in 22% (9/41) of pts. One patient (2%; 1/41) achieved MR, 27% (11/41) of pts had SD, and 1 patient (2%; 1/41) had progressive disease. The MRD negativity rate was 17% (7/41). Fourty pts (with ≥2 ophthalmologic assessments) were evaluable for ocular findings: treatment-related ocular findings developed in 65% (26/40) of pts, including maximum keratopathy visual acuity (KVA) gr.1 in 20% (8/40), gr.2 in 37.5% (15/40), and gr.3 in 7.5% (3/40) of pts. KVA gr.3 occured after 2nd, 3rd and 3rd dose of belamaf. At the data cut-off, 22% (10/45) of pts remain on treatment. After a median follow-up of 26.8 months (IQR 24.2;31.3),among patients receiving ≥3 belamaf infusions, mPFS was 17.5 months (11.7;NA), ORR 82% (23/28), and MRD negativity rate 25% (7/28). **Conclusions:** In the study, the primary endpoints were successfully achieved: the incidence of KVA gr.3 was substantially decreased, while efficacy was maintained. These results support modification of the original belantamab dosing schedule to mitigate ocular adverse events without compromising clinical efficacy. Despite the inclusion/exclusion criteria mirrored DREAMM-7 study, direct comparison with any DREAMM study is limited by an older, more heavily pretreated cohort (median of 3 prior LOT).

PA-048

Belantamab Mafodotin Triplets Versus Active-Control Triplets in Relapsed or Refractory Multiple Myeloma

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Introduction: Belantamab mafodotin, a BCMA-directed antibody-drug conjugate, has re-emerged as a promising therapeutic strategy in relapsed/refractory multiple myeloma (RRMM) following positive phase III combination studies. However, the overall magnitude of benefit across belantamab-containing triplet regimens versus active-control triplets has not been quantitatively synthesized. **Methods:** A systematic review and pairwise meta-analysis of randomized phase III trials was performed using an inverse-variance random-effects model. Eligible studies included adults with RRMM who had received at least one prior line of therapy and compared belantamab mafodotin-containing triplets with active-control triplets. Two phase III randomized trials met eligibility criteria: DREAMM-7 and DREAMM-8. DREAMM-7 compared belantamab mafodotin, bortezomib, and dexamethasone versus daratumumab, bortezomib, and dexamethasone. DREAMM-8 compared belantamab mafodotin, pomalidomide, and dexamethasone versus pomalidomide, bortezomib, and dexamethasone. The primary endpoint was progression-free survival (PFS). Secondary outcomes included response depth and ocular toxicity. **Results:** Two phase III trials comprising 796 randomized patients were included. Pooled analysis demonstrated a significant PFS benefit favoring belantamab-containing triplets (HR 0.45, 95% CI 0.35–0.57; $p < 0.0001$), with low heterogeneity ($I^2 = 21.1\%$). Across both studies, belantamab-based therapy was associated with deeper responses, including higher complete response and MRD-negative response rates. Grade ≥3 ocular adverse events were more frequent with belantamab-containing regimens, although discontinuation rates due to ocular toxicity remained relatively low in both pivotal studies. **Conclusions:** Belantamab mafodotin-containing triplets significantly improve PFS compared with active-control triplets in RRMM, with consistent benefit observed across two pivotal phase III studies. These findings support belantamab-based triplets as clinically important off-the-shelf BCMA-directed options in RRMM while emphasizing the importance of careful ocular toxicity monitoring and mitigation strategies.

PA-049

Belantamab Mafodotin, Bortezomib, and Dexamethasone vs Daratumumab, Bortezomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Updated 4-Year Results of the Phase 3 DREAMM-7 Trial

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Introduction: Targeting B-cell maturation antigen (BCMA) has transformed the relapsed/refractory multiple myeloma (RRMM) landscape, delivering unprecedented overall survival (OS) benefits vs daratumumab-based triplet regimens. Belantamab mafodotin (belamaf) is a BCMA-directed antibody-drug conjugate with a multimodal mechanism that avoids T-cell exhaustion and significantly improves progression-free survival (PFS) and OS vs daratumumab, bortezomib, and dexamethasone (DVd). Here, we assessed the sustained long-term benefits of belamaf, bortezomib, and dexamethasone (BVd) vs an anti-CD38–containing triplet regimen in patients with RRMM with ≥1 prior line of therapy (LOT). **Methods:** DREAMM-7 (NCT04246047) is a phase 3, open-label, randomized trial assessing the efficacy and safety of belamaf vs daratumumab with Vd backbone (BVd vs DVd) in patients with

RRMM and ≥1 prior LOT. Patients received 8 21-day cycles of BVd or DVd followed by belamaf or daratumumab alone, from cycle 9 onwards, respectively. The primary endpoint was PFS, with secondary measures including OS, response rates, and safety. The data cutoff for this analysis was Jan 9, 2026. **Results:** At >4 years of follow-up (median, 52.9 months), BVd (n = 243) sustained a continued OS benefit vs DVd (n = 251). In the intention-to-treat (ITT) population, median OS was not reached (NR) for BVd (95% CI, 63.0 months-NR) and was 58.3 months for DVd (95% CI, 41.4 months-NR; HR 0.62, 95% CI 0.46 months–0.82 months). PFS benefit was sustained in the ITT population, and durable PFS and OS were observed across subgroups based on best response. Stringent complete response (sCR) or complete response (CR) rates were 38% with BVd vs 21% with DVd. At 4 years, OS was 98% in patients with sCR and 82% in those with CR in the BVd arm, indicating durable survival. Median PFS was NR with BVd in patients with sCR or CR, vs 56.2 months (95% CI, 28.0 months-NR) and 45.0 months (95% CI, 36.6 months–52.5 months) with DVd, respectively. No new safety concerns emerged after >4 years; adverse event (AE) rates were consistent with prior analyses, with no new fatal AEs and stable infection rates. Health-related quality of life remained consistent, supporting the long-term tolerability of belamaf monotherapy. **Conclusions:** After >4 years, BVd OS benefits remained superior to DVd. Many patients achieved deep remission and PFS benefit, with a safety profile consistent with the known profile of belamaf. These results, along with the ability for outpatient administration, support BVd as a potential new standard-of-care in RRMM at first relapse or later. Sponsorship: GSK (study ID: 207503). Copyright statement: © 2026 European Haematology Association. Reused with permission.

PA-050

Belantamab Mafodotin, Pomalidomide, and Dexamethasone (BPd) Demonstrated Improved Outcomes as Second-Line Therapy vs Pomalidomide, Bortezomib, and Dexamethasone (PVd) in Patients With Multiple Myeloma

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Introduction: Targeting BCMA has transformed the relapsed/refractory multiple myeloma (RRMM) treatment landscape. Belantamab mafodotin represents an accessible and unique BCMA-targeting modality as an antibody-drug conjugate and was recently approved as part of triplet therapy for RRMM. At the primary analysis of DREAMM-8 (median follow-up, 21.8 months; data cutoff [DCO]: January 29, 2024), BPd demonstrated significant improvement in progression-free survival (PFS) vs PVd in patients with RRMM who had ≥1 prior line of therapy (LOT) (hazard ratio [HR], 0.52; 95% CI, 0.37–0.73; P < 0.001). Longer-term follow-up (median, 35.8 months; DCO: July 7, 2025) found a 2.5-fold higher median PFS benefit with BPd vs PVd (32.6 vs 12.5 months; HR, 0.49; 95% CI, 0.36–0.67). Herein, we assess the magnitude of BPd treatment benefit vs PVd in a subgroup of patients who only received 1 prior LOT. **Methods:** DREAMM-8 (NCT04484623) is a phase 3, open-label, randomized trial evaluating the efficacy and safety of BPd vs PVd in patients with RRMM with ≥1 prior LOT. All patients were lenalidomide exposed and had not received prior BCMA-targeted therapy. The primary endpoint was PFS. Secondary endpoints included overall survival (OS), PFS2, duration of response (DOR), response rates, and minimal residual disease (MRD) negativity (next generation sequencing threshold of 10^{-5}). This post hoc analysis assessed efficacy in a subgroup of patients with only 1 prior LOT. **Results:** Of the 302 patients in DREAMM-8, 159 (BPd, n = 82; PVd, n = 77) had received only 1 prior LOT (2L) and had a median follow-up of 36.8 months (DCO: July 7, 2025). PFS in 2L favored BPd vs PVd treatment (24-month PFS: 65% vs 36%, respectively; median not reached vs 18.4 months; HR, 0.46; 95% CI, 0.29–0.72). PFS benefit was also trending in favor of BPd vs PVd across key subgroups, including patients who were lenalidomide refractory, were anti-CD38 exposed, and had high-risk cytogenetics. BPd exhibited deeper and more durable response vs PVd in 2L: complete response or better (≥ CR) rate was 51% (42/82) vs 23% (18/77), respectively; the ≥ CR-based MRD-negativity rate was 39% (32/82) vs 7% (5/77); and among patients with ≥ CR, the MRD-negativity rate was 76% (32/42) vs 28% (5/18). DOR at 24 months was 77% vs 39%, respectively. BPd benefit was also maintained following subsequent therapies (PFS2 at 24 months: 74% vs 58%; HR, 0.48; 95% CI, 0.30–0.78). OS remains immature. **Conclusions:** BPd as 2L treatment in patients with RRMM demonstrated durable benefits in PFS, DOR, and PFS2, in addition to deep responses. This analysis further supports the use of BPd as early as first relapse. With BCMA-targeted treatments making notable advancements in outcomes for patients with RRMM, belamaf

combinations offer both broad accessibility to durable outcomes as well as a patient-centric profile, with extended dosing intervals and outpatient administration. **Sponsorship:** GSK (study ID 207499)
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PA-051

Beyond Consensus Genomic Staging: Genomic Heterogeneity of Relapsed Standard-Risk Multiple Myeloma

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Introduction: Consensus Genomic Staging (CGS) refines genomic risk stratification in newly diagnosed multiple myeloma (NDMM). However, a subset of patients (pts) classified as standard-risk (SR) still relapse, suggesting residual biological heterogeneity within the SR group. We characterize relapsed CGS-defined SR pts and investigate the genomic similarities between high-risk (HR) and relapsed SR pts. **Methods:** We analyzed 474 NDMM pts profiled by Unique Molecular Assay (UMA), a targeted NGS panel designed to detect clinically relevant mutations, copy-number alterations and immunoglobulin heavy-chain translocations. Genomic data was used to classify pts according to CGS criteria. Relapse information was available for the whole cohort, while progression-free survival (PFS) data was available for 211 pts. The prognostic value of CGS was assessed using Kaplan-Meier and Cox regression analyses. Pts were then classified into 4 CGS/outcome-defined groups: HR relapsed (HR-R, 32/474), HR non-relapsed (HR-nR, 38/474), SR relapsed (SR-R, 130/474), and SR non-relapsed (SR-nR, 274/474). Unsupervised clustering and pairwise similarity analyses were used to investigate the genomic architecture of SR-R pts. **Results:** In the PFS cohort, CGS significantly discriminated clinical outcome, with HR pts showing inferior PFS compared to SR pts (HR 2.36, 95% CI 1.30–4.31; p = 0.005; log-rank p = 0.004). Nevertheless, a subset of SR pts experienced relapse, supporting the need for deeper characterization. Unsupervised clustering of all pts identified two main genomic clusters. HR-R patients were strongly enriched in Cluster 1 (28/32, 87.5%), together with more than half of SR-R pts (74/130, 56.9%). Within Cluster 1, SR-R pts showed partial similarity with HR-R cases (mean coefficient of similarity: 0.684), while retaining a distinct profile. HR-R cases were mainly enriched in classical HR lesions, including t(4;14), TP53/del17p and t(14;16), whereas SR-R pts showed higher frequencies of t(11;14), NRAS mutations and rare IgH translocations. Comparison of SR-R pts in Clusters 1 and 2 confirmed their biological heterogeneity. Specifically, intra-cluster similarity (0.760 for Cluster 1; 0.726 for Cluster 2) was significantly higher than inter-cluster similarity (0.632). SR-R of Cluster 1 were characterized by t(11;14), NRAS mutations and rare IgH translocations, whereas Cluster 2 SR-R showed a distinct RAS-MAPK-like profile. **Conclusions:** CGS effectively stratifies PFS in NDMM; however, a clinically-relevant subset of CGS-defined SR pts still experiences relapse. These SR-R pts are biologically heterogeneous. One subgroup partially overlaps with HR-R pts, despite a distinct genomic landscape, enriched for t (11;14), NRAS mutations and IgH-translocation, whereas the other exhibits a KRAS/RAS-MAPK-like genomic architecture. These findings support further validation of UMA-derived genomic features to refine relapse-risk assessment among CGS-defined SR patients.
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PA-052

Biallelic del(1p) and TP53 Mutation Rates and Their Overlap with 2+HRCA High-Risk in Newly Diagnosed Multiple Myeloma: Results of an ISO-Accredited NHS Genomics Laboratory Hub

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Introduction: The IMS-IMWG 2025 high-risk multiple myeloma (HRMM) guideline introduced homozygous del(1p32) and TP53 single-nucleotide variants (SNV) as independent risk factors, in addition to co-occurrence of 2+ high-risk cytogenetic abnormalities (HRCA), a validated high-risk group. Most data on homozygous del(17p) and TP53 SNVs in MM published so far are from exploratory research studies, providing limited information on co-occurrence of other HRCA. Since 2023, TP53 mutation calling by NGS alongside HRCA testing by FISH is standard diagnostic care for newly diagnosed MM (NDMM) at the Royal Marsden Hospital's UK National Health Service (NHS) Genomics Laboratory Hub. Here, we report detection rates of the new risk factors and their overlap with traditional HRCA in a standard care setting. **Methods:** We retrospectively reviewed all transplant-eligible NDMM patients treated between 2021 and 2026 and included all who underwent both TP53 NGS profiling as per ISO accreditation and testing for all HRCA t(4;14), t(14;16), t(14;20), del(1p), gain(1q) and del(17p) from CD138-purified (>90%) BM as part of routine NHS diagnostic workup. This study was approved by the RMH institutional review board as a Service Evaluation. Data was analysed in RStudio v4.4.0 (v2024.12.0). **Results:** 102 patients with complete genomic data were

included. Considering firstly HRCA results without NGS, 24 patients (23.5%) fulfilled IMS-IMWG CGS criteria for HRMM. Of these, 8 patients (7.8%) carried del(17p), of which 2 also carried t (14;16)/gain(1q) and biallelic del(1p). The remaining 6 classified per IMS-IMWG as high-risk by del(17p) alone, but all carried co-occurring other HRCAs as well: gain/amp(1q) (n = 4), t(4;14) (n = 1), del(1p) (n = 1). When taking NGS results into account, 4 cases (3.9%) showed TP53 mutation, of these, 2 with concurrent del (17p) of the other allele; both additionally carried further HRCA (gain(1q) and del(1p)). The other 2 patients harboured TP53 mutations without del(17p), but both tumours again carried an additional HRCA (gain(1q) and t(14;16)); as per IMS-IMWG CGS criteria only the TP53 mutation qualified them as HRMM.

Including NGS information, 26 (25.5%) patients were HRMM according to IMS-IMWG; of these, 24 cases carried 2+HRCA and 2 TP53 mut and 1 HRCA. Biallelic del(1p) was present in 5 cases (5%), but all again carried 2+ HRCA. 31 patients (30%) carried a single HRCA not considered HRMM, including gain/amp(1q) (n = 21), t (4;14) (n = 6), t(14;16) (n = 1) and heterozygous del(1p) (n = 1). **Conclusions:** In this real-world diagnostic analysis, only 2 NDMM patients (2%) was identified as HRMM solely based on TP53mut by NGS and both also carried an additional HRCA. All other IMS-IMWG CGS HRMM patients carried 2+ HRCA. While molecular diagnostics should be considered as standard in NDMM care, NGS-based diagnostic strategies should be optimised to detect structural variants, as HRCA still constitute most prognostic information in MM.

PA-053

Biallelic del(1p32) Drives a Clonal, Aggressive Multiple Myeloma State Through Transcriptional Reprogramming and Non-Coding RNA Dependencies

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Introduction: Biallelic deletion of 1p32 [del(1p32)] is among the strongest adverse prognostic lesions in multiple myeloma (MM). In clinical practice, biallelic del(1p32) is typically defined by loss of CDKN2C and/or FAF1, two tumor suppressor genes located within the minimally deleted region. However, the biological basis of its high-risk phenotype and associated therapeutic liabilities remains poorly defined. **Methods:** To define the clinical and biological consequences of del(1p32), we analyzed three independent MM patient datasets (CoMMpass, GAMER, and IFM2009) using copy-number and transcriptomic profiling. To model this lesion mechanistically, we generated isogenic MM cell lines with biallelic del(1p32) using CRISPR-based chromosome engineering. Engineered clones were validated by copy-number analysis, qPCR, and whole-genome sequencing to confirm the intended breakpoints. Functional studies assessed tumor growth in vitro and in vivo, clonogenicity, apoptosis, immunogenicity, and drug sensitivity. **Results:** Biallelic del(1p32) was identified in 2–5% of patients across newly diagnosed MM cohorts. Both monoallelic and biallelic del(1p32) showed a clonal cell fraction >80%, indicating that 1p32 loss is typically an early clonal event. Across all three datasets, copy-number analysis defined a recurrent focal deleted region comprising 58 genes, including CDKN2C and FAF1. Transcriptomic analysis confirmed significantly reduced expression of CDKN2C, FAF1, and additional genes within the minimally deleted region in patients with biallelic del(1p32) compared with wild-type cases.

Engineered clones were confirmed to have the expected breakpoint localization by whole-genome sequencing and carried reduced expression of CDKN2C and FAF1. Functionally, del(1p32) clones demonstrated increased clonogenicity, reduced apoptotic sensitivity by BH3 profiling, and accelerated tumor growth in vivo. They also displayed reduced immunogenic features, including impaired markers of immunogenic cell death by flow cytometry, and decreased sensitivity to IMiDs and CELMoDs in cell competition assays. Integration of isogenic and patient transcriptomic datasets showed enrichment of programs associated with proliferation, survival, and immune evasion. Notably, a dysregulated non-coding RNA program emerged in both patients and engineered models, including modulation of a lncRNA program associated with poor outcome. A Cas13 CRISPR screen further provided confirmation of selective dependency on the lncRNA in del(1p32) cells giving rationale for further analysis. **Conclusions:** Biallelic del(1p32) is a clonal driver lesion that marks a highly aggressive subtype of MM. Beyond loss of CDKN2C and FAF1, this alteration is associated with broader transcriptional rewiring, including actionable non-coding RNA dependencies. These findings provide a mechanistic framework for del(1p32)-driven disease and identify candidate therapeutic vulnerabilities in this genetically defined MM subgroup.

PA-054

Bioengineered Nanovesicles Potentiate CAR-T Therapy in Myeloma via Antigen Reinforcement, TIGIT Blockade, and STING Activation

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Introduction: Chimeric antigen receptor T (CAR-T) cell therapy has revolutionized the treatment landscape of multiple myeloma (MM), yet its clinical efficacy remains constrained by tumor antigen loss and immunosuppressive signaling. Current strategies to enhance antigen expression, such as lentiviral vectors, require direct tumor

injection, restricting their applicability in hematological malignancies. **Methods:** We report a bioengineered nanovesicle platform that co-expresses MM antigens (GPRC5D/BCMA) and TIGIT on its surface while encapsulating a STING agonist (STINGa-23) to potentiate CAR-T therapy. **Results:** This multifunctional platform simultaneously mitigates checkpoint-mediated immunosuppression via CD155/TIGIT pathway blockade, restores tumor antigen presentation by providing auxiliary tumor antigens (GPRC5D/BCMA), and elicits robust innate immune activation through STING agonist delivery. In vivo, both subcutaneous and orthotopic bone marrow MM models demonstrated that these nanovesicles synergize with CAR-T cells, augmenting T cell activation, inducing profound tumor regression. **Conclusions:** By integrating antigen supplementation, checkpoint blockade, and innate immune stimulation within a single platform, this strategy offers a versatile and promising approach to surmount existing limitations of CAR-T therapy in MM.

PA-055

Blood Transfusion Management and Transfusion-Related Outcomes in Daratumumab-Treated Patients with Multiple Myeloma

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Introduction: Daratumumab, used for the treatment of multiple myeloma(MM), binds to the CD38 antigen and shows strong and selective therapeutic efficacy. However, because the CD38 antigen is also partially expressed on the surface of red blood cells, it causes interference in pre-transfusion testing leading to false positive results and delays in blood availability for transfusion. This panagglutination can persist up to 6 months after the last Daratumumab infusion. **Methods:** To overcome the interference caused by daratumumab, the following two approaches were implemented. 1) Through a pre-transfusion consultation, patient information was obtained before drug administration, and blood samples were collected to perform red blood cell(RBC) phenotyping (Rh C/c/E/e, Kidd, Duffy) and unexpected antibody screening. 2) If testing had not been performed before drug administration, pre-transfusion testing was carried out using DTT (dithiothreitol)-treated RBCs to identify compatible blood. The study population was divided into two groups. The first group consisted of patients who received daratumumab for relapsed/refractory (R/R) MM from April 2019. The second group consisted of newly diagnosed MM patients eligible for autologous hematopoietic stem cell transplantation(ASCT) who received daratumumab as first-line therapy and were prospectively collected from February 2025. **Results:** A total of 34 patients with R/RMM received daratumumab as fourth-line or later therapy between April 2019 and March 2026. In the group of newly diagnosed transplant-eligible MM patients, a total of 14 patients received daratumumab between February 2025 and March 2026. The median age was 68 years (range, 62–76) in the R/R MM group and 64 years (range, 52–69) in the NDMM group. The median RBC transfusion requirement was 1.8 U/month in the R/R MM group and 0.4 U/month in the NDMM group; in the NDMM group, most RBC transfusions were administered during the period of ASCT. In the R/R MM group, alloantibodies were detected in both RBC antigen typing and alloantibody screening tests. Among these patients, 6 had multiple alloantibodies. In the NDMM group, 12 patients (42.8%) were positive for alloantibodies. Febrile non-hemolytic transfusion reactions occurred during or after RBC transfusion in 12 patients (35.2%) in the R/R MM group and 5 patients (35.7%) in the NDMM group; however, no hemolysis occurred in either group. The panagglutination reaction (strength 1+ to 2+) observed in the initial antibody screening and identification tests disappeared, and all tests became negative, confirming that the reactivity was a drug-induced false positive rather than due to alloantibodies. **Conclusions:** In patients receiving daratumumab, an appropriate and safe transfusion can be achieved by performing RBC phenotypes before daratumumab administration.

PA-056

Bortezomib-Based Regimen Significantly Reduces Bone Resorption Rate Compared to Lenalidomide-Based in Newly Diagnosed Elderly Multiple Myeloma Patients: Results from the Italian Real Phase IV Trial

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Introduction: Skeletal related events characterized Multiple Myeloma (MM) patients with a survival impact especially in the elderly. It is established that both immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) have an impact on bone remodeling markers. This prospective multicenter study longitudinally evaluated several cytokines and chemokines and biomarkers of bone remodeling in elderly newly diagnosed (ND) MM patients included in the Real MM trial (NCT03829371 funded by the Italian Medicines Agency AIFA - Independent Research), designed to compare Bortezomib-Melphalan-Prednisone (VMP) vs Lenalidomide-Dexamethasone (Rd) and in the following up-dated with the introduction of the

anti-CD38 mAb Daratumumab (Dara). **Methods:** A subgroup of forty-three patients was enrolled including those treated with VMP (n = 15) or Rd (n = 14) with a second, expanded cohort of 14 patients receiving Dara-based combinations: Dara-Rd (n = 8) or Dara-VMP (n = 6). Peripheral plasma samples were collected at baseline, 4 months (T4), and 9 months (T9). Bone turnover markers (CTX and P1NP), cytokines and chemokines involved in osteoclast activation (RANKL, OPG, RANKL/OPG ratio, MIP-1α, MIP-3α, and Activin A), and osteoblast activity (osteocalcin) were quantified by ELISA. Patients were stratified according to treatment regimen, clinical response, and the treatment with the bone active agent zoledronic acid (ZA). Bayesian longitudinal models were used to evaluate biomarker changes over time, accounting for lower and upper limit of detections. Trend comparisons between treatment groups, type of response and ZA were explored. **Results:** First, we found that Rd treatment was associated with a significant reduction between T0 and T9 and a significantly different trend with VMP of MIP-3α, and OPG levels, whereas VMP induced a marked reduction in CTX, levels. Response-stratified analyses showed a significant decrease in CTX among responders at T9 (−64.3%) supporting an association between clinical response and reduced osteoclastic activity. Analyzing the entire cohort of patients including those treated with Dara, we found that patients treated with ZA showed a marked reduction in CTX (−81%), together with decreased PINP levels. We found that lenalidomide-based treatment was associated with a significant reduction in Activin A and OPG levels, together with increased RANKL and RANKL/OPG at the different timepoints and with a significant reduction of MIP-3α levels at T9 as compared to Bortezomib-based treatment. On the other hand, PI-based regimen was associated to a significant reduction of CTX and osteocalcin levels. Response-stratified analyses confirmed a significant decrease in Activin A and CTX levels among responders while PINP decreased over time irrespective of response status. **Conclusions:** Overall, this study suggest that Bortezomib-based regimen exerts a significant and stronger inhibitory effect on bone resorption activity as compared to lenalidomide-based regimen in elderly NDMM patients.

PA-057

BOSS: Safe and Feasible Outpatient Step-Up Dosing of Elranatamab in Relapsed/Refractory Multiple Myeloma

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Introduction: Elranatamab, a B-cell maturation antigen-directed bispecific antibody, induces deep responses in relapsed/refractory multiple myeloma (RRMM) but is associated with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), leading to routine inpatient step-up dosing (SUD). To improve scalability and access, we developed the Bispecific Outpatient Safe Step-up (BOSS) protocol for structured outpatient administration of elranatamab. **Methods:** In this real-world quality improvement initiative, we compared outpatient elranatamab SUD using the BOSS protocol versus contemporaneous inpatient SUD at Mass General Brigham Cancer Institute between March 2024 and November 2025. The BOSS protocol incorporated structured daily assessments, standardized dexamethasone prophylaxis on dosing and non-dosing days, predefined escalation pathways, and symptom-driven management without prophylactic tocilizumab or remote vital sign monitoring devices. Tocilizumab was reserved for persistent CRS. Primary endpoints included incidence and severity of CRS and ICANS. Secondary endpoints included hospitalization, infections, hematologic toxicity, and healthcare utilization. **Results:** Twenty-six patients underwent outpatient SUD under BOSS and 34 underwent inpatient SUD. CRS occurred in 23.1% versus 55.9% of patients, respectively ($p = .02$), predominantly grade 1 events and no grade ≥3 CRS in either cohort. ICANS occurred in 0% versus 8.8%, respectively. Most CRS occurred after the first step-up dose. In exploratory analysis, treatment under BOSS was independently associated with lower CRS risk (adjusted OR 0.20, 95% CI 0.05–0.71; $p = .02$). Only 11.5% of BOSS patients required hospitalization, with median hospital stay of 0 versus 5 days. Infection rates were similar between cohorts (15.4% vs 17.6%). Exploratory analyses demonstrated lower CRS incidence with higher cumulative dexamethasone exposure during SUD. **Conclusions:** The BOSS protocol enabled safe outpatient step-up of elranatamab with reduced CRS incidence and hospitalization burden, without prophylactic tocilizumab or remote monitoring devices. This scalable outpatient model maintained acceptable safety while supporting broader implementation of outpatient bispecific antibody therapy.

PA-058

BP2202: An Off-the-Shelf iPSC-Derived BCMA-Targeted Cellular Therapy for Multiple Myeloma

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Introduction: BCMA-targeted autologous CAR-T cells and T cell engagers achieve meaningful responses in relapsed/refractory multiple myeloma (RRMM), yet disease recurrence is common. Autologous CAR-T cells are limited by patient-derived manufacturing, long vein-

to-vein time and product variability, while T-cell engagers require repeated dosing that increases treatment burden and infection risk. Meanwhile, conventional allogeneic CAR-T approaches in lymphoma have failed to show durable responses, mainly due to poor persistence. Thus, readily available "off-the-shelf" allogeneic products with improved durability are critically needed. Invariant natural killer T (iNKT) cell is a unique T cell subset with an invariant Vα24-Jα18 TCR recognizing monomorphic CD1d-presented glycolipid, enabling safe allogeneic use without GvHD and potent antitumor activity via TCR signaling. Notably, allogeneic iNKT cells orchestrate endogenous antitumor immunity, especially activation of cytotoxic T cells, potentially promoting durable antitumor responses.BP2202 is a gene-edited, induced pluripotent stem cell (iPSC)-derived BCMA-targeted iNKT cell therapy integrating immunomodulatory functions of iNKT cells with CAR technology and scalable master cell bank-based manufacturing to overcome durability limitations of conventional allogeneic CAR-T. Here, we present the preclinical characterization of BP2202 and the design of a first-in-human phase 1 study. **Methods:** BP2202 was evaluated for phenotype, CAR expression, antigen-specific cytotoxicity, cytokine production, and in vivo antitumor activity. Cytotoxicity against BCMA-positive multiple myeloma cell lines was assessed using luciferase-based killing assays, and antitumor activity was evaluated in xenograft mouse models using bioluminescence imaging. Genomic safety assessments of gene-edited iPSC included karyotyping, optical genome mapping, whole genome sequencing, and off-target analysis. The phase 1 study is an open-label, multicenter, dose-escalation trial evaluating BP2202 in patients with RRMM after at least 3 prior lines of therapy. Patients receive lymphodepletion followed by a single infusion of BP2202. Primary objectives include safety and determination of the recommended phase 2 dose. **Results:** BP2202 demonstrated antigen-dependent cytotoxicity against BCMA-positive tumor cell lines and induced tumor growth inhibition in xenograft models. Product characterization demonstrated consistent CAR expression and reproducible manufacturing. Comprehensive genomic analyses confirmed preserved chromosomal integrity without detectable significant structural abnormalities or notable off-target editing events. **Conclusions:** BP2202 is an off-the-shelf iPSC-derived BCMA-targeted iNKT cell therapy that demonstrates promising preclinical antitumor activity, favorable genetic safety profiles, and highly reproducible manufacturing. These findings support the clinical development of BP2202 as a novel allogeneic cell therapy for multiple myeloma.

PA-059

Brain FDG-PET as an Imaging Biomarker of CAR-T Movement and Neurocognitive Treatment-Emergent Toxicity

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Introduction: MNT is an increasingly recognized neurocognitive and hypokinetic movement disorder that develops in patients receiving B-cell maturating antigen (BCMA)-targeting CAR-T for multiple myeloma. Diagnosis is challenging due to phenotypic heterogeneity. Although pre-treatment myeloma burden and post-treatment high absolute lymphocyte count (ALC) are described risk factors, there are no established biomarkers. Prior FDG-PET descriptions of MNT have noted frontal-striatal hypometabolism. **Methods:** Twelve MNT cases were identified from a prospectively maintained immune effector cell (IEC) program compliance database (N = 330). Thirty-four neurologically intact cases with high ALC (> 3 × 109/L) and myeloma burden served as a comparison cohort. Pre- and post-treatment full body FDG-PET, were processed using an institutional pipeline to generate age-matched Z-scores for brain regions of interest (ROI). Linear mixed effects models were fit to compare ROI Z-scores pre- and post-treatment. Models included fixed effects of time (pre- vs. post-treatment), ROI, and their interaction, with subject included as a random intercept to account for repeated measures. A second model incorporated group membership and its interactions with time and ROI to examine between-group differences. False discovery rate (FDR) correction was applied for multiple comparisons ($\alpha = 0.05$). **Results:** Model-estimated post-treatment Z-score change from baseline within the MNT group was greatest in the putamen, caudate, and pallidum, all surviving FDR correction ($p < 0.05$). These effects remained stable and significant when the comparison cohort was incorporated into a combined model. No significant baseline differences in ROI Z-scores were observed between groups. **Conclusions:** Brain FDG-PET in MNT cases revealed significantly decreased basal ganglia metabolism post-treatment. This regional hypometabolism is in keeping with clinical presentation, supporting FDG-PET as a potential imaging biomarker. Additional validation is needed to confirm these findings.

PA-060

Building Fairer AI: Race Adds Minimal Predictive Value to Biologically Grounded Machine Learning Models in Multiple Myeloma

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Introduction: As artificial intelligence (AI) becomes increasingly integrated into oncology, concerns regarding algorithmic bias and the appropriate use of race in predictive models have intensified. In multiple myeloma (MM), racial disparities in incidence and outcomes are well recognized; however, it remains unclear whether race contributes meaningful predictive information for biologically grounded disease metrics once relevant clinical and laboratory

variables are incorporated. We evaluated the impact of race and ethnicity on machine learning models predicting M-protein levels in a large real-world MM dataset. **Methods:** Clinical and laboratory data were obtained from the HealthTree MM registry. A total of 619 patients were included, including 542 with complete race and ethnicity information. Random forest regression models were developed to predict M-protein levels using routinely available clinical and laboratory variables. Model A included prior M-protein values, serum total protein, race, and ethnicity. Model B incorporated additional biologically relevant variables including immunoglobulin levels, albumin, anthropometric data, and free light chain ratio. Models were trained using an 80/20 training-validation split. Performance was evaluated using root mean squared error (RMSE) and coefficient of determination (R^2). A sensitivity analysis was performed using a rebalanced dataset created by reducing the proportion of Non-Hispanic White patients. **Results:** In Model A, inclusion of race and ethnicity produced only negligible improvement in predictive performance, with RMSE improving from 0.2634 to 0.2631 and R^2 increasing from 0.7440 to 0.7445. In the rebalanced sensitivity analysis, inclusion of race similarly failed to meaningfully improve model performance. In Model B, which incorporated a broader set of biologically informative laboratory features, inclusion of race and ethnicity slightly worsened model performance (RMSE 0.2524 vs 0.2555; R^2 0.7670 vs 0.7604). Across all model configurations, prior M-protein values, serum total protein, and immunoglobulin measurements were the strongest predictors, whereas race and ethnicity consistently ranked among the least important variables. Predicted and observed M-protein values demonstrated strong concordance across models, indicating robust overall predictive accuracy. **Conclusions:** Race and ethnicity contributed minimal independent predictive information for M-protein estimation once biologically relevant laboratory variables were included. These findings support a biologically grounded, race-agnostic modeling approach for disease burden assessment in MM while emphasizing the importance of evaluating predictive equity across diverse patient populations. Future studies should validate these findings in larger and more racially representative cohorts and explore whether race contributes differently to models predicting treatment response, toxicity, or survival, where structural and access-related factors may play a larger role.

PA-061

Cardiovascular Risk Across Lines of Treatment in Multiple Myeloma: Insights from a National UK Real-World Database

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Introduction: Cardiovascular complications due to disease-related factors and cumulative treatment exposure have been reported in patients with multiple myeloma (MM). However, the extent to which cardiovascular risk varies across lines of treatment and over the disease course remains unclear. **Methods:** Two national UK surveys of people living with MM were undertaken in 2023 and 2025 using online and postal methods. Recruitment was achieved through charity e-newsletter and social media. Participants reported their most recent line of therapy and any cardiotoxicities experienced during treatment, including heart problems, blood pressure abnormalities, dyspnea, and oedema (n = 541). Participants also reported their treatment status. Binary logistic regression was used to evaluate associations between lines of therapy (first, second, ≥third line) and cardiovascular-related outcomes. Both unadjusted and adjusted models were explored, adjusting for age, receiving lenalidomide maintenance therapy, and treatment status. Paired analyses compared pre- and post-diagnosis cardiovascular conditions within individuals. **Results:** A total of 541 and 627 participants were included from the 2023 and 2025 surveys, respectively. Across multiple models, there was no consistent association between line of therapy and most cardiovascular outcomes. Heart problems showed no significant association (adjusted OR 1.41, 95% CI 0.77–2.58), hypotension showed no difference (OR 1.04, 95% CI 0.50–2.15), and oedema showed a non-significant trend (OR 1.48, 95% CI 0.92–2.38), with estimates stable after adjustment. Dyspnea demonstrated the most consistent association. Compared with ≥third-line therapy, second-line therapy was associated with increased odds of dyspnea (adjusted OR 1.63, 95% CI 1.08–2.46, p = .019), while first-line therapy showed a non-significant increase (OR 1.43, 95% CI 0.92–2.22, p = .111). An association between first-line therapy and hypertension was observed (OR 2.24, 95% CI 1.03–4.89, p = .042), but was not supported by overall model significance and was attenuated after adjustment. Descriptive comparisons showed a higher number of reported cardiovascular-related risk factors post-diagnosis compared with pre-diagnosis, such as raised cholesterol (24 vs 46). **Conclusions:** Line of therapy was not a consistent determinant of cardiovascular risk in this MM cohort. However, a reproducible increase in dyspnea during second-line therapy, alongside a higher number of post-diagnosis conditions known to increase the risk of future cardiovascular events, suggests a period of potential heightened and accumulated cardiopulmonary risk. These findings support the need for targeted cardiovascular monitoring across the treatment pathway in MM.

PA-062

Care CAR-T Success, Neurological Failure: Real-World Burden of Severe Non-ICANS Neurotoxicity After BCMA-Directed CAR-T in Multiple Myeloma

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Introduction: Beyond cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS),

delayed non-ICANS neurologic toxicities after BCMA-directed CAR-T cells are increasingly recognized. We analyzed incidence, phenotypes, management, and outcomes of severe non-ICANS neurotoxicity at a single large-volume center and derived practical implications for interdisciplinary care pathways. **Methods:** We retrospectively analyzed 117 consecutive patients with multiple myeloma treated with BCMA-directed CAR-T cells at a single center between January 2024 and December 2025. Non-ICANS neurotoxicity was defined per EBMT guidance (onset after CRS resolution) and adjudicated by joint hematology-neurology review after exclusion of alternative etiologies. Syndromes included cranial nerve palsy, parkinsonism-like movement/neurocognitive toxicity, encephalitis, and Guillain-Barré syndrome-like presentations. CAR-T expansion kinetics and absolute lymphocyte count (ALC) were analyzed descriptively. **Results:** Severe non-ICANS neurotoxicity occurred in 10/117 patients (8.5%). Median onset was 45 days post-infusion (range, 11–160 days). Syndromes comprised cranial nerve palsy (n = 5), Parkinsonism-like syndromes (n = 3), encephalitis (n = 2), and Guillain-Barré syndrome-like presentations (n = 3); overlap and sequential evolution were common. CRS occurred in 90% (grade ≥3 in 10%), and ICANS in 20% (no grade ≥3). All affected patients achieved a complete response; however, non-relapse mortality in the neurotoxicity group was 50% vs. 8.4% in controls. Expansion-kinetics signals were prominent: 9/10 patients had peak ALC >3 × 10^9/L; median CAR-T copies at neurotoxicity onset were 2.23 × 10^5/10^6 leukocytes (range, 1.24 × 10^2–1.09 × 10^6). Immune-directed escalation (corticosteroids ± IVIG, cytokine blockade, cytotoxic or intrathecal therapies) was frequently required, with inconsistent neurologic recovery and substantial infectious morbidity. **Conclusions:** Delayed non-ICANS neurotoxicity after BCMA-directed CAR-T cells is clinically heterogeneous, often severe, and associated with high non-relapse mortality despite deep myeloma responses. Prominent expansion-kinetics signals support risk-oriented monitoring, but post-hoc CAR-T reduction did not reliably result in neurological recovery. These findings argue for standardized, interdisciplinary neurology-oncology pathways with predefined triage, diagnostics, and escalation algorithms to improve recognition and management as CAR-T use broadens beyond specialized centers.

PA-063

Carfilzomib, Iberdomide, and Dexamethasone (KID) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Results from a Phase 1/2 Study

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Introduction: Standard upfront regimens demonstrate stringent complete response (sCR) rates of 10–15% following induction, and 40% following consolidation in patients (pts) with newly diagnosed multiple myeloma (NDMM). Iberdomide (iber), a cereblon-E3 ligase modulator, exerts antitumor effects and increases immune activation. Iber 1, 1.3, and 1.6 mg doses were evaluated in combination with carfilzomib (CFZ) and dexamethasone regimen (KID) in pts with NDMM during phase 1. Iber 1.6 mg was selected for the phase 2 dose (P2D). Based on emerging data from BMS trials on 3/17/2025, the P2D was revised to 1 mg. Interim analysis from the phase 1/2 KID study in NDMM pts (NCT05199311) is reported. **Methods:** Adults with autologous stem cell transplantation (ASCT)-eligible NDMM were enrolled in this multicenter study. Pts received KID for 2–3 28-day cycles followed by ASCT. The phase 2 primary objective is to evaluate whether ≥50% of pts achieves sCR/CR. At data cutoff 04/30/26, 58 evaluable pts received at least one dose, and 23 remain on active tx. Median age was 67 years (range 37–78), 52% male, 22% black, 14% Hispanic, and 44% ISS stage 2/3. Twenty-eight pts (48%) had high-risk cytogenetics: t(4;14) (n = 7), t(4;16) (n = 4), del (17p) (n = 9), 1q21 gain (n = 21), and MYC (n = 1). Nineteen (33%) were high-risk by the revised IMWG criteria. **Results:** Fifty-eight pts completed a median of 3 cycles, with 85 days median tx duration. During phase 2, 25 pts received 1.6 mg and 24 received 1 mg. Fifty-eight pts were response evaluable. Median follow-up was 13.3 months. The median number of stem cells mobilized in the 49 pts (84%) who received ASCT was 10.45 × 106 cells/kg (range 3.93–29.8). At interim analysis, best ORR, sCR/CR, VGPR, and PR rates were 98%, 31%, 21%, and 47%. The MRD negativity rate is 63% in 16 evaluable pts. The ORR, sCR/CR, VGPR, and PR rates at 3-months post ASCT in the 36 evaluable pts were 97%, 31%, 56%, 11%; and for the 28 evaluable high-risk subset, 96%, 32%, 25% and 39%, respectively. The number of pts in follow-up at time of data cutoff at 6, 12 and 24 months were 42, 29, and 17 respectively (PFS), and 42, 30, and 18 (OS). The OS at 6, 12, and 24 months were 98% (95%–100%), 98.1% (95%–100%), and 95% (88%–100%) overall and 100% (100%–100%), 100% (100%–100%), and 93% (80%–100%) for the high-risk cohort. The PFS at 6, 12, and 24 months were 96% (92%–100%), 94% (87%–100%), and 90% (81%–100%) overall and 100% (100%–100%), 94% (84%–100%), and 86% (69%–100%) for the high-risk subset. Fifty pts (86%) had adverse events (AEs), with 22% anemia, 14% neutropenia, 9% thrombocytopenia, and 36% infection (all grade 1/2). Serious AEs occurred in 12 pts, including atrial fibrillation, and erythema multiforme. **Conclusions:** Induction tx with KID achieved 31% sCR/CR rates post ASCT overall and 31% in the high-risk NDMM pts at interim analysis, despite short tx duration. All pts were successfully mobilized. Further studies will evaluate KID with post-ASCT iber + elranatamab consolidation followed by iber maintenance.

PA-064

CAR-HEMATOTOX Beyond CAR T-Cell Therapy: Utility for Stratifying Hematologic and Infectious Risk in Bispecific Antibodies

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Introduction: The CAR-HEMATOTOX score (CAR-HT) was developed to predict hematologic toxicity and infections after CAR T-cells therapy, but its ability to identify a similar high-risk phenotype after bispecific antibodies (BsAbs) remains less defined. We evaluated whether CAR-HT identifies patients at higher risk of grade 4 neutropenia and infection in a BsAbs-treated cohort and compared its behavior with that observed in CAR-T cells therapy. **Methods:** We conducted a single-center retrospective study in 193 patients with multiple myeloma treated with CAR T-cells or BsAbs between 2018 and 2025. Because some patients received more than one qualifying immunotherapy, the analysis included 220 treatment lines. CAR-HT was available in 214 evaluable treatment lines and classified as low or high risk. In BsAbs-treated patients, early infection was defined as infection by day 90. Group comparisons used chi-square/Fisher exact and Mann-Whitney U tests. Associations with grade 4 neutropenia (G4 neutropenia) and infection were evaluated using logistic regression with cluster-robust standard errors at the patient level. Adjusted models included age, infections, comorbidities, and hypogammaglobulinemia. Discrimination was explored using AUC. **Results:** Median age was 63 years (38–88), 54.4% were male, and median number of prior lines was 4 (RIQ 3–5). Regarding the immunotherapy type (BsAbs vs CAR T-cells), 59.5% of treatment lines involved BsAbs and 40.5% CAR T-cells; 42.1% were classified as high CAR-HT risk. In the evaluable cohort, high CAR-HT was associated with G4 neutropenia (55.6% vs 36.3%; OR, 2.19; 95% CI, 1.28–3.77; p = 0.004). Among CAR T-cells–treated patients, high CAR-HT was associated with G4 neutropenia (97.4% vs 78.0%; p = 0.008) and longer hospitalization stay (median/IQR, 14 [14–29] vs 14 [14–15] days; p = 0.038). Among BsAbs-treated patients, high CAR-HT was associated with higher incidence of infections by day 90 (87.9% vs 54.2%; p = 0.004), G4 neutropenia (23.5% vs 8.1%; p = 0.016), and longer hospital stay (median, 11 vs 7 days; p = 0.0015). In adjusted analyses restricted to BsAbs, high CAR-HT remained associated with infection by day 90 (OR, 6.10; 95% CI, 1.62–22.98; p = 0.008), higher incidence of G4 neutropenia (OR, 3.01; 95% CI, 1.02–8.85; p = 0.046), and longer neutropenia duration (median, 2 vs 0 days; p = 0.0001). CAR-HT showed acceptable discrimination for infection by day 90 (AUC, 0.712) and modest discrimination for G4 neutropenia (AUC, 0.651). No significant interaction was observed between CAR-HT risk group and immunotherapy type for G4 neutropenia (p interaction = 0.328). **Conclusions:** In multiple myeloma patients receiving BsAbs, CAR-HT identifies increased risk of hematotoxicity and early infection, with similar hematotoxicity associations across BsAbs and CAR T-cell therapy. These findings support CAR-HT as a practical pretreatment tool to guide monitoring, growth factor planning, and infection-directed supportive care in the BsAbs setting.

PA-065

CAR-Tscm Cells as an Effective Immune Treatment to Multiple Myeloma Patients

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Introduction: Since T memory stem cell (TSCM) is a kind of cell with strong self-renewal ability, long-term persistence, proliferation ability and anti-tumor activity, and is an ideal candidate cell for cancer immunotherapy. We aimed to explore the amount of TSCM cells in multiplt myeloma (MM) and the established a method to expansion TSCM in vitro, and to further explore the effect of CAR-T cells prepared by TSCM on MM cells. **Methods:** TSCM cells (CD45RA+CCR7+CD62L+CD95+) were detected with Flow cytometry, further induced TSCM cells expansion in vitro by using IL-2+MEKi+Il-15 combination, TSCM cell-based CAR-T cells were constructed in vitro, further the therapeutic effect of CAR-Tscm cells in MM-loaded NSG mouse model were explored. **Results:** The proportion of TSCM cells is reduced in patients with MM, but their function is stronger than that of CTL cells, and the use of IL-2+ Meki+Il-15 in vitro can induce the expansion of TSCM cells and promote their antitumor capacity; Further, Targeting BCMA CAR-Tscm cells as an effective immune treatment to multiple myeloma patients. CAR-T cells were constructed using TSCM cells in vitro, and in vitro experiments confirmed that they had similar killing effects to conventional CAR-T cells on MM cells in an NSG mouse model of MM tumor burden; CAR-Tscm cells were demonstrated to have similar effects to conventional CAR-T therapy, and demonstrated stronger antitumor effects than conventional CAR-T in contralateral tumorigenic models. **Conclusions:** CAR-Tscm cells are a potentially effective treatment for multiple myeloma.

PA-067

CB-011, an Allogeneic Anti-BCMA CAR-T Cell Therapy with Immune Cloaking, for Patients with Relapsed/Refractory Multiple Myeloma (CaMMouflage Phase 1 Trial)

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Introduction: CB-011 is an allogeneic anti-BCMA CAR-T cell therapy with immune cloaking manufactured from healthy donor T cells. It features 4 genome edits made with the CRISPR-Cas12a chRDNA genome-editing technology: (1) insertion of a BCMA-specific CAR, (2) TRAC gene knockout (KO) to reduce risk of GvHD, (3) B2M gene KO to reduce T cell-mediated rejection, and (4) B2M–HLA-E fusion insertion to blunt NK cell-mediated rejection. CaMMouflage is a Phase 1 trial (NCT05722418) evaluating the safety and efficacy of CB-011 in patients (pts) with r/r MM and to determine the RP2D. **Methods:** Pts received ≥3 prior lines of therapy (including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody). Pts received lymphodepletion (LD) for 3 days with 300 mg/m2 or 500 mg/m2 of cyclophosphamide (cy) and 30 mg/m2 of fludarabine, followed by a single infusion of CB-011 at doses of 50 million (M), 150M, 300M, 450M, or 800M CAR-T cells. The recommended dose for expansion (RDE) was 450M CAR-T cells after the 500 cy LD regimen. **Results:** As of Sep 24, 2025, a total of 48 pts received CB-011. The median age was 68.5 years (49–84). Pts received a median of 4 prior lines of therapy (3–11), and 17% received prior BCMA-targeted therapy. 56% of pts had high-risk cytogenetics and 35% had extramedullary disease. In pts who received the 500 cy LD regimen (N = 35), infections occurred in 49% of pts (14%, grade ≥3), CRS occurred in 31% of pts (3%, grade ≥3), ICANS occurred in 9% of pts (no grade ≥3), immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome occurred in 9% of pts (3%, grade ≥3), and prolonged grade ≥3 cytopenias occurred in 33% of pts. No cases of GvHD, immune effector cell-associated enterocolitis, parkinsonism, or cranial nerve palsies were observed at any dose level. At the RDE, two deaths occurred [pneumonia (unrelated), ICAHT (related)] and one grade 4 Guillain-Barré Syndrome (related), which is resolving. These events prompted implementation of prophylactic measures/early intervention. For BCMA-naïve pts who received the RDE (500 cy LD and 450M CAR-T cell dose) of CB-011 (N = 12), the ORR was 92% and the ≥CR rate was 75%. At a median follow-up of 8.3 months, 7/12 (58%) pts were in a VGPR or better at ≥6 months. Of the MRD-evaluable pts, 10/11 (91%) achieved MRD negativity at 10-5 threshold. CB-011 exhibits a central memory CD8T cell phenotype at peak of expansion. CB-011 expansion directly correlated with clinical responses. Rapid recovery of endogenous T and NK cells was observed with endogenous B cells recovering within 6 months regardless of clinical response. Updated data will be presented. **Conclusions:** In a high-risk, heavily pretreated r/r MM pt population, CB-011 drove deep and durable responses with a manageable safety profile. Based on these results, the RDE is 450M CB-011 CAR-T cells after 500 cy LD. The dose expansion phase of CaMMouflage is enrolling BCMA-naïve and prior BCMA therapy-exposed r/r MM patients.

PA-068

CD3-Engaging Bispecific Antibodies Convert Human Regulatory T Cells into Cytotoxic Effectors

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Introduction: Bispecific T-cell engagers (BTCEs) have revolutionized therapy for multiple myeloma (MM) and B-cell malignancies by redirecting cytotoxic T cells toward malignant targets, yet the immunological determinants of their efficacy and resistance remain poorly understood. Immunosuppressive regulatory T cells (Tregs) accumulate early in MM, but whether BTCEs actively modulate this population to impact therapeutic outcomes remains unknown. **Methods:** We performed longitudinal single-cell RNA/TCR/ATAC-sequencing and high-dimensional spectral flow cytometry of 17 newly diagnosed multipe myeloma (NDMM) patients across induction therapy. 11 patients were treated with teclistamab plus daratumumab, lenalidomide, and dexamethasone (Tec-DRD, n = 11) in the ongoing MajesTEC-5 (HD10/DSMMXX) trial (NCT05695508); 6 patients recived standard-of-care DRD as

controls (n = 6). Functional validation utilized plasma cell-T-cell co-cultures, killing assays, cytokine ELISAs, and qPCRs of key T cell signaling pathways. For mechanistic investigations focused on the AP-1 transcription factor complex CRISPR mediated perturbation and phosphorylation profiling of primary Tregs were performed. Generalizability was tested in vitro using three BTCEs (teclistamab (BCMA × CD3), blinatumomab (CD19 × CD3), glofitamab (CD20 × CD3)) to redirect primary human Tregs towards BCMA+, CD19+, and CD20+ cell lines. Nontargeting BTCEs and anti-CD3 antibodies were used as controls. **Results:** Spectral flow cytometry revealed profound post-treatment Treg shifts in Tec-DRD-treated patients, characterized by naive Treg loss, memory Treg expansion, increased activation, and elevated cytotoxic markers. Concordantly, single-cell genomics showed BTCE-induced transcriptional and epigenetic reprogramming of Tregs into FOXP3low IL2RAlowcytotoxic phenotype ("exTregs") expressing NKG7, GZMA/B, TBX21, and CCL5, which was absent in DRD controls. Isolated exTregs mediated direct plasma cell lysis in vitro, strictly depending on BTCE-mediated antigen-specific synapse formation. IMiDs synergized with BTCEs by destabilizing the suppressive Treg phenotype via Helios (IKZF2) downregulation, augmenting granzyme production. Mechanistically, scATAC-seq revealed increased chromatin accessibility at AP-1 motifs, confirming a BATF/JUNB-driven transcriptional program governing effector conversion. This cytotoxic reprogramming was conserved across BCMA, CD19, and CD20-targeting BTCEs. **Conclusions:** Our findings uncover a novel mechanism where BTCEs actively convert suppressive Tregs into cytotoxic, pro-inflammatory effectors that contribute to antitumor activity. Multi-color flow cytometry validates these dynamics in patients, showing a shift toward activated, cytotoxic memory Tregs. We identified the BATF/JUNB axis and IMiD-mediated Helios destabilization as targetable regulators of this process, supporting rational combination regimens to enhance T-cell-redirecting immunotherapies.

PA-069

CEVOLUTION: A Randomized Phase III Trial Comparing Cevostamab Plus Pomalidomide and Dexamethasone (Pom-Dex) Versus Standard of Care (SOC) in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Efficacious new treatments are needed for RRMM patients (pts) with prior anti-CD38 antibody (Ab) and lenalidomide (len) exposure. FcRH5 is ubiquitously expressed on malignant plasma cells. Cevostamab, a FcRH5xCD3 T-cell-engaging bispecific Ab, has shown promising activity and manageable safety as monotherapy in late-line RRMM. Combining cevostamab with MM therapies that augment T-cell activity could enhance efficacy. Pomalidomide (pom), an IMiD that exhibits potent T-cell co-stimulatory effects, is clinically active when given alone or with dexamethasone (dex) in RRMM. In the Arm B randomized dose-expansion of the Phase Ib CAMMA 1 study, cevostamab plus pom-dex had manageable safety and induced durable remissions in pts with RRMM, the majority of whom were triple-class exposed and refractory to their last therapy (Harrison et al. ASH 2025). We describe the design of the open-label, multicenter, randomized Phase III CEVOLUTION study that aims to compare the efficacy and safety of cevostamab plus pom-dex vs SOC in pts with RRMM who have received an anti-CD38 Ab and len as part of 1–3 prior lines of therapy. **Methods:** Additional inclusion criteria include measurable disease, an ECOG PS of 0 or 1 and informed consent. Prior exposure to pom and BCMA, GPRC5D and/or FcRH5-targeted agents is not allowed. Pts will be randomized 1:1 to cevostamab plus pom-dex (Arm A) or investigator's choice of SOC (Arm B), stratified by number of prior lines (1 vs 2 vs 3), ISS stage (1 vs >1) and choice of SOC. In Arm A, step-up doses of cevostamab will be given on Cycle (C) 1 Day (D) 1, C1D2 (or D3 or D4) and C1D8. Target doses (70 mg) will be given on C1D9 (or D10 or D11), D1 and D15 of C2–7 (Q2W) and D1 of C8+ (Q4W). Pom (D1–21) will be given from C2+. In Arm B, pts will receive investigator's choice of either daratumumab plus pom-dex, elotuzumab plus pom-dex or carfilzomib plus dex, with the choice informed by the pts prior treatment exposure and refractoriness to individual classes of agents. In both arms, treatment will continue until disease progression or unacceptable toxicity. The primary objective is to compare the efficacy of cevostamab plus pom-dex vs SOC based on dual primary endpoints of rate of minimal residual disease-negative complete response at the 10-5 level at 9 months and progression-free survival. Key secondary endpoints are the rate of very good partial response or better, overall survival, change from baseline in the disease symptom scale of the EORTC QLQ-MY20 at 9 months and change from baseline in the global health status/quality of life scale of the EORTC QLQ-C30 at 9 months. Safety, pharmacokinetics, immunogenicity and pharmacodynamics will also be assessed. **Results:** CEVOLUTION will enroll ~380 pts across ~140 global sites. First patient enrollment is expected in Q2 2026. **Conclusions:** CEVOLUTION is a pivotal Phase III trial that is expected to inform the clinical efficacy and safety of cevostamab plus pom-dex in pts with RRMM.

PA-070

Characteristics and Outcomes of Central Nervous System Multiple Myeloma

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Introduction: Central nervous system (CNS) myeloma is a rare extramedullary (EM) presentation, with poor prognosis. Here we present a series on CNS myeloma cases. **Methods:** We evaluated MM patients (pts) diagnosed & treated for CNS myeloma at our institution between 1/2020–4/2026. Complete response (CR) was defined as resolution of CNS lesions on Magnetic Resonance Imaging (MRI) & no atypical plasma cells in cerebrospinal fluid (CSF), partial response (PR) was either of the 2 as above, & no response (NR) otherwise. **Results:** Five pts were identified: 4 males, median age 65 years (range (R): 55–69), 4 Caucasians. At diagnosis, median R-ISS score was 2 (R:1–3), 3 pts non-CNS EM disease (EMD). 2 pts had high risk (HR) MM according to International Myeloma Working Group classification 2025 for HRMM. At diagnosis, median bone marrow (BM) plasma cell % was 28 (R: 7–77). 1 pt had plasma cell leukemia (≥5% circulating plasma cells). At CNS myeloma diagnosis, 3 pts had no evidence of systemic disease based on monoclonal labs. Two pts had concurrent non-CNS EMD. 4 of 5 were triple refractory & four had prior autologous stem cell transplant (ASCT). The median prior lines of treatment were 2 (R:1–3). None had received Chimeric Antigen Receptor-T cell or Bispecific antibodies. Median progression free survival (PFS) after 1st line treatment was 20 months (m) (R: 2–48) & median PFS after ASCT was 14.5 m (R:3–23). Median time to CNS myeloma development from diagnosis was 23.4 m (R: 11–50). All pts had both MRI & CSF confirmation. 3 pts had involvement of both brain/cranial nerves & spinal cord, while 2 only had the former. Presenting symptoms included cranial nerve palsies (4/5), gait instability (1/5) & lower extremity weakness (1/5). Median CSF plasma cell % was 65 (R: 44–93). Pts were treated with a combination of CNS directed therapy (intrathecal (IT) chemotherapy: 5/5, steroids: 2/5, brain radiation: 3/5). Pts received a median of 4 (R:1–16) doses of IT therapy, 4/5 received thiotepa (2 in combination with methotrexate & cytarabine, & mercaptopurine respectively), & 1 received methotrexate alone. Systemic treatment included combination of proteasome inhibitors, immunomodulatory drugs, anti-CD38 antibodies, selinexor, & other novel therapeutics (1 received ciltacabtagene autoleucel (ciltacel), & another received talquetamab followed by teclistamab). CNS response to treatment was CR (1/5), PR (2/5), NR (1/5), & not assessed (1/5). Pts with CSF clearance (2/5) had received ciltacel & VD-PACE, while 2/5 with radiographic response had received ciltacel & daratumumab-pomalidomide. Median overall survival from myeloma diagnosis was 28 m (R: 14–75), while median survival from CNS myeloma diagnosis was 5 m (R: 3–25). 1 patient (received ciltacel) was alive at the end of the study. **Conclusions:** CNS myeloma pts had a dismal prognosis. All pts relapsed within 30 m of ASCT, pointing to functionally high-risk disease. This highlights the need for increased awareness for early identification & CNS directed therapies.

PA-071

Characteristics of Infections in Patients Treated with Bispecific Antibodies and the Impact of Immunoglobulin Replacement: A Single Center Experience

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Introduction: Bispecific antibodies (BsAbs) have demonstrated remarkable activity in heavily pretreated multiple myeloma patients, but are associated with substantial infection risk in both clinical trials and real-world settings, driven by T- and B-cell dysfunction, hypogammaglobulinemia and prior use of immunosuppressive therapies. Given their increasing use and indications, also in earlier lines, we describe infection incidence and characteristics as well as the role of Ig replacement in a cohort of BsAb treated patients. **Methods:** This single center analysis included 148 consecutive myeloma patients (79 males and 69 females), treated with BsAbs (n = 125 targeting BCMA, n = 15 GPRC5d and n = 8 combination) starting treatment between 1/2022 and 1/2026; 11 patients received two sequential therapies and one patient three consecutive treatment lines with BsAbs. All patients received prophylaxis for VZV and PJP; CMV monitoring was individualized based on baseline assessment of viral load. Immunoglobulin (Ig) replacement strategy changed over time and was adopted routinely later during the study period. **Results:** Patients had a median of 2 prior lines of therapy; the median follow up after start of BsAb was 9 months. At least one infection occurred in 102 (68%) patients. Median time to first infection was 61 days and in 59% the first infectious episodes occurred during the first 2 cycles of therapy. The most frequent infection sites were lower (44%) and upper (34%) respiratory tract, GI (9%) and urinary tract (6%). Most infections were grade 2 (42.5% of all patients had at least one Gr 2 infection) but 30.4% had at least one Gr≥3 infection (including grade 5 in 10.8%). BsAb therapy was discontinued in 13 (9%) patients do to the severity and the complications of the infection. The median number of infectious episodes per patient was 1.7 (IQR 0–2), with 31% of patients having 3 or more grade 2–5 infections. At the time of first infection, 55% of patients were in disease remission. Higher number of prior lines was associated with numerically higher incidence of infections. 67.5% of the patients received Ig

supplementation; 40% started Ig replacement prophylactically. An infection occurred in 75% of patients not on prophylactic Ig vs. 25% of patients receiving Ig supplementation. Both upper and lower respiratory tract infection rates of both microbial and viral origin were reduced with prophylactic Ig but the prophylactic Ig reduced mostly grade 2 and had less impact on grade 3–5 infections. **Conclusions:** Use of BsAbs is associated with a significant burden of infections, including severe (Gr≥3) associated with need for hospitalization or death. Although early prophylactic use of Ig supplementation does not abolish this risk, it can help in the significant reduction of infection burden. Nonetheless, further optimization of prophylactic strategies is required while physicians and patients should be alert as serious infections can occur despite prophylactic measures.

PA-072

Characterization of Hematologic Adverse Events and Infections with Mezigdomide, Carfilzomib, and Dexamethasone (MeziKd) in Relapsed/Refractory Multiple Myeloma (RRMM): Phase 3 SUCCESSOR-2 Trial

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Introduction: In the phase 3 SUCCESSOR-2 trial (NCT05552976), MeziKd improved progression-free survival vs Kd (median 18.0 vs 8.3 months) in patients (pts) with RRMM previously treated with anti-CD38 monoclonal antibodies (mAbs) and lenalidomide (LEN). Hematologic adverse events (AEs) and infections were the most frequent toxicities. This analysis evaluates the incidence, timing, and clinical management of neutropenia, thrombocytopenia, and infections associated with MeziKd. **Methods:** Adult pts with RRMM and ≥1 prior line of therapy (including anti-CD38 mAbs and LEN) were randomized to MeziKd or Kd. Hematologic AEs and infections were assessed for incidence, severity, seriousness, time to onset, and duration. Dose modifications were permitted. Neutropenia was also managed with granulocyte colony-stimulating factor (G-CSF), and infections with anti-infective prophylaxis. **Results:** At the data cutoff (January 15, 2026), this analysis included 288 pts treated with MeziKd and 186 with Kd. Median follow up was 10.6 months. The most common grade (Gr) 3/4 hematologic AEs in the MeziKd vs Kd arm were neutropenia (61% vs 9%) and thrombocytopenia (39% vs 23%); no Gr 5 hematologic AEs were reported. In the MeziKd and Kd arms, time to onset and duration of Gr 3/4 neutropenia were similar. In each arm, 7% of pts with Gr 3/4 thrombocytopenia had concurrent bleeding. Overall, 73% of pts in the MeziKd arm had an infection of any Gr (Gr 3/4 34%) vs 54% (Gr 3/4 16%) in the Kd arm; Gr 4 (6% vs 1%) and Gr 5 (2% vs 1%) events were uncommon. Gr 3/4 infections occurred earlier with MeziKd (median 73 days vs Kd 114 days), but did not translate into more prolonged infections (median duration 10 vs 8 days). Serious infections occurred in 37% (MeziKd) and 16% (Kd) of pts, with pneumonia being the most common. Most infections (MeziKd, 84%; Kd, 98%) were not concurrent with Gr 4 neutropenia. Any-Gr hypogammaglobulinemia occurred in 10% (MeziKd) and 6% (Kd) of pts; immunoglobulin replacement therapy was given in 32% vs 21%. Antiviral prophylaxis compliance was high in all pts. Mezi dose interruptions or reductions occurred due to neutropenia (38% and 16%, respectively), thrombocytopenia (20% and 14%), and infections (52% and 6%). Mezi discontinuations due to neutropenia (< 1%) or infection (2%) were uncommon; no pts discontinued Mezi due to thrombocytopenia. In the MeziKd arm, 89% of pts with Gr 3/4 neutropenia received G-CSF; median Mezi treatment duration was longer in pts who received G-CSF than the overall MeziKd group (40 vs 38 weeks). **Conclusions:** In SUCCESSOR-2, increased neutropenia, thrombocytopenia, and infections observed with MeziKd vs Kd were manageable with standard clinical practice (dose modifications, G-CSF, infection prophylaxis), with low Mezi discontinuation due to these AEs. G-CSF for Gr 3/4 neutropenia was an effective strategy to maintain treatment. MeziKd represents a clinically feasible outpatient treatment option for anti-CD38 mAb- and LEN-exposed RRMM.

PA-073

Characterization of the IKZF1 Interactome in Multiple Myeloma and Its Modulation by CELMoDs

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Introduction: IKZF1 is a key transcription factor in multiple myeloma (MM) that supports plasma cell survival and is targeted for proteasomal degradation via cereblon (CRBN) by IMiDs and CELMoDs. Despite clinical efficacy, IMiDs resistance frequently arises, often due to CRBN loss or mutation. To better understand IKZF1 function and resistance mechanisms, we mapped the IKZF1 interactome in MM and assessed its remodeling under CELMoD treatment. **Methods:** IKZF1 interactors were identified using TurboID proximity labeling in MM.1S cells expressing IKZF1-TurboID or nuclear (NLS-)TurboID controls, followed by mezigdomide treatment with proteasome inhibitor, streptavidin enrichment, and LC-MS analysis. Complementary, a CRISPR-Cas9 BISON library screen was performed in MM.1S cells expressing mCherry-IKZF1, treated with mezigdomide. FACS-sorted mCherryhigh cells underwent sgRNA sequencing to identify proteasome system members regulating IKZF1. **Results:** TurboID-based proximity labeling enabled a comprehensive characterization of the IKZF1 interactome in MM. Consistent with its known role as a transcriptional regulator, IKZF1 associated with established interaction partners including members of the Ikaros family (IKZF3/4), NuRD complex, and SUMOylation factors. In addition, we identified a broad set of proximal proteins such as components of the AP-1 transcription factor complex, MAPK signaling pathways, APC/C, proteasome components, and nuclear transport machinery. GSEA highlighted pathways including TNFα/NF-κB signaling, interferon response, and CD40 signaling. Notably, IKZF1 associated with MM-essential proteins such as PRDM1, MCL1, and CCND2. Furthermore, our assay uncovered TRIM ligases and Cullin-Ring ligases (CRL), specifically CRL1 and CRL3 members proximal to IKZF1.

Under mezigdomide treatment, IKZF1 showed increased association with the CRL4-CRBN complex and the 26S proteasome, alongside enrichment of negative regulators of NF-κB (CYLD, TNFAIP3). In contrast, AP-1 and ribonucleoprotein complexes were reduced, while APC/C and core NF-κB components (RELA, NFKBIE) remained stable. GSEA revealed enrichment of mitotic spindle and Rho GTPase signaling, whereas inflammatory signaling, MYC targets, and TNFα/NF-κB pathways were reduced.

CRISPR screening confirmed CRBN, DDB1, and RBX1 as key mediators of IKZF1 degradation. Integration with proteomics data is consistent with a potential direct involvement of IKZF1 in NF-κB signaling, with joint hits including NF-κB regulators, although CRBN-dependent degradation remained the dominant mechanism under mezigdomide. **Conclusions:** This study provides the first comprehensive map of the IKZF1 interactome in MM, integrating proximity labeling and functional genomics. We reveal extensive, MM-specific IKZF1 interactions and a network of NF-κB regulators associated with IKZF1, suggesting crosstalk between IKZF1 regulation and NF-κB signaling under CELMoD treatment. These findings may inform strategies to overcome drug resistance.

PA-074

Characterizing Plasma Cell Leukemia Treatment Patterns and Data Gaps in a Patient-Powered Registry: A Call to Action for EHR Integration

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Introduction: Plasma Cell Leukemia (PCL) is a rare and aggressive plasma cell malignancy with historically dismal clinical outcomes. Patient-powered registries offer a unique vehicle to aggregate real-world data (RWD) for rare diseases, yet data completeness remains an ongoing challenge. We evaluated the HealthTree Registry PCL cohort to map baseline clinical characteristics, advanced treatment utilization, and structural data gaps. **Methods:** Real-world data from 53 patients with a PCL diagnosis in the HealthTree Registry (data cut: May 2026) were evaluated. Patients were stratified by disease subtype (Primary PCL [pPCL], Secondary PCL [sPCL], or self-reported PCL with no subtype) and clinical validation source (Electronic Health Record [EHR]-confirmed vs. patient self-reported only). **Results:** The cohort (n = 53) included 33 pPCL (62%), 12 sPCL (23%), and 8 (15%) self-reported PCL with no subtype patients, with a median age at diagnosis of 67 years. Overall, 34 patients (64.2%) had EHR-confirmed diagnoses, while 19 (35.8%) were self-reported only. The data validation source heavily dictated tracking capabilities: 64.7% of EHR-confirmed patients had detailed line-of-therapy (LOT) records compared to 0% of self-reported patients. Among the 22 treated (all EHR-linked) patients, utilization of advanced therapeutics was remarkably high: 10 (45.5%) received bispecific antibodies, 7 (31.8%) received CAR-T cell therapy, and 10 (45.5%) underwent a stem cell transplant across highly heterogeneous, unique treatment sequences. Cytogenetic (FISH) data was available for 28 patients (52.8%), with 64% (18/28) harboring ≥1 high-risk feature, including del(17p) (10/23, 43%), t(4;14) (3/10, 30%), and t (14;16) (6/11, 55%). However, cytogenetics were completely missing for 25 patients (47.2%), and vital status capture is currently limited, restricting immediate survival analyses and highlighting a key target for upcoming registry enrichment. **Conclusions:** Patient-powered registries successfully capture real-world utilization of novel advanced therapies in rare plasma cell dyscrasias, but data maturity relies heavily

on direct clinical data linkage. To mitigate these identified data gaps and enrich this cohort, a targeted advocacy campaign will launch concurrently with the expected opening of the QUANTUM (Alliance A062401; NCT07605416) trial on July 1, 2026. This initiative will focus on expanding PCL registry recruitment and systematically engaging self-reporting patients to authorize EHR integration, transforming consumer-entered profiles into robust, clinically validated real-world evidence.

PA-075

Chemo-Free Mobilization with Upfront Plerixafor Improves Efficiency and Reduces Procedural Burden in Multiple Myeloma

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Introduction: Stem cell mobilization is essential for autologous stem cell transplantation (ASCT) in multiple myeloma (MM). In the era of novel induction therapies, particularly lenalidomide and anti-CD38 monoclonal antibodies, impaired mobilization has become increasingly recognized, highlighting the need for optimized strategies in routine clinical practice. **Methods:** We retrospectively analyzed 220 consecutive MM patients undergoing first mobilization prior to ASCT at a single tertiary center. Patients received either upfront plerixafor plus G-CSF (PLE group, n = 98) or cyclophosphamide plus G-CSF (CY group, n = 122). Primary endpoints included mobilization success and CD34+ yield. Secondary endpoints included apheresis sessions, toxicity, engraftment, and survival. Multivariable analysis identified predictors of optimal collection (>4 × 10^6 CD34+ cells/kg on day 1). **Results:** Upfront plerixafor significantly improved mobilization success compared with CY-based mobilization (85.7% vs 74.6%, P = 0.042) and increased day-1 CD34+ yield. The PLE group required fewer apheresis sessions (median 1 vs 2 days, P < 0.001), indicating a substantial reduction in procedural burden. Chemotherapy-based mobilization was associated with markedly higher rates of febrile neutropenia (42.6% vs 0%, P < 0.02) and increased antibiotic use. Engraftment kinetics and survival outcomes were comparable between groups. Cyclophosphamide mobilization, lower baseline platelet count, and lower peripheral CD34+ levels independently predicted suboptimal collection. **Conclusions:** In this large real-world cohort, upfront plerixafor provided superior mobilization efficiency with reduced toxicity and procedural burden compared with chemotherapy-based strategies, without compromising transplant outcomes. These findings support a shift toward chemo-free mobilization approaches and suggest potential benefits in healthcare resource utilization, particularly in the context of modern induction therapies. This pragmatic strategy may have broad applicability across diverse clinical settings.

PA-077

CIBMTR Real-World Outcomes of Frail Patients Treated with Idecabtagene Vicleucel

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Introduction: Idecabtagene vicleucel (ide-cel) is approved for patients (pts) with relapsed/refractory multiple myeloma (RRMM) after ≥2 prior lines of therapy. A prior real-world study (Akhtar et al. Blood Adv. 2025;54:212) evaluated outcomes by frailty with a median follow-up of 11.6 mo. Using data with a longer follow-up and more pts, this analysis further assesses ide-cel effectiveness and safety in frail pts. **Methods:** This retrospective study used real-world data from the CIBMTR registry. It included pts who received commercial ide-cel for RRMM between 12 May 2021 and 10 August 2023 and had the 100-day post-infusion form completed. Outcomes included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Frailty was determined based on age, hematopoietic cell transplantation-specific comorbidity index, and ECOG PS (score ≥2: frail). This same frailty definition was used by Akhtar et al, which is an adapted version of the simplified frailty index (Facon et al. Leukemia. 2020;34:224; Yohay et al. Br J Haematol. 2024;205:2370). Frailty status could not be determined for 56 of 996 pts (5.6%) as ≥1 components of the frailty index were missing. **Results:** Of 996 pts, 461 (46.3%) were frail. Median follow-up was 24.4 mo. Frail pts were older than non-frail pts (median: 68.1 y vs 64.5 y), had higher prevalence of comorbidities (95.9% vs 61.8%), high-risk cytogenetics (26.5% vs 19.2%), and ECOG PS score ≥2 (11.1% vs 0.0%). Time from diagnosis to infusion was similar between frail and non-frail pts; however, frail pts were significantly older at diagnosis than non-frail pts. ORR (95% CI) was comparable in frail and non-frail pts (77.0% [72.9–80.8] vs 78.5% [74.5–82.1]), including VGPR+ rates (62.3% vs 63.7%). Median PFS (95% CI) was 10.7 (9.1–12.1) mo and 11.5 (9.5–12.5) mo. At 2 y, 25.6% (21.2–30.1) of frail pts and 26.7% (22.5–31.1) of non-frail pts were alive and progression-free. OS (95% CI) at 24 mo was 59.1% (54.1–63.7) vs 64.0% (59.2–68.4). Grade ≥3 cytokine release syndrome occurred in 4.3% of frail vs 2.3% of non-frail pts. Frail pts had higher rates of grade ≥3 immune cell–associated neurotoxicity syndrome (ICANS; 6.7% vs 3.8%; P = 0.04). Treatment-related mortality (95% CI) was comparable in frail vs non-frail pts at 12 mo (4.9% [3.2–7.2] vs 3.2% [1.9–5.1]) and 24 mo (6.4% [4.3–9.0] vs 5.0% [3.2–7.3]), with no evidence of a difference over the entire follow-up (P = 0.29). Relapse rates were similar at both timepoints with no difference over time (P = 0.94). Prolonged cytopenia occurred in

32.1% vs 25.1% (P = 0.023) and infections in 64.9% vs 60.8% (P = 0.22). Main causes of death in frail pts were myeloma progression (30.2%), bacterial infection (2.4%), and pulmonary failure (1.3%). Longer follow-up data will be reported in the presentation. **Conclusions:** With extended follow-up, ide-cel demonstrated comparable effectiveness and broadly similar safety, except for higher ICANS, in frail and non-frail pts, supporting its use across a wide RRMM population.

PA-078

CIBMTR Real-World Outcomes of Older Patients Treated with Idecabtagene Vicleucel

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Introduction: Idecabtagene vicleucel (ide-cel) is approved for patients (pts) with relapsed/refractory multiple myeloma (RRMM) after ≥2 prior lines of therapy. RRMM is increasingly prominent in the elderly population, with a median age at diagnosis of 71 y (Turresson et al. Eur J Haematol. 2018;101:237). A prior real-world study (Akhtar et al. Blood Adv. 2025;54:212) reported outcomes by age with a median follow-up of 11.6 mo. Using data with a longer follow-up, more pts, and an age cut-off of 75 y, this analysis further evaluates effectiveness and safety of ide-cel in older pts. **Methods:** This retrospective study used real-world data from the CIBMTR registry. It included pts who received commercial ide-cel for RRMM between 12 May 2021 and 10 August 2023 and had the 100-day post-infusion form completed. Outcomes included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Pts were analyzed by age (>75 y vs ≤75 y). **Results:** Of 996 pts, 149 (15.0%) were aged >75 y. Median follow-up was 24.4 mo. Compared with pts ≤75 y, pts >75 y had numerically higher prevalence of comorbidities (83.9% vs 77.3%), high-risk cytogenetics (28.2% vs 22.2%), and ECOG PS score ≥2 (9.4% vs 4.4%). Median age at diagnosis was 66.3 y for all pts. Time from diagnosis to infusion was similar between groups. Time from leukapheresis to infusion was also similar between pts >75 y and ≤75 y (median [IQR], 45 [42–49] days vs 46 [42–50] days). There was no evidence of reduced ORR (95% CI) in pts >75 y vs ≤75 y (84.6% [77.7–90.0] vs 76.7% [73.7–79.5], P = 0.03), including VGPR+ rates of 67.8% vs 62.2%. Median PFS (95% CI) was comparable (12.4 [10.6–17.2] mo vs 10.2 [9.3–11.8] mo, respectively). At 2 y, 29.5% (21.3–38.2) of pts >75 y and 25.2% (22.1–28.4) of pts ≤75 y were alive and progression-free. OS (95% CI) at 24 mo was similar (56.4% [46.9–64.9] vs 61.8% [58.2–65.1]). Grade ≥3 cytokine release syndrome occurred in 2.0% of pts >75 y vs 3.7% of pts ≤75 y, while grade ≥3 immune cell–associated neurotoxicity syndrome (ICANS) occurred in 8.1% vs 4.7% (P = 0.09). Treatment-related mortality (95% CI) was higher in pts >75 y at 12 mo (6.9% [3.5–11.8] vs 3.6% [2.5–5.1]) and 24 mo (10.1% [5.5–16.2] vs 4.9% [3.6–6.6]). Prolonged cytopenia occurred in 22.1% of pts >75 y and 29.9% of pts ≤75 y. Infection rates (60.4% vs 63.0%) were similar between groups. The 3 main causes of death of pts >75 y included myeloma progression (28.9%), bacterial and viral infections (4.7%), and intercranial hemorrhage (1.3%). Longer follow-up data will be reported in the presentation. **Conclusions:** With extended follow-up, ide-cel effectiveness (ORR, PFS), as well as safety, was broadly comparable across age groups, albeit with numerically higher treatment-related mortality in older patients. Findings are directionally consistent with 6-mo outcomes reported for an earlier data cut and continue to highlight the benefit of ide-cel in older pts who may typically be overlooked for CAR T therapy.

PA-079

Ciltacabtagene Autoleucel as Early versus Late Line of Therapy for Patients with Relapsed Refractory Multiple Myeloma: A Real-World Analysis

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Introduction: While ciltacabtagene autoleucel (cilta-cel) has demonstrated remarkable efficacy for relapsed refractory multiple myeloma (RRMM), real-world data evaluating the impact of timing of administration remain limited. **Methods:** We performed a single center retrospective analysis of RRMM patients receiving commercial cilta-cel, stratified into early (1–3 prior lines of therapy [LOT]) and late (≥4 LOT) groups, to assess efficacy and safety outcomes. Primary endpoints included progression-free survival (PFS) and overall survival (OS). Univariable and multivariable Cox proportional hazards models were constructed to evaluate predictors of outcomes. Inverse probability weighting (IPW) was applied to adjust for baseline imbalances between groups, including disease burden, functionally high-risk (FHR) disease, cytogenetic risk, and extramedullary disease (EMD). **Results:** A total of 223 patients were included in the analysis, 50 (23%) received cilta-cel early and 173 (77%) received it late. Early and late groups had received median of 3 (1–3) and 5 (4–11) prior

LOT, respectively. While median age (65 years) at infusion, rates of high-risk cytogenetics (49%), EMD (19%), and FHR disease (58%) were comparable between the two groups, patients in the late group had higher rates of prior BCMA therapy (17% vs 0%). Median follow-up was 18 months for the entire cohort, and 13 months vs 21 months in the early and late groups, respectively. The 12-month PFS was 71% (95% CI, 65–78%) for entire cohort, and 86% (95% CI, 75–97%) vs 68% (95% CI, 61–76%) in early vs late groups (p = 0.06), respectively. The 12-month OS was 87% (95% CI, 83–92%) for entire cohort, and similar across early vs late groups (87% vs 87%, p = 0.7). Among patients without prior BCMA exposure within late group, outcomes were favorable, with 12-month PFS and OS of 74% (95% CI, 68–81%) and 89% (95% CI, 85–94%) (p = .003), respectively. Best response rates were comparable between early vs late groups (ORR 98% vs 94%; CR≥ 74% vs 66%). Safety outcomes, including CRS (86% vs 75%), ICANS (6% vs 6.4%), grade ≥3 cytopenias (20% vs 16%) and infections (10% vs 17%) at day +90, and 12-month non-relapse mortality (7.3% vs 5%), were similar between early vs late groups, respectively. Similarly, there were no differences in peak ALC >3.0 in first 30 days (28% each) and risk of non ICANS neurological toxicities (10% each) at day +90. In univariable analyses, later-line therapy was associated with numerically inferior outcomes, though not significant after multivariable adjustment and sensitivity analysis on IPW. Independent predictors of inferior survival included EMD (HR 1.98), high-risk cytogenetics (HR 2.32), and FHR disease (HR 3.03). **Conclusions:** While timing alone may not independently determine outcomes, underlying disease biology remains the dominant driver of survival following cilta-cel, supporting earlier use in patients with adverse features of EMD, high risk cytogenetics, and FHR disease.

PA-080

CIP2A-Centered Survival Signaling in Myeloma Cells: Therapeutic Potential of Osteoblast-Derived Extracellular Vesicles

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Introduction: Protein phosphorylation plays an important role in tumor progression. PP2A, a major serine/threonine phosphatase, is inactivated in many types of cancers. It has been reported that TAK1 is highly expressed and phosphorylated in MM cells, which is vital for MM cell growth, survival, and interaction with the bone marrow microenvironment. In the present study, we aim to clarity the role of the regulation of PP2A activity in sustainable activation of major growth and survival signaling pathways in MM cells and explore the therapeutic implications of targeting this pathway. **Methods:** PP2A activity, CIP2A expression, and signaling pathways were analyzed in MM cell lines cultured alone or with of bone marrow stromal cells, TNF-α, or IL-6. CIP2A function was assessed by genetic silencing and pharmacological inhibitor Celastrol treatment. TAK1 inhibition studies evaluated its role in CIP2A regulation. Mature osteoblast-derived extracellular vesicles (OB-EVs) were isolated from osteogenic cultures using a Hydrogel Adsorption Separation (HAS)-based method. The effects of OB-EVs on MM cell viability and signaling pathways were evaluated by immunoblotting and apoptosis assays. The role of miR-125b was examined using miR-125b agomir and antagomir gain- and loss-of-function experiments. **Results:** PP2A activity was suppressed in MM cells in association with overexpression of cancerous inhibitor of PP2A (CIP2A). Both TAK1 phosphorylation and CIP2A expression were further enhanced in MM by co-culture with bone marrow stromal cells as well as stimulation with TNF-α or IL-6. Genetic silencing of CIP2A or treatment with the CIP2A inhibitor Celastrol suppressed TAK1 expression and phosphorylation and induced apoptotic cell death in MM cells. Interestingly, TAK1 inhibition reduced CIP2A expression to restore PP2A activity in MM cells, suggesting the TAK1-CIP2A-PP2A axis as an important therapeutic target. Besides TAK1-mediated pathways, CIP2A inhibition suppressed IGF1-induced Akt phosphorylation. In sharp contrast to bone marrow stromal cells, precursor of osteoblast, mature osteoblasts induce apoptosis in MM cells with repression of IRF4 and MYC through their elaborating extracellular vesicles (OB-EVs). Importantly, OB-EVs markedly downregulated CIP2A expression along with marked attenuation of IRF4, MYC, TAK1, and Akt-mediated signaling in MM cells. Although OB-EVs contained various miRs, we found that the downregulation of CIP2A was mediated at least in part by miR-125b. Notably, OB-EVs preferentially induced cell death in MM cells without apparent toxicity to surrounding normal hematopoietic cells, supporting their therapeutic potential without harmful hematopoietic toxicity. **Conclusions:** These findings suggest that OB-EVs disrupt a CIP2A-centered survival network sustaining MM cells in the bone marrow microenvironment, highlighting OB-EVs or delivering their containing miRs as a promising therapeutic strategy targeting MM cells acquiring drug resistance in bone marrow niche.

PA-081

Circulating Plasma Cells and C-Reactive Protein Improve ISS-Based Risk Stratification in Japanese Multiple Myeloma

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Introduction: Circulating plasma cells (CPCs) are associated with poor outcomes in multiple myeloma (MM), but the optimal cutoff in Japanese patients remains undefined. C-reactive protein (CRP), reflecting inflammation and interleukin-6 activity, may also have prognostic value. We aimed to establish a simple prognostic model using routinely available International Staging System (ISS), CPC, and CRP data. **Methods:** We retrospectively analyzed 2,068 patients with symptomatic MM or primary plasma cell leukemia registered in a multicenter registry through December 2025. Patients diagnosed by 2018 were assigned to the test cohort (n = 1,507), and those diagnosed from 2019 onward to the validation cohort (n = 561). In the test cohort, the optimal CPC cutoff for predicting 5-year overall survival (OS) was determined using survival ROC analysis and then evaluated in the validation cohort. The primary endpoints were OS and improvement in ISS-based prognostic performance by adding CPC and CRP. Secondary endpoints included clinical features and outcomes among CPC positive patients. Statistical analyses included $\chi 2$ test, Kruskal-Wallis test, log-rank test, Cox proportional hazards models, C-index, and integrated discrimination improvement (IDI). **Results:** A CPC cutoff of 0.3% was identified as optimal in the test cohort. CPC ≥0.3% (CPC+) was also a significant adverse prognostic factor in the validation cohort (hazard ratio [HR] 2.67, 95% confidence interval [CI] 1.72–4.15; $p < 0.001$). CPC+ patients had a higher frequency of ISS stage III, high-risk cytogenetic abnormalities (HRCA), and t(11;14). An apparent OS benefit of upfront daratumumab-containing therapy was not observed in CPC+ patients. In multivariable analysis adjusted for age, performance status ≥2, extramedullary disease, ISS stage III, HRCA, creatinine, calcium, lactate dehydrogenase, and platelet count, both CPC+ (HR 1.80, 95% CI 1.31–2.47; $p < 0.001$) and CRP >0.3 mg/dL (CRP+; HR 1.61, 95% CI 1.23–2.11; $p < 0.001$) remained independent adverse factors for OS. CRP+ was also significantly associated with poor OS among CPC+ patients. Compared with ISS alone (C-index, 0.600), prognostic performance improved after adding CPC+ (C-index, 0.617; $p < 0.001$; IDI, 0.006; $p = 0.009$) and improved further after adding both CPC+ and CRP+ (C-index, 0.645; $p < 0.001$; IDI, 0.016; $p < 0.001$). Based on HRs for OS in the test cohort, ISS stage III, CPC+, and CRP+ were each assigned 1 point. This simple additive prognostic score stratified patients into low (0), intermediate (1), and high (≥2) risk groups and significantly discriminated OS in the validation cohort ($p < 0.001$). **Conclusions:** In this Japanese real-world cohort, CPC ≥0.3% was identified and validated as a clinically relevant cutoff for adverse prognosis. Combining ISS with CPC and CRP, all readily available in routine practice, significantly improved OS prediction and enabled simple, reproducible risk stratification.

PA-082

Circulating Plasma Cells Identify a Disseminated Genomic High-Risk Phenotype Within IMS-IMWG 2025 Staging in Newly Diagnosed Multiple Myeloma

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Introduction: The 2025 International Myeloma Society/International Myeloma Working Group consensus genomic staging (CGS) system has improved genomic risk stratification in multiple myeloma (MM). However, genomic staging alone does not capture whether a high-risk clone has acquired a disseminated phenotype. We investigated whether circulating plasma cells refine CGS-based risk stratification and provide a longitudinal marker of residual circulating disease in newly diagnosed multiple myeloma. **Methods:** We retrospectively analyzed 631 MM patients from the NICHE cohort (NCT04645199) who underwent CPC assessment by multiparametric flow cytometry or next-generation flow cytometry. **Results:** CPC was detectable in 63.9% evaluable patients and showed a right-skewed distribution. Baseline CPC correlated with bone marrow plasma cell infiltration and increased progressively with the number of high-risk cytogenetic abnormalities. A cohort-derived CPC threshold of 0.38% identified patients with inferior progression-free survival and remained independently associated with PFS after adjustment for established risk factors. Importantly, CPC refined prognostic stratification specifically within the CGS high-risk subgroup. Patients with CGS-HR/CPC-high disease had markedly shorter PFS than both CGS-HR/CPC-low and CGS standard-risk patients, defining a disseminated genomic high-risk phenotype comprising 12.4% of evaluable NDMM patients. During follow-up, detectable peripheral blood residual CPC identified patients with inferior outcomes, including among those achieving deep serologic responses, and complemented bone marrow MRD for relapse risk discrimination. **Conclusions:** CPC integrates tumor burden, adverse genomic architecture, and peripheral blood dissemination into a clinically informative biomarker. Incorporating baseline CPC into IMS-IMWG 2025 CGS identifies a disseminated genomic high-risk phenotype, while post-treatment CPC detection extends this framework to dynamic residual disease monitoring. These findings support prospective validation of CPC-integrated risk stratification and peripheral blood disease surveillance in newly diagnosed multiple myeloma.

PA-083

Circulating Tumor Cells and Plasma MYD88 Mutation Allele Fraction as Prognostic Markers for Staging and Ibrutinib Response in Waldenström Macroglobulinemia

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Introduction: Characterization of liquid biopsy in Waldenström's macroglobulinemia (WM) as represented by the presence of circulating tumor cells (CTCs) and cell-free tumor DNA (ctDNA), may provide a powerful tool for disease burden estimation taking advantage of the non-invasive approach and the ability to capture the spatial heterogeneity that bone marrow (BM) biopsy may miss. In this study, we evaluated the feasibility of detecting CTCs in patients with IgM monoclonal gammopathies (IgM-MG) and quantified the MYD88L265P mutation allele frequency (MAF) in matched ctDNA as means of more comprehensive and noninvasive assessment of disease burden. **Methods:** We performed multiparameter flow cytometry to detect CTCs as determined by clonal B cells (CD19+ IgM+ with light chain restriction) at giga per liter (10^9/L) in the peripheral blood of patients with IgM-MG. Samples were stained with established phenotypic WM markers including positive expression of CD19, CD20, IgM, CD22, CD25, CD27 and exclusion of CD5 and CD23. Light-chain restriction was evaluated with surface kappa and lambda antibodies. In parallel, we performed ddPCR assay for the quantification of MYD88L265P MAF in ctDNA. **Results:** Among the 196 patients with IgM-MG, CTCs were detected in 70%. Specifically, CTCs were detected in 22 out of 66 IgM-MGUS (35%, median:0.001, range: 0.0004–0.029 × 10^9/L), in 33 out of 43 with asymptomatic WM (aWM; 76%, median: 0.0031, range: 0.001–0.3 × 10^9/L) and in 81 out of 91 symptomatic WM patients (sWM; 89%, median: 0.05 × 10^9/L, range: 0.002–1.7 × 10^9/L), with significant differences in the CTC distributions among the disease groups (Kruskal-Wallis, $p < 10^{-6}$). Concurrently, MYD88L265P MAF was evaluated in plasma samples available from the same patient cohort (n = 116). Similarly, MYD88L265P MAF (in patients harboring the mutation) was higher in sWM with a median of 4.6% (range: 0.62–86.41%) compared to aWM (median: 1.33%; range: 0.12–19.91%) and IgM-MGUS patients (median: 0.53%; range: 0.1–8.59%) indicating its potential use for monitoring tumor burden in WM (Kruskal-Wallis, $p < 0.001$). Furthermore, we analyzed 37 sequential samples of WM patients at diagnosis and 6 months post-ibrutinib (IBR) therapy. Patients achieving partial response (PR) or better after 6 months of therapy were defined as responders (RG, n = 24) while patients with less than PR were defined as non-responder (NRG, n = 13). CTCs counts pre- and post-IBR were higher in the NRG compared to the RG ($p = 0.0002$) at diagnosis which decreased significantly in the RG post therapy ($p = 0.025$) but not in the NRG and was also associated with shorter progression-free survival ($p = 0.01$). Concurrently, MYD88L265P MAF in ctDNA significantly decreased in RG ($p = 0.0076$), while slightly increased in the NRG patients ($p = 0.6$). **Conclusions:** Our findings support the potential of liquid biopsy with CTCs and MYD88L265P MAF as a potential tool for assessing dynamic changes in disease status and treatment efficacy.

PA-085

Clearance Kinetics of Monoclonal Immunoglobulin Detected by Mass Spectrometry in Multiple Myeloma Patients in Complete Response

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Introduction: The interpretation of persistent monoclonal protein (MP) detectable by mass spectrometry (MS) after achieving deep responses in multiple myeloma (MM) remains a challenge, as it can reflect both residual disease and the physiological clearance of the monoclonal immunoglobulin. The objective of this study was to characterize the kinetics of MP elimination by MS in a cohort of MM patients with no detectable disease by immunofixation (IFE), next-generation flow cytometry (EuroFlow) in bone marrow, and PET/CT during follow-up. **Methods:** A total of 268 serum samples from 37 MM patients evaluated between May 2022 and January 2026 were analyzed. Serum MP was evaluated using mass spectrometry with quantitative immunoprecipitation (EXENT®) using anti-IgG/A/M, and total kappa and lambda beads. Determinations were performed serially, from the point of IFE negativity until MS negativity, disease progression, or the last available evaluation. **Results:** The median age was 64 years (range: 40–88). The IgG isotype was the most frequent (73%), followed by IgA (23%), with a similar distribution between kappa (54%) and lambda (46%) light chains. The median follow-up period per patient was 203 days (range, 28–791), with a mean sampling interval of 36.9 days. Twenty-eight patients (76%) achieved MP negativity by MS, with a median time to negativity of 119 days (range: 56–567) and 90% of conversions to negative occurred within the first 10 months after IFE negativity. The cumulative probability of MS negativity showed differences according to the monoclonal

protein subtype (log-rank p = 0.058). Faster clearance was observed in AL and GK isotypes, while GL showed more prolonged persistence. At 6 months, MS negativity rates were 80% for AL and 73.3% for GK, compared to 41.7% for GL and 40% for AK. The overall median half-life of MP was 52 days. The AL isotype presented a significantly lower half-life compared to AK, GK, and GL (18 vs. 51, 52, and 180 days, respectively). Persistent MP detectable by MS was observed in 9/37 patients and was most frequent in the AK isotype (75.0%), followed by GL (27.3%), AL (16.7%), and GK (13.3%). No clear association was identified with the type of treatment received, including anti-CD38 or TCE/CAR-T. Disease progression was numerically more frequent among patients with persistent MP by MS than among those who achieved MS negativity (22.2% vs. 3.6%), suggesting a potential trend toward higher progression risk. **Conclusions:** The majority of MM patients who achieve negativity by IFE, MRD in bone marrow, and PET/CT subsequently achieve MP negativity by MS, generally within the first 10 months. Isotype-specific differences in MS negativity rates and MP half-life highlight the ability of MS to capture dynamic clearance patterns, suggesting that persistent MS-detectable MP after deep response may reflect physiological immunoglobulin clearance in some patients, while also supporting the value of longitudinal MS monitoring to refine response assessment.

PA-086

Clinical and Biological Predictors of Durable Response to Idecabtagene Vicleucel in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: BCMA-directed CAR T-cell therapy has transformed the treatment of relapsed/refractory multiple myeloma (RRMM). Although idecabtagene vicleucel (ide-cel) is associated with lower response rates and shorter survival than ciltacabtagene autoleucel, a meaningful subset of patients achieves long-lasting responses. The clinical and biological features of these long-term responders remain incompletely defined. This multicenter retrospective study aimed to identify predictors of durable response to ide-cel in a real-world setting. **Methods:** RRMM patients treated with ide-cel at 11 U.S. academic centers (09/2022–07/2025) were analyzed. Durable response was defined as PFS ≥2 years, based on the 15.7-month median PFS in KarMMa-3. Inverse probability of censoring weighting (IPCW) accounted for non-random loss to follow-up. Key patients' baseline characteristics were selected using IPCW-weighted LASSO and included in a multivariable logistic regression. **Results:** Of 681 patients (76% triple-class refractory, 34% penta-refractory), 114 (17%) achieved durable PFS ≥2 years. Durable responders more often had ECOG 0–1 (90% vs 77%), less extramedullary (18% vs 31%) and paraskeletal disease (22% vs 34%), fewer high-risk cytogenetics (21% vs 35%), and less likely to have received bridging therapy (61% vs 77%). Baseline ferritin (390 vs 979 ng/mL) and CRP (2.0 vs 6.9 mg/L) were markedly lower in durable responders. On multivariable analysis, ECOG 2–4 (OR 0.33; 95% CI 0.14–0.78; p = 0.012), del(17p) (OR 0.49; 95% CI 0.25–0.97; p = 0.040), and ferritin ≥500 ng/mL (OR 0.45; 95% CI 0.24–0.84; p = 0.012) were independently associated with reduced odds of durable response. Lack of paraskeletal disease (OR 0.55; 95% CI 0.30–0.99; p = 0.047) trended toward better outcomes. Ferritin retained independent significance after adjusting for performance status, supporting a biologically distinct contribution beyond functional frailty. Any-grade CRS (90% vs 83%) and ICANS (23% vs 24%) rates were similar; no parkinsonian-like neurotoxicity was seen. At median follow-up of 19.5 months, overall median PFS and OS were 8.1 and 35.1 months. Among durable responders, estimated 36-month PFS and OS were 66.8% and 93.6%. **Conclusions:** In this real-world multicenter cohort, ide-cel achieved durable disease control in 17% of heavily pre-treated RRMM patients. Durable response was independently predicted by three strata: functional status, cytogenetics, and systemic inflammation. Ferritin's independence from ECOG suggests a distinct inflammatory mechanism, consistent with observed association between inflammation and impaired CAR-T efficacy. These observations support the development of a risk-adapted predictive tool for patient selection incorporating functional, genomic and inflammatory variables.

PA-087

Clinical and Prognostic Significance of CD20 Expression in Newly Diagnosed Multiple Myeloma: A Multicenter Retrospective Study

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Introduction: CD20 is aberrantly expressed in a subset of multiple myeloma (MM) patients and has been associated with distinct biological features, including enrichment of t(11;14). However, its prognostic significance in the era of modern therapies remains unclear. **Methods:** We conducted a multicenter retrospective cohort study including newly diagnosed MM (NDMM) patients from seven tertiary centers. CD20 expression was assessed by flow cytometry and/or immunohistochemistry. Patients were matched 1:1 by age and sex. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier and Cox regression models. Subgroup and landmark analyses were performed to explore the interaction with clinical variables and treatment response. **Results:** A total of 302 patients (151 CD20-positive and 151 CD20-negative) were included after matching. CD20-positive patients showed a higher frequency of t(11;14) (15.2% vs. 7.3%, P = 0.013) and a lower rate of ≥VGPR (73.5% vs. 87.4%, P = 0.002). With a median follow-up of 31.4 months, CD20-positive patients had inferior PFS (median 39.6 months vs. not reached, P = 0.032) and OS (3-year OS: 77.2% vs. 87.1%, P = 0.010). In multivariable analyses, CD20 expression showed a trend toward inferior PFS (hazard ratio [HR] 1.58, 95% confidence interval [CI] 0.99–2.53, P = 0.055) and remained independently associated with inferior OS (HR 2.23, 95% CI 1.05–4.73, P = 0.036). Subgroup analyses showed consistent effects across most strata without significant interaction. Landmark analysis demonstrated that survival differences were attenuated among patients achieving ≥VGPR, suggesting that the adverse prognostic impact of CD20 is largely mediated through inferior treatment response. **Conclusions:** CD20 expression identifies a biologically distinct subgroup of MM associated with inferior survival outcomes and lower depth of response in the modern treatment era. Further studies are warranted to clarify its potential role in biological risk stratification.

PA-088

Clinical and Treatment Factors Associated With Super-Response in Multiple Myeloma: Identifying Patients Most Likely to Approach the IMS Emerging Cure Criteria

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Introduction: The emerging concept of cure in multiple myeloma (MM) establishes a measurable endpoint: sustained minimal residual disease (MRD) negativity, and prolonged time off anti-MM therapy. However, access to longitudinal MRD testing is limited; thus, real-world datasets do not yet contain this data, and treatment-free follow-up is needed to classify all patients who are likely cured. Super-Responders (SR) represent a surrogate population in which cured-like phenotypes and truly cured patients are most likely to be found. By studying how SR differ from Early Relapsers (ER), we can begin to identify the factors associated with exceptional disease control and generate hypotheses for how more patients may reach a cure. **Methods:** In this study, a cohort of 551 MM patients was detected in the HealthTree registry meeting the following criteria: Super-Responders (SR), first Line of Therapy (LoT1) durability of > = 60 months (n = 252), and Early Relapsers (ER), LoT1 durability of <=18 months (n = 299). The factors compared between these groups, including baseline clinical demographics (age, race, R-ISS staging, and beta-2-microglobulin levels), were summarized as medians and compared using Wilcoxon rank-sum and Fisher's tests. Time to Next Treatment (TTNT) factors were analyzed using Cox regression models, including treatment, best clinical response to LoT1, and the presence of high-risk cytogenetic markers (translocations, del17p, and gain1q21). **Results:** SRs had a younger median age at diagnosis (59 vs. 61 years; p < 0.001), lower median beta-2-microglobulin (2.9 vs 3.3; p = 0.025), and lower R-ISS stage (p = 0.041). Notably, high-risk cytogenetic abnormalities did not show a statistically significant difference between these groups. SRs received intensive induction, with 41% undergoing a Proteasome Inhibitor (PI) + Immunomodulatory Drug (IMiD) + High-dose transplant regimen, compared to only 8% of ERs. 72% of SRs achieved a Complete Response or Stringent Complete Response compared to the 11% of the ERs. Median TTNT of SRs was 83.4 months and 5.35 months for ERs (p < 0.001). **Conclusions:** In this cohort, SRs mainly represent patients with mature follow-up who achieved exceptional disease control after using LoT1 strategies more than five years ago. Although SRs had more favorable clinical features, the analyzed high-risk cytogenetic markers did not distinguish them from ERs. The clearest differentiators were treatment structure and response depth; patients with cure-like phenotypes who achieved early, deep, and durable responses appeared to be most favored among this group, particularly after PI+IMiD plus transplant-based therapies. Newer regimens may achieve similar or greater cure outcomes, but current follow-up data remain immature and require longer observation with MRD testing to meet the current cure definition. Further study of this SR population is needed to identify which patients meet the cure criteria to improve our cure-driven practice guidelines.

PA-089

Clinical Benefit of Anti-CD38 Monoclonal Antibodies in Newly Diagnosed Multiple Myeloma: Analysis of the Subgroup with Renal Impairment

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Introduction: The incorporation of anti-CD38 monoclonal antibodies (anti-CD38 mAbs) into the treatment of multiple myeloma (MM) has led to a significant improvement in patient survival. However, few studies evaluate the long-term clinical impact in patients who present renal impairment (RI) at diagnosis. The aim of this study was to determine whether the addition of anti-CD38 mAbs to first-line treatment improves the survival of patients with MM and to assess their effect in those presenting with RI. **Methods:** We performed an observational, retrospective, single-center study that included patients diagnosed with MM between 2016 and 2025 at the Institut Català d'Oncologia of Girona (Spain). Clinical and biological characteristics at diagnosis, treatment response, progression free survival (PFS) and overall survival (OS) were analyzed in both the overall cohort and the RI subgroup. Outcomes were compared according to whether patients received anti-CD38 mAb-based therapy or not. **Results:** A total of 326 patients were included, with a median follow-up of 79.3 months (59.0–100), of whom 68 (21%) had RI. In the overall cohort, median OS and median PFS were 79.3 months and 33.6 months, respectively. The addition of anti-CD38 mAbs improved both OS and PFS regardless of whether patients underwent autologous hematopoietic stem cell transplantation. In the RI subgroup, the median age was 69 years, 62% were male, and according to the R-ISS classification: stage I (2.9%), stage II (61.8%), stage III (20.4%), and unavailable in 14.7% of cases. High-risk cytogenetics (according to IMWG 2015 criteria) were present in 20.8% of cases. 78% of patients did not receive anti-CD38 mAbs, whereas 22% did as part of the new treatment regimens in the last years. The overall response rate in this subgroup was 57.3% (sCR 14.7%; CR 13.2%; VGPR 20.6%; PR 8.8%). Median OS was 51.4 months, with a 1-year OS rate of 72.6% and a 3-year OS rate of 55.3%. Median PFS was 20.6 months, with a 1-year PFS rate of 61.7% and a 3-year PFS rate of 35%. Patients who received anti-CD38 mAbs showed better 3-year OS, reaching 66%, compared with 54.7% among those who did not receive them ($p = 0.038$). No statistically significant differences were observed in PFS. **Conclusions:** The addition of anti-CD38 mAbs improved OS in patients with MM receiving first-line treatment. In our cohort of patients with RI treated with anti-CD38 mAbs, higher OS and a trend toward improved PFS were observed (without reaching statistical significance due to the limited sample size). These findings highlight the improvement in clinical outcomes compared with older therapeutic regimens.

PA-090

Clinical Characteristics of Non-Amyloid MGRS in China: A Multicenter Real-World Study Based on the 2025 RPS/IKMG Consensus

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Introduction: Monoclonal gammopathy of renal significance (MGRS) is a clonal hematologic disorder that induces renal injury via toxic paraproteins. In 2025, Renal Pathology Society (RPS)/ International Kidney and Monoclonal Gammopathy Research Group (IKMG) consensus standardized the terminology and diagnostic criteria for MGRS-associated renal lesions, but large-scale real-world evidence is insufficient to validate this consensus. This study aimed to investigate the clinical characteristics, treatment responses, and prognosis of non-AL amyloid MGRS in China based on the latest consensus. **Methods:** A multicenter retrospective study was performed at ten Chinese hospitals from 2012 to 2024. Patients with pathologically confirmed non-AL amyloid MGRS were enrolled, re-identified and reclassified according to the 2025 RPS/IKMG criteria. Baseline characteristics, renal and hematologic responses, renal survival, and overall survival were analyzed. Hematologic response and renal response were according to the amyloidosis criteria. Renal survival was defined as end-stage kidney disease (ESKD) or dialysis. Survival analysis was conducted using Kaplan-Meier method and Cox regression. **Results:** A total of 129 patients were included. Monoclonal immunoglobulin deposition disease was the most frequent subtype (MIDD) ($n = 76$), followed by monoclonal gammopathy–associated glomerulonephritides ($n = 46$), monoclonal gammopathy–associated crystalline nephropathies ($n = 4$), and non-crystalline light chain proximal tubulopathy (LCPT) ($n = 5$). Kappa light chain was the predominant subtype (82.5%). Among 110 patients with estimated glomerular filtration rate (eGFR) more than 15 ml/min at baseline, 101 patients received clone-directed treatment. The hematologic response rate with very good partial response (VGPR) or better was 64.8% in 91 evaluable patients. The renal response rate was 68.1% in 94 evaluable patients. After a median 3.3

years' follow-up, baseline eGFR >30 mL/min and renal response were independent favorable factors for renal survival. A difference in serum free light chain < 180 mg/L and hematologic response ≥ VGPR correlated with higher renal response rates. Among 9 LCPT cases, renal impairment was mild and no ESKD occurred. Of 19 patients with ESKD at baseline, only one had durable renal response and sustained dialysis independence. **Conclusions:** In this real-world multi-center study, we first classified non-AL amyloid MGRS according to the 2025 RPS/IKMG consensus. MIDD and monoclonal gammopathy–associated glomerulonephritides are the main subtypes. Baseline eGFR >30 mL/min and early renal response independently predict favorable renal outcomes.

PA-091

Clinical Characteristics, Treatment Patterns, and Outcomes of Primary and Secondary Plasma Cell Leukemia: A Multicenter Retrospective Cohort Study

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Introduction: Plasma cell leukemia (PCL) is a rare and highly aggressive plasma cell neoplasm that comprises primary (pPCL) and secondary (sPCL) subtypes. Owing to its rarity and biological heterogeneity, the optimal treatment strategy remains undefined. **Methods:** This retrospective study included 127 PCL patients (circulating plasma cells [CPCs] ≥5%) from five tertiary centers in China, enrolled between September 2012 and October 2025. Categorical variables were compared using the Chi-square test or Fisher's exact test, and continuous variables using the Mann–Whitney U test. Survival analysis was performed using Kaplan-Meier curves and Cox proportional hazards models. **Results:** Among 127 patients, 69 (54.3%) were male, with a median age of 63 years (range, 17–86). The median percentage of CPCs was 25.0% (range, 5.0–96.5%). 87 patients (68.5%) had pPCL and 40 (31.5%) had sPCL. Compared to pPCL patients, sPCL patients had lower hemoglobin (65 vs. 79 g/L, P = 0.025) and platelet counts (40 vs. 89 × 10^9/L, P < 0.001), with elevated lactate dehydrogenase levels (463 vs. 327 U/L, P = 0.027). High-risk cytogenetic abnormalities were more frequent in sPCL, although the difference was not statistically significant (P = 0.224). Proteasome inhibitor (PI)-based triplet regimens were more commonly administered in pPCL than sPCL (76.5% vs. 38.9%, P = 0.002), whereas daratumumab-based quadruplet regimens were more frequently used in sPCL (30.6% vs. 13.6%, P < 0.001). CAR T-cell therapy was delivered to 10 pPCL and 6 sPCL patients. Hematopoietic stem cell transplantation (HSCT) was performed in 19 pPCL patients (24.1%) but in none with sPCL. Treatment responses were markedly inferior in sPCL, with ≥ very good partial response (VGPR) rates of 3.2% versus 61.9% in pPCL (P < 0.001). During a median follow-up of 24.9 months, the median progression-free survival (PFS) and overall survival (OS) for the entire cohort were 4.1 months (95% CI, 2.1–6.0) and 9.5 months (95% CI, 1.9–17.0), respectively. Median OS was significantly longer in pPCL than sPCL (16.6 vs. 1.7 months, P < 0.001). Among pPCL patients, HSCT significantly improved OS (33.0 vs. 15.7 months, P = 0.006), with no survival advantage between autologous and allogeneic transplants. Neither PI-based triplets nor daratumumab-based quadruplets conferred a survival advantage. In contrast, CAR T-cell therapy was associated with favorable outcomes in both subtypes. Multivariable analysis identified extramedullary disease (HR 4.011, P = 0.036) and CAR T-cell therapy (HR 0.274, P = 0.040) as independent predictors of OS in sPCL, while HSCT (HR 0.207, P = 0.008) and achievement of ≥VGPR (HR 0.150, P < 0.001) independently predicted superior OS in pPCL. **Conclusions:** Despite the advent of novel therapies, the prognosis of PCL remains poor. pPCL patients generally have a better response to treatment than sPCL patients, and HSCT remains a key therapeutic option. CAR T-cell therapy may represent a promising treatment modality for PCL patients in the future.

PA-092

Clinical Efficacy and Safety Analysis of Tandem Autologous Hematopoietic Stem Cell Transplantation in the Treatment of High-Risk Multiple Myeloma

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Introduction: Autologous hematopoietic stem cell transplantation (ASCT) is a core therapeutic approach for multiple myeloma (MM). Patients with high-risk multiple myeloma are confronted with a high risk of early relapse and poor prognosis after single ASCT. Domestic and international guidelines recommend tandem second transplantation to improve remission depth and reduce relapse risk, while relevant clinical studies and data remain insufficient in China. **Methods:** A retrospective analysis was conducted on the clinical data of 19 patients with high-risk multiple myeloma who received tandem autologous hematopoietic stem cell transplantation. The clinical efficacy, safety and long-term survival outcomes of this regimen were systematically evaluated. **Results:** The enrolled patients had a high proportion of high-risk cytogenetic abnormalities and extramedullary lesions with high malignancy. The remission level was gradually improved after induction therapy, the first transplantation and the second tandem transplantation. The complete remission rate and negative rate of minimal residual disease both reached 78.9% after the second transplantation. With a median follow-up of 52 months, the 5-year progression-free survival rate was 56% and the 5-year overall survival rate was 79%, which were superior to those of conventional

pharmacotherapy. All patients successfully completed two sessions of transplantation without transplantation-related mortality, and hematopoietic reconstitution was achieved smoothly. Adverse reactions were mainly mild hematological and non-hematological toxicities. The second transplantation did not increase the risk of severe adverse reactions, and all patients showed favorable tolerance. **Conclusions:** Tandem autologous hematopoietic stem cell transplantation can effectively deepen disease remission, optimize long-term survival and possess satisfactory safety profile, which provides reference for clinical treatment selection. Nevertheless, this study is a single-center retrospective research with limited sample size. Further multicenter, large-sample prospective studies are required for subsequent verification.

PA-093

Clinical Efficacy and Safety of Epronermin Plus Selinexor (CPT+S) in Newly Diagnosed Ultra-Frail Patients with Multiple Myeloma

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Introduction: Ultra-frail newly diagnosed multiple myeloma (NDMM) patients present a major clinical challenge, particularly those predicted to be intolerant to standard induction or who experience severe early toxicities. There is an urgent need for an effective, low-toxicity regimen to control disease and reverse myeloma-induced frailty. This study evaluated the efficacy and safety of Epronermin (CPT) plus Selinexor (S) as a transitional, fitness-optimizing regimen in this high-risk population. **Methods:** We retrospectively reviewed 10 NDMM patients treated with CPT+S. Inclusion strictly targeted ultra-frail or highly intolerant patients: 1) severe intolerance to standard regimens (e.g., ≥Grade 3 infections, neuropathy, or myelosuppression); or 2) predicted poor tolerance (age >80, or IMWG frailty score ≥2 at baseline/during treatment). Patients lost to non-medical follow-up were excluded from efficacy evaluations. We assessed safety, overall response rate (ORR) in evaluable patients, successful transition to standard therapy, and non-responder (NR) characteristics. **Results:** Median age was 71.5 years. All 10 patients had poor baseline performance status (ECOG ≥3) and aggressive cytogenetics (60% 1q21 amplification, 50% TP53 abnormalities). Three patients lost to follow-up were excluded, leaving 7 evaluable. Overall, CPT+S demonstrated excellent tolerability (n = 10). Intolerable Grade 3/4 adverse events were rare, avoiding severe cardiovascular/neurological toxicities and myelosuppression typical of standard care. In the evaluable cohort (n = 7), ORR was 57.1% (4/7; 1 CR, 2 VGPR, 1 PR). Median PFS was 7.3 months, and OS was 11.7 months. Importantly, disease control drove substantial performance status improvements, enabling these initially ultra-frail patients to successfully transition to standard sequential therapies (e.g., anti-CD38 regimens). Conversely, 3 patients (42.9%) showed no response. These NR patients exhibited a "dual high-risk" profile: 100% carried high-risk cytogenetics (TP53/1q21 abnormalities), and their frailty stemmed from irreversible, acute organ failure at baseline (e.g., destroyed lung, acute heart failure) rather than simple chronic decline. **Conclusions:** For NDMM patients intolerant or predicted intolerant to standard therapies, CPT+S is a highly valuable de-escalated transitional strategy. With a 57.1% ORR and excellent safety, it effectively reduces tumor burden and improves patient fitness, enabling a bridge to standard sequential therapies. However, efficacy remains limited in patients with both high-risk cytogenetics and irreversible acute organ failure, highlighting the need for alternative early interventions in this specific subgroup.

PA-094

Clinical Impact of Diagnosis to Treatment Interval in Transplant-Ineligible NDMM Treated with DRd: A Multicenter Real-World Study in Japan

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Introduction: Daratumumab, lenalidomide plus dexamethasone (DRd) is a standard initial treatment for transplant-ineligible newly diagnosed multiple myeloma (TIE-NDMM). Diagnosis to treatment interval (DTI) has been reported as a prognostic factor in hematological malignancies. However, its clinical impact in DRd-treated TIE-NDMM remains unclear. We retrospectively investigated the association between DTI and clinical outcomes using real-world data in nine Japanese hospitals. **Methods:** Patients received autologous stem cell transplantation after DRd were excluded. Diagnosis for myeloma was defined as the date of bone marrow aspiration. An optimal cutoff of DTI was determined by the ROC. Renal insufficiency was defined as eGFR < 40mL/min. **Results:** A total of 268 patients were included. Median age was 75 years (range, 26–92). The proportion with performance status 2 or more (PS2), frailty using simplified frailty score, and renal insufficiency were 26.1%, 65.3%, and 23.4%, respectively. The proportion of the second revision of International Staging System stage I, II, III and IV were 10.4%, 22.2%, 46.1%, and 21.3%, respectively. Minimal residual disease (MRD)-negativity, complete response (CR) and overall response rates were 12.9% (n = 34), 29.1% and 89.9%, respectively. Median DTI was 15 days (range, 0–988). The optimal cut-off value of DTI for PFS was 15. The short DTI group had significantly higher proportion of patients with frailty, PS2, IgG-subtype disease, renal insufficiency, and advanced R2-ISS stage than the long DTI group (P < 0.001, < 0.001, 0.045, 0.009, and 0.005). There was no significant difference of treatment response between long and short DTI groups. With a median follow-up time of 22.2

months (range, 0.1–67.3), the 2-year progression-free survival (PFS) and overall survival (OS) were 74.6% and 86.2%. The 2-year PFS was significantly higher in the long DTI group than in the short DTI group (85.7% vs 62.3%; hazard ratio [HR], 0.484; 95% confidence interval [CI], 0.306–0.765; P = 0.002). In univariate analysis, frailty, PS2, renal insufficiency, R2-ISS, and CR were identified as significant prognostic factors for PFS. In multivariate analysis, long DTI remained independently associated with improved PFS (HR, 0.543; 95% CI, 0.308–0.956; P = 0.034). The 2-year duration of treatment (DOT) and time to next treatment (TTNT) rate were also significantly higher in the long DTI group than in the short DTI group, significantly (67.5% vs 43.6%; HR, 0.557; 95%CI, 0.396–0.784; P < 0.001; and 78.0% vs 54.0%; HR0.471; 95%CI, 0.314–0.708; P < 0.001, respectively). Finally, there was no significant difference in 2-year OS between the long and short DTI (89.7% vs 82.4%; HR, 0.613; 95%CI, 0.344–1.094; P = 0.098). **Conclusions:** Shorter DTI was associated with inferior PFS, DOT, and TTNT, but not OS, suggesting that DTI may function as a clinical risk indicator, with patients requiring early treatment representing a clinically vulnerable population that warrants careful management.

PA-095

Clinical Implications of Discordant Frailty Assessment in Non-Transplant Eligible Patients with Newly Diagnosed Multiple Myeloma: Results from the Randomized Phase IV REAL MM Trial

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Introduction: In non-transplant eligible (NTE) patients (pts) with newly diagnosed multiple myeloma (NDMM), frailty assessment plays a key role in first-line treatment decisions (EHA-EMN 2025 guidelines). The International Myeloma Working Group (IMWG) frailty score (FS) is the gold standard, while the Simplified FS is a faster alternative for routine use. However, discordance between these tools may misclassify some pts, leading to an inconsistent use of frailty-adapted therapies. We evaluated the impact of frailty score discordance in NTE NDMM pts enrolled in the REAL MM trial. **Methods:** REAL MM is a randomized, multicenter, phase IV trial (NCT03829371, funded by the Italian Medicines Agency AIFA - Independent Research) comparing bortezomib-melphalan-prednisone (VMP) +/− daratumumab (DVMP) vs. lenalidomide-dexamethasone (Rd) +/− daratumumab (DRd) in real-life NTE NDMM pts. In the first part, pts were randomized 1:1 to 9 VMP cycles vs continuous Rd; from July 2022, to DVMP vs DRd. The IMWG-FS and Simplified-FS were used to assess frailty classes. Multivariate analysis was performed adjusting for treatment allocation and cytogenetic risk. **Results:** A total of 401 pts were enrolled and randomized to receive VMP (n = 114), Rd (n = 117), DRd (n = 83), or DVMP (n = 87). Median follow-up was 28.8 months (95% CI 26.7–32.3). According to the IMWG-FS, 225 (56%) pts were defined as fit/intermediate-fit (non-frail) and 176 (44%) as frail. According to the Simplified-FS, 186 (46%) pts were classified as non-frail and 215 (54%) as frail. The discordance rate between the two scores (FSs) was 19.7%, and the majority of discordant pts were fit/intermediate-fit by IMWG-FS but frail by Simplified-FS (59/401, 15%). Focusing on this pt population (n = 59), median progression-free survival (mPFS) of discordant pts was significantly different from that in pts classified as frail by both FSs (mPFS NR vs 26.1 months) in a multivariable analysis including randomization arm and cytogenetic risk (HR 0.55, 95% CI 0.33–0.89; p = 0.016). This difference was maintained focusing the analysis on pts receiving daratumumab upfront (HR 0.37, 95% CI 0.14–0.99; p = 0.047). On the other hand, discordant pts had similar outcomes to those of pts who were non frail according to both FSs (HR 1.16, 95% CI 0.69–1.94; p = 0.58), suggesting that the Simplified-FS may overestimate frailty. **Conclusions:** Our analysis showed that pts classified as frail by Simplified-FS but fit/intermediate-fit by IMWG-FSs had better clinical outcomes than those frail by both FS and similar outcomes to those fit/intermediate-fit by both FSs. The Simplified-FS may overestimate frailty, whereas the IMWG-FS may better capture frailty status. Currently, according to the latest guidelines suggesting a frailty-adapted approach (quadruplet for non-frail and triplets for frail pts), IMWG-FS remains the gold standard for pt stratification to avoid undertreatment.

PA-096

Clinical Outcomes and Predictors of Survival in Central Nervous System (CNS) Multiple Myeloma: A Retrospective Cohort Study

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by clonal plasma cell infiltration into the bone marrow. While extramedullary involvement is relatively uncommon, central nervous system (CNS) involvement represents an exceptionally rare manifestation with dismal outcomes, with median survival ranging from 3–13 months. CNS involvement in MM is likely the result of emerging aggressive subclones after increasing lines of therapy (LOT). Given its poor outcomes, there is an unmet need to define treatment approaches including use of intrathecal (IT) chemotherapy, radiation therapy (RT) in conjunction with CNS penetrating systemic therapies. This retrospective cohort study evaluated clinical characteristics and outcomes among patients with CNS-MM. **Methods:** Patients with CNS-MM diagnosed via cerebrospinal fluid (CSF) analysis or MRI between 2014–2026 were included. Data collected included baseline demographic characteristics, treatment history, date of MM diagnosis, date of CNS-MM diagnosis, neurological symptoms, and overall survival (OS). Descriptive statistics were used to summarize patient and disease characteristics. Univariate Cox proportional hazards regression was applied to evaluate predictors of overall survival. **Results:** Nineteen patients (4 newly diagnosed, 15 relapsed/refractory) with CNS-MM were identified. Thirteen patients (68.4%) were male and six (31.6%) were female. Median age at CNS-MM diagnosis was 70 years (range 34–75 years), median prior LOT were 3 (range 0–12) and median time from MM diagnosis to CNS involvement was 14.0 months (range 0–83 months). Sixteen patients had MRI findings of CNS MM and 9 had clonal plasma cells in cerebrospinal fluid. Sixteen patients received combination IT therapy (methotrexate, cytarabine and hydrocortisone) and 3 received IT thiotepa. Nine patients received both IT and RT. Ten patients received palliative care services during their clinical course. Median OS (mOS) following CNS-MM diagnosis was 4.9 months (95% CI, 2.3–18.4). On univariate Cox regression analysis, ECOG status was the only statistically significant predictor of OS. High-risk cytogenetics were not significantly associated with time from MM diagnosis to CNS involvement (median 10.0 vs. 16.0 months; $p = 0.70$) or time from CNS-MM diagnosis to death ($p = 0.95$). Although not statistically significant, numerically longer mOS was observed among patients who underwent prior stem cell transplantation (5.7 vs. 3.2 months), received bispecific antibodies (BsAb, 7.8 vs. 2.9 months), or received chimeric antigen receptor therapy (CART, 12.4 vs. 3.2 months). **Conclusions:** CNS-MM remains an aggressive manifestation of MM with poor survival outcomes. Although patients receiving CAR T-cell therapy and/or BsAbs in our cohort demonstrated numerically longer overall survival, these findings did not reach statistical significance, likely due to the small sample size. Effect of novel immunotherapies in patients with CNS MM may require further investigation in larger cohort studies.

PA-097

Clinical Profile and Outcomes of Patients with Monoclonal Gammopathy of Undetermined Significance at a Tertiary Centre in North India

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant plasma cell disorder that carries risk of progression to multiple myeloma (MM) and related conditions. Most epidemiological data come from high-income countries. There is limited information from low- and middle-income countries (LMICs). **Methods:** We conducted a retrospective analysis of consecutive MGUS cases diagnosed at our institute from January 2010 to December 2025. MGUS was defined as serum monoclonal protein level less than 3 g/dL and bone marrow (BM) plasma cells less than 10%, with absence of myeloma-defining events. We reviewed medical records for demographic details, referral sources, comorbidities, laboratory findings, BM findings, imaging results, and follow-up outcomes. Follow-up duration was calculated from the time of diagnosis to the last visit, progression, or death. **Results:** Fifty-five patients were included. Median age was 62 years (range 36–85 years); 36 (65.5%) were males. Hypertension (58.3%) and diabetes mellitus (47.2%) were the commonest comorbidities, followed by chronic kidney disease (41.8%). Majority of patients were referred from nephrology (19/55, 34.5%), followed by internal medicine (27.3%), and other specialities [endocrinology (7.3%), neurology (5.5%), rheumatology (5.5%), gastroenterology (5.5%), and dermatology (1.8%)]. IgG was the predominant subtype (40/55, 72.7%), followed by IgM (10.9%) and IgA (9.1%); 38/55 (69.1%) were kappa subtype. Median M-protein value was 0.45 g/dL (range 0–2.1 g/dL); 4 patients (7.2%) had M-protein ≥1.5 g/dL. Abnormal FLC ratio was present in 29/42 (69.0%) evaluable patients; median FLC ratio 1.86 (range 0.1–18.8). By Mayo model, 18.9% had low-, 62.2% had intermediate-, and 18.9% had high-risk MGUS. Median BM plasma cells were 5% (range 2–9%). FISH abnormalities were detected in 6/

34 patients (17.6%), most frequent being t(11;14) (n = 4). Baseline PET-CT and whole-body low-dose CT were documented in 36/55 patients (65.5%); non-myelomatous findings (osteopenia, lymphadenopathy, and degenerative changes) were seen in 11/55 patients (20.0%). Median follow-up duration was 15.9 months (range 1–172 months); 23/55 patients (41.8%) were lost to follow-up. One patient (1.8%) progressed to MM after 69 months, and mantle cell lymphoma was diagnosed in 1 patient (1.8%) after 23 months. Five patients (9.1%) died during follow; median overall survival was not reached. **Conclusions:** In our study, MGUS patients presented with diverse clinical and radiologic features. Most patients exhibited a low-burden disease and the progression to overt MM was uncommon. Baseline imaging abnormalities were not infrequent, necessitating further evaluation. A significant proportion of patients were lost to follow-up, revealing a critical gap in longitudinal care in resource-limited settings. These findings underscore the necessity for cross-specialty awareness, standardized referral pathways, and structured follow-up programs for MGUS patients in LMICs.

PA-098

Clinical Screening for Monoclonal Gammopathy – Prevalence and Outcomes

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic condition characterized by the presence of a monoclonal protein in the blood. While often benign, MGUS is clinically significant due to its potential progression to plasma cell disorders such as multiple myeloma, amyloidosis, or Waldenström's macroglobulinemia. The decision to screen for a monoclonal protein is typically guided by clinical suspicion based on unexplained clinical findings. In this study, we wanted to understand the positivity rate in a clinically screened population, the rationale behind testing among those testing positive and the outcomes of those identified to have MGUS. **Methods:** We searched for monoclonal protein study order among patients seen at Mayo Clinic between January 2019 to May 2023 using Mayo Data Explorer which gives access to entire Mayo Clinic data. We collected the demographics, the reason for testing for those with a positive test result, any subsequent diagnosis of myeloma or related disorders, and survival through chart review. Individuals with a known diagnosis of monoclonal gammopathy prior to 2019 were excluded. Those diagnosed with a symptomatic plasma cell disorder within 6 months of the positive test were not classified as MGUS. The study was approved by the Institutional Review Board (IRB) at Mayo Clinic. **Results:** We identified 122,641 unique individuals. Median age at testing was 63 (IQR 51–72); 78% were ≥50. Among these, 4287 (3.5%) had a monoclonal protein identified. Among those ≥50, it was 4.2% compared to 1.1% for those < 50 years, P < 0.001; there was a gradual increase in the positivity rate over age deciles (Figure). Among these 149 (3%) had a symptomatic monoclonal gammopathy, most commonly myeloma or light chain amyloidosis. The clinical reason for ordering monoclonal protein testing was neuropathy (18%), followed by renal disease or proteinuria (12%) and cardiac evaluations, including heart failure and cardiomyopathy workups (10%). Anemia (7%) suspected hematologic or oncologic disorders (6%), and central or peripheral neurologic symptoms (6%) also represented major drivers for testing, while the reason could not be ascertained in 4%. With a median estimated follow up of 39 months, 72 individuals progressed to a symptomatic plasma cell disorder, with a 5-year progression estimate of 3.3%. The 5-year overall survival was inferior for those with a MGUS identified – 71% vs 80%, p < 0.001. **Conclusions:** In this large retrospective cohort screened for suspected clinical conditions, the prevalence increased with age and appeared similar to that reported in population-based screening. Neuropathy, renal disease, and suspected cardiac disease were the most common clinical indications leading to monoclonal protein testing and subsequent MGUS diagnosis. Individuals with a monoclonal protein identified had an inferior survival even after excluding those who developed a subsequent symptomatic plasma cell disorder.

PA-099

Clinical Study on the Transition of First-Line Bortezomib Intolerance to Carfilzomib in Multiple Myeloma

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Introduction: Proteasome inhibitors (PIs) are backbone therapy for NDMM. The long-term application of bortezomib is limited due to peripheral neuropathy (PN). Carfilzomib offers better efficacy with reduced PN. Currently, there is a lack of real-world data on in-class transition (iCT) from bortezomib to carfilzomib in Chinese NDMM patients. **Methods:** A clinical study was conducted in 30 myeloma patients who experienced intolerable adverse events, including grade ≥1 painful PN, during the treatment with first-line bortezomib-based regimens in the First Affiliated Hospital of Soochow University and Soochow Hopes Hematology Hospital from March 2023 to March 2026. Efficacy and safety following transition to carfilzomib were evaluated. **Results:** A total of 30 MM patients were included. The cohort had a median age of 60 (36–75) years. 14 cases (46.7%) were in the high-risk cytogenetic group according to mSMART 3.0 criteria. The median treatment cycle of bortezomib before iCT was 4 (1–6). Among the causes of intolerance, there were 29 cases (96.7%) of PN and 1 case (3.3%) of diarrhea. With a median follow-up of 22 (1–37) months, at 1 month,3 months, 6 months,12 months, 2/29

(6.9%), 24/27 (88.9%) 24/26 (92.3%), and 23/23 (100.0%) of patients reduced by one grade in PN after transition. At 6 months after transition, All patients' peripheral neuropathic pain symptoms had disappeared. After 2 months of transition, there was a significant decrease in ONLS (from baseline 6.14 ± 0.37 to 4.50 ± 0.31, P < 0.001) and TNS (from baseline 3.21 ± 0.19 to 2.75 ± 0.15, P = 0.004). In terms of efficacy analysis, the conversion rate of ≥CR increased from 33.3% to 70.0% (P < 0.001), and the sCR rate and MRD negative conversion rate increased from 33.3% to 63.3% (P = 0.001). The 1-year and 2-year progression free survival (PFS) rates were 83.1% and 69.2%. Assessment of patients' quality of life using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) showed that after 3 months' transition, patients' overall quality of life improved (P < 0.001). Significant improvements were observed in physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. **Conclusions:** The transition of first-line bortezomib intolerance to carfilzomib can significantly improve symptoms such as PN and deepen remission. This strategy is feasible and effective in routine clinical practice.

PA-100

Clinical Trial Evidence Informing Efficacy and Safety of FDA-Approved Treatments in Relapsed and Refractory Multiple Myeloma (RRMM) for Patients (Pts) After Quadruple-Class Exposure (QCEx)

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Introduction: Pts with RRMM who have prior QCEx to proteasome inhibitors (PI), immunomodulatory drugs (IMiD), anti-CD38 monoclonal antibodies, and B cell maturation antigen (BCMA)-targeting therapies have poor prognosis. We examined the efficacy and safety of approved treatments in this population to establish a benchmark for emerging treatments. **Methods:** A systematic literature review (SLR) was conducted to identify clinical trials published between 14-Jan-2016 and 09-Jan-2026 in Ovid MEDLINE, Embase, CENTRAL, CDSR, and at key conferences. Eligible trials enrolled purely QCEx or broader RRMM populations, provided outcomes were reported for a subgroup of >10 pts in which ≥80% had QCEx RRMM. FDA-approved RRMM regimens were eligible. Outcomes included ORR, CRR, duration of response (DOR), MRD-negativity, PFS, OS, and safety. **Results:** QCEx RRMM subgroups from 8 single-arm trials were identified; 7 investigated 4 BCMA-targeting therapies (cilta-cel, CARTITUDE-2 [n = 20]; ide-cel, KarMMa [n = 28]; elranatamab, MagnestisMM-1/2/3/9 [n = 87]; teclistamab, MajesTEC-1 [n = 40]) and 1 investigated a GPRC5D bispecific antibody (BsAb; talquetamab, MonumenTAL-1 [n = 75]). All trials reported outcomes for RRMM subgroups with 100% QCEx, except MonumenTAL-1 (96%). Type of prior anti-BCMA varied by subgroup, ranging from 100% in the CARTITUDE-2 subgroup receiving non-cellular agents (BsAb, 40%) to 100% in the KarMMa subgroup receiving ide-cel. ORR ranged from 21.4% to 66.7%, CRR from 0% to 42.3%, MRD-negativity from 17.5% to 57.1%, and median DOR from 12.3 mo (median follow-up [mFU] 18 mo) to 19.2 mo (mFU 30.3 mo); the highest ORR, CRR, MRD-negativity, and longest DOR were observed in MonumenTAL-1. Median PFS ranged from 1.0 mo (mFU 13.3 mo) to 9.1 mo (mFU 18.0 mo) and was most prolonged in CARTITUDE-2. Median OS ranged from 12.1 mo (mFU 11.3 mo) to 28.3 mo (mFU 30.3 mo), with the greatest duration in MonumenTAL-1. Immunotherapy-related AEs were high across all trials in the QCEx subgroup. Grade (G) 3–4 AEs occurring in ≥5% pts were observed in CARTITUDE-2 (neurotoxicity, 10%; neutropenia, 85%) and MajesTEC-1 (infections, 32.5%; neutropenia, 65%). GPRC5D-related on-target, off-tumor (OTOT) toxicities (ie, nail, skin, rash, or taste-related, and weight loss) were observed in 32.1% to 75.6% of the QCEx subgroup in MonumenTAL-1—most were low-grade events. **Conclusions:** This SLR underscores the paucity of approved treatment options and the suboptimal clinical profiles of existing RRMM therapies for pts after QCEx. Anti-BCMA rechallenge was associated with diminished efficacy and high rates of G3–4 toxicity. Among agents evaluated, talquetamab demonstrated the highest response rates and greatest survival, supporting GPRC5D BsAb as a clinically meaningful therapeutic option in this population. Nevertheless, its efficacy remains suboptimal, and the elevated incidence of OTOT toxicities continues to pose a notable clinical challenge. These findings reinforce the urgent unmet need for innovative treatments for RRMM after QCEx.

PA-101

Clinicobiological Characteristics, Contemporary Outcomes and Real-World Treatment Patterns in AL Amyloidosis: A Tertiary Center Experience from Asia

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Introduction: Treatment approaches for AL amyloidosis have historically been heterogeneous especially prior to the approval of daratumumab(dara)-VCD. However, Asian patients remain under-represented in clinical trials, and real-world data from the region are limited. We performed a retrospective analysis of patients with AL amyloidosis to characterize disease presentation, treatment patterns,

and clinical outcomes at a tertiary referral center. **Methods:** 55 patients with biopsy-proven AL amyloidosis diagnosed in Singapore General Hospital between March 2006 to February 2026 were identified from our IRB-approved institutional plasma cell disorders database. Clinical characteristics, treatment patterns, overall response rates (ORR), progression-free survival (PFS) and overall survival (OS) were evaluated. **Results:** Median age at diagnosis was 62 years (IQR 56–68), and 66% were male. Primary AL amyloidosis (AL) was present in 54.5%, AL amyloidosis with concurrent multiple myeloma in 43.6% and localized AL amyloidosis associated with a low-grade B-cell clone in 1.8%. Cardiac, renal, liver and other organ involvement (nerve, larynx, tongue) were seen in 65%, 47%, 6% and 6% of patients, respectively. 16 patients (29%) had involvement of ≥2 organs at diagnosis, while 2 (4%) had involvement of ≥3 organs. Advanced cardiac involvement (Mayo 2012 stage III-IV) was present in 51% of patients at diagnosis. The most common cytogenetic abnormalities were t(11;14) (46%), 1q21 amplification (16%) 17p deletion (6%). Frontline treatment was heterogeneous, with 24% receiving dara-VCD, 55% receiving triplet regimens (VCD 47%, VTD 4%, VRD 2%, KMP 2%) and 10% receiving doublets (VD 6%, RD 2%, MP 2%). 26% underwent autologous stem cell transplantation (SCT). Patients with localized amyloidosis were treated with local RT or observation. ORR (≥PR) was 54.5% across all treatment groups. Patients treated with Dara-VCD demonstrated a numerically higher ORR compared with all other treatment cohorts (11/13 (84.6%) vs 19/42 (45.2%); p = 0.118). Median PFS and OS for the entire cohort were 30 and 82 months, respectively. Although ORR was not significantly different between patients who underwent SCT and those who did not (9/14 (64.3%) vs 21/41 (51.2%); p = 0.537, SCT was associated with significantly improved PFS (32 vs 9 months; p = 0.018) and OS (not reached vs 14 months; p = 0.005). **Conclusions:** More than half of patients presented with advanced-stage disease, highlighting the need for earlier recognition and diagnosis of AL amyloidosis. While treatment approaches were heterogeneous, outcomes were consistent with historical experience from older regimens like VCd. Dara-VCd was associated with better responses although survival outcomes remain immature. Longer follow-up in this contemporary cohort is required to determine whether these improved responses translate into durable survival outcomes in clinical practice.

PA-102

Clonotype-Level Evolution Revealed by Longitudinal NGS-MRD Monitoring Refines Risk Stratification in Newly Diagnosed Multiple Myeloma

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Introduction: Next-generation sequencing-based measurable residual disease monitoring (NGS-MRD) enables sensitive detection of residual disease in multiple myeloma. Beyond binary MRD status, longitudinal tracking of B-cell receptor (BCR) clonotypes may reveal dynamic changes in residual tumor composition. We investigated whether clonotype-level evolution detected by serial NGS-MRD could refine risk stratification in newly diagnosed multiple myeloma (NDMM). **Methods:** We retrospectively analyzed NDMM patients who underwent NGS-MRD assessment using immunoglobulin rearrangement sequencing. Baseline trackable BCR clonotypes were defined by predefined clonal rearrangement criteria and followed longitudinally. Survival analyses were performed using time-dependent Cox models. **Results:** Among 156 patients who underwent NGS-MRD assessment, baseline trackable BCR clonotypes were identified in 151 patients (96.8%), with 436 baseline trackable clonotypes detected. Most patients had 1–3 baseline trackable clonotypes, while 76.2% showed multi-locus IG rearrangement patterns. Serial NGS-MRD monitoring revealed substantial heterogeneity in MRD dynamics. Baseline clonotype complexity was associated with less favorable MRD dynamics. Patients with fewer baseline trackable clonotypes or single-locus IG rearrangement patterns more frequently achieved MRD negativity without resurgence, whereas patients with ≥3 baseline trackable clonotypes or multi-locus patterns were enriched for persistent MRD positivity or MRD resurgence. However, baseline clonotype complexity alone showed limited standalone prognostic value. We therefore next investigated whether longitudinal changes in clonotype composition could further refine risk stratification. Therefore, we next reviewed serial NGS-MRD data to characterize longitudinal changes in BCR clonotype composition during treatment. Clonotype-level evolution was defined as either the post-treatment emergence of a trackable clonotype during follow-up or a clonotype compositional shift among baseline trackable clonotypes. Clonotype-level evolution was observed during MRD-positive intervals. In time-dependent analysis, MRD-positive patients with clonotype-level evolution had significantly inferior PFS compared with MRD-positive patients without evolution (HR, 2.71; 95% CI, 1.24–5.90; P = 0.012). In multivariable time-dependent Cox analysis adjusting for ASCT, CGS risk, and baseline thrombocytopenia, clonotype-level evolution remained independently associated with inferior PFS (HR, 3.47; 95% CI, 1.79–6.73; P = 0.00023). **Conclusions:** Longitudinal NGS-MRD monitoring provides clonotype-level information beyond MRD negativity or positivity. Clonotype-level evolution identifies a high-risk subgroup among MRD-positive NDMM patients and may improve risk-adapted monitoring and intervention strategies.

PA-103

Companion Flow Cytometry Assay for Ex Vivo Tracking of Effector T-Cell Engagement with BiTE Antibodies in Outpatient Multiple Myeloma Treatment

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Introduction: BiTE therapies, such as elranatamab, are highly effective but pose significant risks of CRS and neurotoxicity, often necessitating inpatient step-up dosing. To support outpatient treatment, the Bispecific Outpatient Safe Step-up (BOSS) program was created for safe administration through structured monitoring and prophylactic dexamethasone. Additionally, we developed a companion flow cytometry assay to assess BiTE antibody binding to patient effector T cells ex vivo. **Methods:** Blood samples were obtained from 12 patients, including 7 treated with elranatamab (BCMA), 2 with teclistemab (BCMA), and 3 with talquetamab (GPRC5D). At the same time, a flow cytometry protocol was optimized using PBMCs from healthy donors. Strategy 1 involved using fluorescently labeled recombinant target proteins (BCMA-AF647, GPRC5D-AF488) at various concentrations, incubation times, temperatures, and fixation settings. Strategy 2 employed a secondary anti-human IgG (H+L) antibody to detect the human IgG portion of bispecifics across different isotypes. The final panel included viability, CD3, CD4, CD8, CD19, CD11b, and CD33 markers. The assay was validated over time with both fresh and frozen PBMCs from the BOSS program. **Results:** Strategy 1 (target proteins) showed poor resolution in elranatamab-treated cells (4.88%) and talquetamab-treated cells (33.4%) from healthy donors. In contrast, Strategy 2 (secondary anti-human IgG) provided excellent separation, detecting 99.6% binding on elranatamab-treated cells and 99.8% on talquetamab-treated cells, with minimal background in healthy controls (< 0.75%). Longitudinal analysis showed high agreement between fresh and frozen PBMCs from patients. For instance, at Cycle 5 Day 1 in an elranatamab patient, freshly prepared vs. frozen cell metrics closely matched: CD3+ (44.0% vs. 41.8%), CD4+ (6.88% vs. 6.66%; hIgG + 97.6%, MFI 1556 vs. 92.9%, MFI 1735), and CD8+ (80.5% vs. 80.7%; hIgG+ 97.7%, MFI 1308 vs. 98.1%, MFI 1631). In BiTE-treated patients, IgG binding in CD4 and CD8 cells exceeded 98% by C2D1. However, recent immunotherapies emerged as key confounders: one patient treated with the anti-CD38 antibody isatuximab a month before baseline showed extensive nonspecific background binding on T cells, especially CD8+ T cells, leading to exclusion from analysis. Additionally, the recent administration of tocilizumab (anti-IL-6R) was a potential confounder in three patients. **Conclusions:** We developed a reliable flow cytometry assay to monitor ex vivo effector-target engagement in outpatient bispecific therapy. The high agreement between fresh and frozen samples allows for flexible, centralized immune monitoring over time. Importantly, screening for recent monoclonal antibody treatments, such as anti-CD38 or anti-IL6R, is essential because they can cause background staining due to non-specific T-cell binding. This assay offers a dependable method for analyzing T-cell kinetics and resistance in outpatient settings.

PA-104

Comparative Analysis of Isa SC VRd (ISASOCUT, Weekly Bortezomib) and Isa IV VRd (IMROZ, Twice-Weekly Bortezomib): 20-Month Follow-Up in Transplant-Ineligible Newly Diagnosed Multiple Myeloma Patients

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Introduction: Intravenous (IV) isatuximab (Isa) plus bortezomib (V), lenalidomide (R), and dexamethasone (d) is approved for patients (pts) with transplant-ineligible newly diagnosed multiple myeloma (Ti NDMM) based on the phase 3 IMROZ trial (NCT03319667). The phase 2 ISASOCUT (NCT05889221) study demonstrated the efficacy and safety of subcutaneous (SC) Isa delivered via an on-body injector (OBI) plus VRd in Ti NDMM pts, with weekly (QW) bortezomib as opposed to twice weekly (BIW) in IMROZ. We report an updated comparative analysis on the safety and efficacy of Isa SC OBI (ISASOCUT; QW V) vs Isa IV (IMROZ; BIW V) at 20 months (mos) of follow-up. **Methods:** Isa SC OBI pts (ISASOCUT; n = 74) received 1400 mg Isa SC QW in Cycle (C)1, every 2 weeks (Q2W) in C2–12, and monthly (Q4W) from C13 onward; each C was 28 days. SC bortezomib (1.3 mg/m2) was given BIW in C1 and QW from C2–12. Isa IV pts (IMROZ; n = 265) received 10 mg/kg Isa IV QW in C1, then Q2W, and Q4W from C18 onward. SC bortezomib (1.3 mg/m^2) was given BIW at C1–4. C1–4 was 42 days; C5 onward was 28 days. The ISASOCUT primary endpoint was ≥ very good partial response (VGPR). Efficacy and safety, especially neuropathy, were evaluated. **Results:** Baseline demographics and disease characteristics were generally comparable between Isa SC OBI and Isa IV pts except plasmacytoma at study entry (1.4% and 18.5%, respectively). With a 20-month follow-up, the total V dose was fully administered (planned total bortezomib dose: 48.1 mg/m^2 [ISASOCUT, over 12 mos] and 41.6 mg/m^2 [IMROZ, over 6 mos]). ≥VGPR rate was similar between Isa SC OBI (89.2% [95%

CI: 79.8–95.2]) and Isa IV (88.3% [95% CI: 83.8–91.9]). MRD negativity (MRD-) rate (NGS, 10–5) was 55.4% for Isa SC OBI and 47.9% for Isa IV, MRD- complete response was 37.8% and 43.4%, and sustained MRD- was 27.0% and 12.8%, respectively. PFS at 20 mos was 89.1% (95% CI: 77.9–94.8) for Isa SC OBI and 85.6% (95% CI: 80.5–89.5) for Isa IV. Study drug-related serious treatment-emergent adverse events (TEAEs) occurred in 28.4% of Isa SC OBI and 27.0% of Isa IV pts. Study drug-related non-hematologic grade (G) ≥3 TEAEs occurred in 41.9% of Isa SC OBI and 53.2% of Isa IV pts. Infusion-related reactions (IRRs) were lower with Isa SC OBI (5.4%) than Isa IV (22.1%). A lower incidence of G ≥2 peripheral neuropathy (PN) was observed with Isa SC OBI (QW V, 29.7%) vs Isa IV (BIW V, 40.7%), but incidence of G ≥3 PN was similar (8.1% vs 8.7%, respectively). Isa SC OBI (QW V) was associated with a lower incidence of PN leading to V dose reduction (Isa SC OBI, all G: 21.6%, G ≥3: 0; Isa IV, all G: 33.5%, G ≥3: 3.4%) while the incidence of PN leading to V discontinuation was similar (Isa SC OBI, all G: 5.4%, G ≥3: 4.1%; Isa IV, all G: 9.5%, G ≥3: 2.7%). **Conclusions:** This comparative analysis at 20 mos of follow-up found comparable efficacy with greater tolerability for Isa SC OBI (QW V) than Isa IV (BIW V) for PN and IRRs. This analysis demonstrated Isa SC OBI as an efficacious and well-tolerated treatment for Ti NDMM pts.

PA-105

Comparative Analysis of Single-Center Survival Rates Between Patients Eligible for Autologous Hematopoietic Stem Cell Transplantation and Those Who Did Not Undergo Transplantation in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a malignant hematologic tumor characterized by clonal abnormal proliferation of bone marrow plasma cells, accounting for 10%–15% of all hematologic malignancies. Although standard first-line therapies, including proteasome inhibitors and immunomodulators, as well as novel CAR-T cell therapies, have significantly improved treatment efficacy, MM remains incurable at present. Enhancing remission rates and markedly improving patient progression-free survival (PFS) and overall survival (OS) remain critical challenges. Compared to traditional chemotherapy and newer drug regimens, patients receiving autologous stem cell transplantation (ASCT) exhibit superior PFS and OS outcomes. **Methods:** By comparing the clinical characteristics and long-term survival outcomes of multiple myeloma (MM) patients eligible for autologous stem cell transplantation (ASCT) during the same period—both those who received ASCT and those who did not to provide a basis for clinical treatment decisions. **Results:** All 73 MM patients successfully completed hematopoietic reconstruction without any transplantation-related deaths. As of May 31, 2025, the median follow-up duration was 37.3 (6.0–68.5) months. Follow-up data analysis revealed that the 5-year PFS rate in the ASCT group was 72.6% (95% CI: 60.84%–84.36%), significantly higher than the 43.9% (95% CI: 29.00%–58.80%) in the non-ASCT group; the 5-year OS rate in the ASCT group was 89.7% (95% CI: 63.57%–98.43%), compared with 54.8% (95% CI: 44.41%–65.19%) in the non-ASCT group, with no statistically significant difference in OS rates. The prognostic stratification analysis revealed no statistically significant difference in 5-year PFS between the ASCT group and the non-ASCT group among the standard-risk population (76.7% vs. 53.1%, P = 0.358); the median OS rates were 93.3% (95% CI, 85.86%–100.75%) in the ASCT group and 48.9% (95% CI, 20.28%–77.52%) in the non-ASCT group (P = 0.821). Among high-risk patients, the median PFS was 63.1% (95% CI, 39.58%–86.62%) in the ASCT group and 28.4% (95% CI, 12.0–48) in the non-ASCT group (P = 0.038), indicating a statistically significant difference (see Figure 5). The median OS rates were 81.3% (95% CI, 64.64%–97.96%) in the ASCT group and 59.2% (95% CI, 36.07%–82.33%) in the non-ASCT group (P = 0.486), reflecting an improvement in OS rates but without statistical significance. **Conclusions:** ASCT significantly improves long-term survival in multiple myeloma (MM) patients, demonstrating notable advantages in enhancing quality of life and reducing the need for repeated treatments. However, its benefits are limited in patients with poor induction response, high-risk status, or poor tolerance. Clinical management should adopt individualized therapy based on risk stratification, combining targeted therapies, immunotherapy, and optimized maintenance regimens to further enhance transplantation efficacy and long-term survival.

PA-106

Comparative Effectiveness of Quadruplet vs. Triplet Induction Regimen in Transplant-Eligible Newly Diagnosed Multiple Myeloma: A Target Trial Emulation

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Introduction: Quadruplet induction with daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) has demonstrated superior progression-free survival (PFS) over VRd in randomized controlled trials and is now the standard of care for newly diagnosed transplant-eligible patients with multiple myeloma (TEMM). Large-scale real-world comparative studies of DVRd vs. VRd remain scarce, limiting insights into the real-world applicability of these findings. We conducted a target trial emulation to compare outcomes between DVRd and VRd in TEMM. **Methods:** We conducted a retrospective

cohort study using the Flatiron Health Research Database including patients with TEMM who received DVRd or VRd as first-line (1L) treatment from 9/2019–10/2024. Transplant eligibility was defined as age < 75 years and ECOG status of 0–2 at treatment initiation. Time zero was 1L treatment initiation and assignment to treatment arm was based on regimen received at time zero. Outcomes were PFS and overall survival (OS). To balance baseline characteristics, outcomes were weighted with inverse probability of treatment weights generated from logistic regression incorporating baseline demographic characteristics, clinical variables and index year. Weights were stabilized and truncated at the 1st and 99th percentile; covariate balance was assessed with a target standardized mean difference (SMD) of 0.1. Due to violation of the proportional hazards assumption, treatment effects were estimated using differences in restricted mean survival time (RMST). **Results:** Among 2493 patients who met eligibility criteria (median follow up: 24.2 months; Q1-Q3: 11.5–38.9), 948 received DVRd and 1545 received VRd; 48.6% proceeded to autologous stem cell transplant. Prior to weighting, patients treated with DVRd were younger than those who received VRd (mean, SD: 62.7, 8.8 vs 64.0, 8.2, SMD = 0.15) and more likely had commercial insurance (51.4% vs 43.4%, SMD = 0.16), reside in socioeconomically advantaged areas (Yost index lowest quintile: 11.7% vs 15.7%, SMD = 0.12) and treated at academic centers (34.0% vs 24.3%, SMD = 0.22). Over time, use of DVRd increased over RVd from 4.1% in 2019 to 79.5% in 2024. After weighting, all covariates achieved SMD < 0.1. No significant difference was observed in OS at 36 months (DVRd-84.0%, VRd-84.4%; RMST difference: − 0.1 months, p = 0.89). At 36 months, DVRd was associated with a significantly longer PFS (DVRd-75.2%, VRd-64.4%; RMST difference: 1.5 months, p = 0.003). Differences in PFS at 36 months were wider among patients who did not receive transplant (DVRd-68.2%, VRd-51.4%) compared to those who did (DVRd-81.7%, VRd-76.1%). **Conclusions:** In this real-world target trial emulation, DVRd was associated with a superior PFS compared to VRd. The observed PFS benefit suggests an advantage of quadruplet induction that may not yet be fully captured given short follow-up. Longer follow-up is needed to determine if PFS benefit can translate into improved overall survival.

PA-107

Comparative Efficacy of Carfilzomib-Based Versus Bortezomib-Based Regimens in Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis of Randomized Trials

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Introduction: Proteasome inhibitor–based triplet regimens form the foundation of frontline therapy for newly diagnosed multiple myeloma (NDMM). Bortezomib-based regimens remain widely used standards of care, supported by extensive clinical experience and randomized data. Carfilzomib, a second-generation proteasome inhibitor with greater proteasome selectivity, has demonstrated the ability to induce deeper responses in several clinical trials when incorporated into frontline regimens such as carfilzomib-lenalidomide-dexamethasone (KRd). However, individual randomized trials comparing carfilzomib- and bortezomib-based regimens have produced heterogeneous results with respect to progression-free survival (PFS) and response depth. **Methods:** A systematic literature search was performed across PubMed-MEDLINE, Embase-OVID, CENTRAL, ClinicalTrials.gov, and Web of Science databases up to March 1, 2026. Randomized phase III trials evaluating carfilzomib-based regimens versus bortezomib-based regimens in patients with newly diagnosed multiple myeloma were included. Progression-free survival (PFS) was the primary outcome. Overall response rate (ORR) and complete response or better (≥CR) were secondary outcomes. Effect estimates were pooled using a random-effects inverse-variance model with heterogeneity assessed using the I^2 statistic. **Results:** Four randomized trials comprising patients with newly diagnosed multiple myeloma were included in the analysis. Pooled analysis demonstrated no statistically significant difference in PFS between carfilzomib-based and bortezomib-based regimens (HR 0.79, 95% CI 0.48–1.27), although substantial heterogeneity was observed across studies (I^2 = 69.6%). Carfilzomib-based regimens demonstrated a trend toward higher ORR compared with bortezomib-based regimens (OR 1.26, 95% CI 0.95–1.67) with no observed heterogeneity (I^2 = 0%). Importantly, carfilzomib-based therapy was associated with a significantly greater likelihood of achieving deep responses, with improved rates of complete response or better (OR 1.39, 95% CI 1.04–1.85; I^2 = 26.7%). **Conclusions:** Carfilzomib-based regimens were associated with significantly higher rates of deep response compared with bortezomib-based regimens, although a statistically significant improvement in PFS was not observed. These findings suggest that while carfilzomib may enhance depth of response, the impact of this advantage on long-term disease control remains uncertain. Further studies are needed to clarify the clinical implications of deeper responses and to identify patient populations most likely to benefit from carfilzomib-based frontline therapy.

PA-108

Comparative Efficacy of Elotuzumab, Pomalidomide, and Dexamethasone vs Standard Care Triplets in Relapsed/Refractory Multiple Myeloma After at Least One Prior Line of Therapy: A Network Meta-Analysis

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Introduction: Standard-of-care (SOC) therapy for relapsed/refractory multiple myeloma (RRMM) after ≥1 prior line of therapy has evolved from doublets to triplets, with regimen selection increasingly guided by lenalidomide (R)-refractory status. Several ongoing RRMM trials use elotuzumab–pomalidomide–dexamethasone (EPd) as an active comparator or include EPd within a physician-choice SOC control arm. Robust indirect comparisons are needed to contextualize EPd efficacy relative to other approved and guideline-recommended triplet regimens. **Methods:** We conducted a systematic literature review and network meta-analysis (NMA) of randomized controlled trials evaluating triplet regimens approved and recommended in the US and Europe for patients with RRMM treated with ≥1 prior line of therapy with any prior R exposure and no prior anti-CD38 exposure. As head-to-head trials among triplet regimens are limited, we evaluated prespecified scenarios that assumed clinical equivalence among doublet regimens with similar treatment effects to enable network connectivity; supported by clinical expert opinion and meta-analysis of control arms. Progression-free survival (PFS) hazard ratios (HRs) with 95% credible intervals (CrIs) were synthesized using fixed-effect Bayesian NMA models. Subgroup analyses were performed in R-refractory populations. **Results:** A total of 10 trials assessing eight unique triplet regimens were included for analysis. Assuming equivalence (collapsed nodes) between pomalidomide–dexamethasone (Pd) and bortezomib–dexamethasone (Vd), and between carfilzomib–dexamethasone (Kd) and lenalidomide–dexamethasone (Rd), EPd showed no statistically significant difference in PFS versus any of the eight comparator triplet regimens; HRs (95% CrIs) ranged from 0.81 (0.43–1.54) versus selinexor–Vd to 1.39 (0.69–2.85) versus daratumumab (D)–Kd, with all CrIs crossing 1. In R-refractory patients, EPd demonstrated comparable PFS across the seven triplets with available subgroup data; HRs (95% CrIs) ranged from 0.77 (0.44–1.35) versus DPd to 1.35 (0.64–2.90) versus DKd. In an alternative scenario where Vd was modeled separately and equivalence among Kd, Pd, and Rd was assumed, EPd remained comparable in PFS versus all other triplets in both R-exposed and R-refractory populations. **Conclusions:** This NMA found no statistically significant differences in PFS between EPd and other approved or guideline-recommended triplet regimens in patients with RRMM with ≥1 prior line of therapy, any prior R exposure, and no prior anti-CD38 exposure. Results were consistent in the R-refractory subgroup across alternative pooled doublet scenarios, supporting EPd as an appropriate control among SOC options. Ongoing trials including EPd in anti-CD38–exposed/refractory populations may help further characterize its role as a control arm in this setting.

PA-109

Comparative Pharmacovigilance Analysis of Immune, Infectious and Haematological Adverse Drug Reactions Across Multiple Myeloma Therapeutic Classes: A FAERS-Based Study

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Introduction: The therapeutic landscape of multiple myeloma (MM) has rapidly evolved with the introduction of diverse drug classes, each associated with distinct toxicity profiles. While Adverse Drug Reactions (ADRs) of individual agents are well described, comparative safety patterns across therapeutic classes remain inadequately characterized in real-world settings. This study aims to compare immune, haematological and infectious ADR profiles across major MM therapeutic classes: bispecific monoclonal antibodies (BsAbs), anti-CD38 monoclonal antibodies (MAb), immunomodulatory drugs (IMiDs) and proteasome inhibitors (PI) using the FDA Adverse Event Reporting System (FAERS) data; to evaluate the seriousness of ADRs across therapeutic classes. **Methods:** A retrospective disproportionality analysis of FAERS database from 2020 to 2025 was performed. Signal detection was done using Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR) and Chi-square statistics. Bayesian Shrinkage metrics (Empirical Bayes Geometric Mean and EB05) were used to assess signal robustness. A signal was defined as ROR with 95% confidence interval ≥1 PRR and Chi-square statistics were used as supportive measures to assess consistency of signals. **Results:** A total of 258,545 MM cases were analysed after de-duplication. BsAbs showed the highest immune-related signal among all drug classes (ROR 2.866; EB05 2.343), consistent with its known immune-mediated toxicities. MAbs exhibited consistent signals across all ADR categories with the strongest association observed for infectious ADRs (ROR 1.667; EB05 1.422). PIs demonstrated selective amplification for infectious (ROR 1.412; EB05 1.233) and hematological ADRs (ROR 1.213; EB05 1.115). IMiDs demonstrated no significant disproportionality signals across any ADR categories. BsAbs demonstrated serious ADR rates exceeding 96% across all categories with 61.5% infection related hospitalization. MAbs showed high infectious serious ADR rates (95.6%, 62.1% hospitalized). PIs showed moderate serious ADR rates (93.1% infection, 86.1% hematological) with substantially lower hospitalization rates (58.1% infection, 36.4% hematological). **Conclusions:** These findings suggest that newer therapeutic classes, particularly BsAbs demonstrated greater disproportionality for immune-related ADRs. Distinct class specific toxicity patterns were identified across MM therapeutic classes. IMiDs demonstrated no disproportionality signals despite established toxicity profile, reflecting influence of prolonged exposure or combination therapy. Anti-CD38 MAbs and PIs demonstrated moderate but consistent safety

signals. BsAbs exhibited a pronounced immune-related toxicity profile. These findings highlight the value of comparative pharmacovigilance in understanding class-specific safety patterns and may help refine risk assessment across myeloma therapies.

PA-110

Comparison of Adverse Event (AE) Management Costs of Chimeric Antigen Receptor T-Cell (CAR-T) Therapies in 4L+ Relapsed and/or Refractory Multiple Myeloma (RRMM)

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Introduction: CAR T therapies improve outcomes in patients with relapsed and/or refractory multiple myeloma (RRMM), but are associated with notable safety concerns unique to each product. Differences in adverse event (AE) incidence and management across CAR T therapies directly impact healthcare costs. Understanding these differences in safety and management costs is critical for informing access decisions in RRMM. The objective of this study was to model total per-patient AE management costs of anito-cel, cilta-cel, and ide-cel in 4L+ RRMM from a US health system perspective. **Methods:** Per-patient AE management costs were estimated by applying AE incidence rates to corresponding per-event management costs and summing across events. The base case included AEs of all grades for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), and other grade >3 AEs occurring in >5% of patients for any therapy. Scenario analyses were conducted to include additional special events of interest to CAR T, which included non-ICANS neurotoxicity (Parkinsonism, Guillain-Barré Syndrome, and cranial nerve palsy), immune effector cell-associated enterocolitis (IEC-EC) and secondary primary malignancies (SPMs; myelodysplastic syndrome, acute myeloid leukemia). Unadjusted AE rates for anito-cel, cilta-cel, and ide-cel came from iMMagine-1 (median follow-up [mFU]:15.9 m), CARTITUDE-1 (mFU: 18.0 m) and KarMMa (mFU: 11.4 m), respectively. The per-event AE costs for CRS and ICANS, and annual SPM costs, were obtained from published literature. Costs for other grade >3 AEs were sourced from AHRQ-HCUPNet. Non-ICANS neurotoxicity and IEC-EC costs were derived from published literature validated by clinical experts. All costs were inflated to 2025 values. **Results:** Total per-patient AE management costs for CRS, ICANS, and other grade >3 AEs were $59,381 (anito-cel), $130,403 (cilta-cel) and $139,629 (ide-cel). Adding non-ICANS neurotoxicity and IEC-EC only added $11,973 for cilta-cel as these AEs were not observed with anito-cel or ide-cel. SPMs determined at comparable mFUs further added $2,378, $45,608, and $7,896 for anito-cel, cilta-cel, and ide-cel, respectively. Overall AE costs per patient were lowest for anito-cel ($61,759), compared with cilta-cel ($187,984) and ide-cel ($147,525), corresponding to cost savings of approximately $126,224 and $86,765, respectively. **Conclusions:** In this analysis, anito-cel was associated with the lowest per-patient AE management costs compared with other CAR T therapies in 4L+ RRMM, driven by differences in incidence of high-cost AEs. Findings should be interpreted in the context of cost estimation assumptions and unadjusted cross-trial comparisons, which may also reflect evolving clinical and management practices over time. Overall, these findings highlight the importance of considering safety-related costs alongside clinical outcomes when evaluating CAR T therapies in RRMM.

PA-111

Complete-Genome Multiomics Uncovers Peri/Centromeric Rearrangements as Hidden Drivers of Epigenomic Rewiring in Myeloma

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Introduction: Structural variants (SVs) are central to myeloma (MM) genome complexity; they can disrupt chromatin organization, epigenomic landscape and dysregulate genes without altering coding sequence or copy number. Here, we elucidate SVs involving previously hidden compact heterochromatin near peri/centromeres; dense and repetitive regions, traditionally dismissed as junk DNA, but emerging as critical areas of investigation. **Methods:** srWGS from 23 CoMMpass cases was mapped to CHM13 by BWA-MEM. CoMMpass RNA-seq data (N = 928) were analyzed with control GSE148924 (N = 12) sets. 15 PDXs representing t(11;14), t(4;14), t(14;16), hyperdiploidy, hyperhaploidy were studied by CHM13 multiomics: Illumina srWGS, PacBio HiFi WGS (with DNA methylation) and CantataBio Micro-C. Copy-number variants were detected by CNVRobot, SVs in repetitive regions by in-house tool HeteRobot. Micro-C data were processed by Juicer. **Results:** Compact heterochromatin rearrangements were detected in 61% (14/23) of CoMMpass cases, frequently involving peri/centromeres of chromosomes 8, 12, 15 and 16. Partner-loci breakpoints often disrupted tumor-suppressor genes (CYLD, GAS8, UNC5D) or recombined near proto-oncogenes (MYC, NFKB1), with increased expression compared to control plasma cells. Excluding +1q, peri/centromeric rearrangements showed a trend toward shorter PFS (median 9 vs 51 months, HR 2.88, p = 0.07). In PDXs, +1q was found in 87% (13/15) and resolved as structural rearrangement in 83% (11/13), including 9 chromosomal translocations and 2 tandem duplications. In one t(4;14), complete-genome analysis resolved complex pericentromeric 1q12 jumping translocation involving 6q15, 15p11.2 and 18q11.2; missed by hg38 due to reference

gaps. HiFi mapped 1q breakpoints (impossible by srWGS) while Micro-C confirmed der(1)t(1;18), der(6)t(1;6) and der(15)t(1;15). Phased HiFi methylation showed hypomethylation of loci juxtaposed to 1q pericentromere, a chromatin remodeling pattern identified as a general signature of peri/centromeric rearrangements. Peri/centromeric breakage was not explained by global hypomethylation; methylated CpG levels were lowest in aneuploid (hyperdiploid/hyperhaploid, N = 5, 36.9%) and highest in t(4;14) PDXs (N = 4, 60.0%), but breakage did not follow this gradient. Instead, repeat-specific methylation patterns separated distinct mechanisms: core alpha-centromeric repeats correlated with global euchromatin hypomethylation ($r = 0.76$, $p < 0.001$), whereas HSat2 repeats, including 1q pericentromere, were independent of global pattern ($r = 0.01$). **Conclusions:** Complete-genome multiomics reveals peri/centromeric-associated SVs as recurrent, previously hidden events in MM. These rearrangements rewire DNA topology and local epigenetic state, supporting a role for peri/centromeric regions as regulatory hubs in MM genome instability. Large-scale reprocessing of CoMMpass is now underway, with 97% completed for CHM13 mapping, to confirm their prevalence and suggested clinical impact.

PA-112

Concurrent Coding and Noncoding Single-Cell Transcriptomic Analysis Identifies nc209 as a Mediator of Multiple Myeloma Progression

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Introduction: Although the human genome consists largely of noncoding elements that regulate gene expression, noncoding RNAs (ncRNAs) remain underexplored due to technical challenges in their profiling. To address this, we developed an integrated analytical approach enabling concurrent coding and noncoding transcriptome profiling of new and existing RNA-sequencing data. Using this approach, we identified clinically relevant ncRNAs in the multiple myeloma (MM) bone marrow microenvironment (BMME). **Methods:** To simultaneously profile the coding and noncoding transcriptome, the GENCODE v47 reference annotation was systematically integrated with LncBook v2.1 by removing duplicate transcripts, preserving coding transcripts, and trimming overlapping ncRNA regions. We realigned CD138pos bulk RNA-seq data (N = 942) from the MMRF CoMMpass study and CD138neg single-cell RNA-seq data (N = 483) from the MMRF Immune Atlas initiative to our integrated reference to create a comprehensive ncRNA atlas of MM. **Results:** Our integrated reference annotation expanded the number of quantifiable noncoding genes from 40,875 to 138,296 while preserving all coding genes. Benchmarking confirmed that this approach resolved ambiguous read assignments at overlapping loci and captured high-quality ncRNAs driving clustering and downstream analyses. Application of our framework to the CD138-positive and CD138-negative MM datasets expanded the number of captured noncoding genes from 28,088 to 70,571. To identify ncRNAs associated with high-risk MM cell phenotypes, we clustered patients based on their integrated tumor expression profiles. Fifteen clusters were identified, two of which were significantly enriched for high-risk cytogenetics [amp(1q21) and t(4;14)] and exhibited shorter PFS. Differential expression analysis between high- and standard-risk clusters, followed by a multistep filtering workflow, yielded 19 candidate ncRNAs. The top novel ncRNA, nc209 (ENSG00000310209), correlated with poor PFS (HR = 1.14, p = 0.0025). Network analysis revealed that nc209 is associated with MM-intrinsic and IME-influencing features, including pro-proliferative WNT pathway activation and elevated CCL5 signaling. ChIP-seq analysis uncovered IRF4 binding at the nc209 locus, plausibly connecting ncRNA regulation with pathogenic MM features. Furthermore, single-cell analysis of the CD138neg fraction revealed that high tumor nc209 expression correlated with increased infiltration of anergic CD8 T cells that highly expressed TCR activation markers with low cytotoxicity markers. In vitro, knockdown of nc209 decreased proliferation, whereas overexpression enhanced proliferation, CCL5 expression, and IRF4 activity, highlighting the contribution of nc209 in myeloma aggressiveness. **Conclusions:** Our integrated analysis enables systematic discovery of functional ncRNAs from standard sequencing data. The characterization of nc209 demonstrates this utility, linking high-risk cytogenetics, pro-tumoral pathway signaling, and an altered immune response.

PA-113

Cooperative and Competitive Binding of Transcription Factors Drives the Oncogenic Gene Expression Profile of Multiple Myeloma Cells

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Introduction: Multiple myeloma (MM) is characterised by widespread reprogramming of gene expression, with dysregulation of key transcription factors (TFs) a major contributor to the disease. For example, immunomodulatory drugs (IMiDs) such as

pomalidomide, degrade IKZF1/3, resulting in downregulation of IRF4 and MYC, an effect that is lost in IMiD-resistant patients. Along with PRDM1, which heterodimerises with IKZF3, these TFs are thought to regulate key oncogenes but little mechanistic work has been conducted into the functional relevance of specific TFs in MM gene expression and how they cooperate together. This work defines the functional interplay of key TFs in MM to understand their respective roles in oncogene transcription and assess their potential as novel therapeutic targets in IMiD-resistant patients. **Methods:** We generated MM degron cell lines to induce degradation of PRDM1 and IRF4 alongside using pomalidomide to target IKZF1/3. Pairing this with TF and H3K27ac ChIP-seq and transient transcriptome sequencing (TT-seq) allowed us to explore the effects of rapid protein loss on the binding of other TFs, enhancer activity and nascent gene expression. **Results:** We identified a strong overlap of PRDM1, IRF4, MYC and IKZF1/3 binding to chromatin. All were seen to bind at both enhancers and promoters, including at key MM oncogenes, such as IRF4, XBP1 and CCND2, and immunotherapy targets CD38 and TNFRSF17 (BCMA), suggesting a shared regulatory network. PRDM1 and IKZF1/3 appeared to function primarily as repressors, with widespread increases in histone acetylation, a marker of activation, following degradation of either TF – but surprisingly limited transcriptional responses was observed. Notably, loss of either TF resulted in increased binding of the other, arguing for potential compensatory activities. In support of this, combined degradation of PRDM1 and IKZF1/3 resulted in a greater reduction in cell growth compared to either treatment alone. In contrast, loss of PRDM1 resulted in a slight decrease of IRF4, which in turn downregulates PRDM1 expression and consequently loss of chromatin binding. Loss of IRF4 produced dramatic up- and downregulation of transcription, alongside decreased acetylation. This suggests distinct behaviors for IRF4 compared to PRDM1 and IKZF1/3, combining to drive the same transcriptional network. **Conclusions:** This work suggests a MM gene regulatory network in which specific TFs have unique and redundant roles in gene regulation. PRDM1 is able to partially compensate for IKZF1/3 loss, and vice versa, whereas IRF4 is essential for regulation of many genes. This argues that combined targeting of PRDM1 and IKZF1/3, or direct targeting of IRF4, may be effective therapeutic strategies for IMiD-resistant relapse patients.

PA-114

Co-opting the BAFF-APRIL Pathway in Smouldering Myeloma (SMM) to Fuel Disease Progression

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Introduction: B-cell maturation antigen (BCMA) signalling through B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) is a key regulator of plasma-cell survival and is an emerging therapeutic target in multiple myeloma (MM). However, how BAFF-APRIL signalling evolves during progression from smouldering multiple myeloma (SMM) to symptomatic MM remains poorly understood. We hypothesised that dynamic remodelling of BAFF-APRIL signalling reflects tumour-microenvironment co-evolution during disease progression. **Methods:** We analysed our integrated single-cell atlas comprising bone marrow (BM) and peripheral blood (PB) samples from healthy donors (n = 102), SMM (n = 58) and MM (n = 54). Malignant plasma cells (mPCs) were identified by immunoglobulin clonality. Soluble BAFF, APRIL, BCMA and TACI were quantified by ELISA in BM and PB plasma from SMM (n = 6) and MM (n = 6) patients and integrated with flow cytometry analyses. Longitudinal PB samples from SMM progressors and non-progressors were additionally analysed. **Results:** mPCs demonstrated increased BCMA, TACI and BAFF-R expression in MM compared with SMM ($p < 0.05$), with enhanced NF-κB, MAPK and mTOR signalling. NF-κB activity positively correlated with BCMA expression and the anti-apoptotic target BCL2A1. BAFF and APRIL expression was largely restricted to myeloid populations. Cell-cell interaction analysis identified significantly enhanced BAFF signalling during progression, whereas APRIL signalling remained relatively stable. In healthy donors, BAFF signalling was predominantly directed towards memory B cells; however, progression from SMM to MM was associated with progressive redistribution of BAFF signalling towards mPCs, predominantly through BCMA-mediated interactions. Flow cytometry confirmed increased BAFF protein expression across BM myeloid populations in MM compared to SMM. Despite enhanced BAFF signalling, soluble BAFF and APRIL levels were reduced in MM, while soluble BCMA and TACI increased, suggesting increased ligand sequestration by expanding BCMA-expressing mPCs. Longitudinal analysis of PB plasma identified distinct soluble BAFF-APRIL dynamics between SMM progressors and non-progressors. Patients who subsequently progressed exhibited higher baseline soluble BCMA, TACI and APRIL levels ($p = 0.04$). Progressive disease was associated with declining soluble BAFF and APRIL levels over time in 4/6 and 6/7 patients, respectively, with mean decreases of 32% and 37%. Patients with stable disease demonstrated relatively unchanged ligand levels. **Conclusions:** These findings identify dynamic remodelling of BAFF-BCMA signalling during progression from SMM to MM, characterised by myeloid co-option and preferential rerouting of

survival signalling towards malignant plasma cells. Preliminary longitudinal findings suggest that temporal changes in soluble BAFF-axis components may reflect evolving tumour-microenvironment interactions, representing monitorable biomarkers of disease evolution.

PA-115

Cost per Responder for Teclistamab-Daratumumab versus Daratumumab, Pomalidomide, Dexamethasone (DPd), and Daratumumab, Bortezomib, Dexamethasone (DVd) in Relapsed Refractory Multiple Myeloma Patients

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Introduction: The MajesTEC-3 trial showed markedly superior efficacy of teclistamab in combination with daratumumab (TecDara) versus DPd/DVd in patients (pts) with RRMM with 1–3 prior lines of therapy (LOT). At a median follow-up of 34.5 months, 2.5 times more pts in the TecDara cohort achieved a complete response or better (CR+) (81.8% vs 32.1%; P < 0.001). Median progression-free survival (PFS) was not reached for TecDara and was 18.1 months for DPd/DVd, with 36-month PFS rates of 83.4% for TecDara vs 29.7% for DPd/DVd (HR: 0.17; 95% CI: 0.12–0.23; P < 0.001). Estimated 36-month overall survival also favored TecDara (83.3% vs 65.0%; P < 0.0001). In context of the established clinical efficacy of TecDara and the availability of bortezomib and pomalidomide generics, this study evaluated the economic value of TecDara by comparing cost per CR+ (CP-CR+) vs DVd/DPd from a US perspective. **Methods:** Given the association between deep responses and improved clinical outcomes, CP-CR+ provides a clinically meaningful and readily interpretable measure of treatment value. The CP-CR+ was calculated for each regimen as the 36-month total cost of care (TCOC) divided by the proportion of patients achieving CR+. Comprehensive TCOC was estimated for each regimen, and included wholesale acquisition costs for each drug, inpatient (IP) Tec-Dara step-up doses 1–2 (SUD), management of grade ≥3 adverse events (AEs), drug administration and treatment monitoring (A&M), and drug acquisition and A&M for one subsequent LOT (sLOT) following progression. The cost of sLOT was based on a real-world study and applied to 56.7% of those who progressed. Efficacy, safety, and dosing inputs were derived from the MajesTEC-3 trial (NCT05083169), with the PFS Kaplan-Meier estimates used as a proxy for the proportion of patients remaining on treatment. Cost inputs were obtained from publicly available sources where available. Generic pricing for pomalidomide and bortezomib was assumed. Model was developed in Microsoft Excel™ for Microsoft 365 MSO/Visual Basic for Applications (Microsoft Corp., Redmond, WA). **Results:** Mean 36-month TCOC per patient was $1,393,647 for TecDara (drug: $1,274,836; IP SUD: $9,225; AE: $30,894; A&M: $74,445; sLOT: $4,248), compared with $704,441 for DPd (drug: $406,352; AE: $29,084; A&M: $45,880; sLOT: $223,125), and $635,099 for DVd (drug: $335,168; AE: $29,084; A&M: $47,722; sLOT: $223,125). Despite higher TCOC, TecDara demonstrated the lowest CP-CR+ ($1,703,998) vs DPd ($2,194,890) and DVd ($1,978,833), representing savings of $490,892 and $274,836 per CP-CR+, respectively. **Conclusions:** The CP-CR+ were lower for TecDara vs DPd/DVd, despite the availability of generic pomalidomide and bortezomib. These data demonstrate that TecDara has better economic value driven by its unparallel deep efficacy, supporting its use in earlier LOTs.

PA-116

Cost-Effectiveness of High-Dose Therapy with Autologous Stem Cell Transplantation Versus Non-Transplant Strategy in Newly Diagnosed Multiple Myeloma: A Real-World Institutional Analysis from India

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Introduction: ASCT remains standard consolidation in transplant-eligible newly diagnosed multiple myeloma (NDMM). Low- and middle-income countries (LMICs), affordability often lead to transplant omission. Despite PERSEUS confirming significant PFS benefit with D-VRd→ASCT→D-Lenalidomide (4-year PFS: 84.3% vs 67.7%; HR 0.42), inflation-adjusted, real-world cost-effectiveness data from Indian centres using corrected treatment sequencing are lacking. **Methods:** Institutional ASCT bill amounts analysed for 164 NDMM patients (2007–2026). Costs reported in USD at 2026 mid-market exchange rate (₹93.84/USD), with parallel 2026 inflation-adjusted values (healthcare CPI, 9%/year, MOSPI/RBI). Five-state Markov model (10-year horizon, 5% discount rate) constructed for six arms using real-world sequencing: ASCT arms included 4 induction cycles (D-VRd/VRd/VCd) + HDT-ASCT + maintenance; non-ASCT arms had 6 induction cycles + maintenance (D-Lenalidomide, Lenalidomide, or Bortezomib). Mobilisation costs included in ASCT arms. Transition probabilities derived from PERSEUS and IFM2009. EQ-5D utilities: PFS 0.80, relapse-1 0.65, relapse-2 0.50. ICER assessed against India's willingness-to-pay (WTP) threshold of 3 × per capita GDP (~$586/QALY at 2026 rates). **Results:** Mean age 51 years; transplant-related mortality 1.8%; mean ASCT admission duration 23.6 days. Annual ASCT volume tripled from 5–7/year (2007) to 13–15/year (2026). Overall mean

ASCT cost $13,002 (nominal), rising to $14,036 in 2026. After medical inflation adjustment, real cost of ASCT declined 54.2% — from $30,625 in 2007 (2026-equivalent USD) to $14,036 in 2026 — reflecting sustained institutional efficiency as programme volume scaled. Indian ASCT costs remain 3.6–7 × below the US benchmark ($50,000–$100,000). Markov modelling, VRd × 4→ASCT→ Lenalidomide generated 4.74 QALYs at 10-year discounted cost of $33,496, versus 4.05 QALYs at $24,594 for VRd × 6→no ASCT→Lenalidomide (ICER: $12,785/QALY). D-VRd × 4→ ASCT→D-Lenalidomide generated t highest QALYs (5.45) at $59,851, vs D-VRd × 6→no ASCT→D-Lenalidomide (4.63 QALYs; $54,090; ICER: $7,026/QALY). VRd × 4→ASCT→ Lenalidomide dominated D-VRd × 6→no ASCT→D-Lenalidomide — delivering more QALYs at $20,594 lower 10-year cost, as prolonged daratumumab-based maintenance (~$714/month) in non-ASCT arm cumulatively exceeds cost of upfront ASCT consolidation. **Conclusions:** Since 2007, inflation-adjusted ASCT costs have dropped 54%, and current Indian costs are much lower than international rates. VRd × 4→ASCT→Lenalidomide maintenance offers more QALYs at a lower lifetime cost than D-VRd × 6 without ASCT. Adding D-VRd+ASCT+D-Lenalidomide provides the highest QALYs (ICER $7,026/QALY), but long-term value depends on daratumumab pricing. These results support expanding ASCT programs across LMICs.

PA-117

Cost-Savings Associated with Flat-Dosed vs Weight-Based Intravenous Immunoglobulin Replacement in Patients Receiving Ciltacabtagene Autoleucel for Relapsed/Refractory Multiple Myeloma

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Introduction: In patients (pts) with relapsed/refractory multiple myeloma (RRMM), anti-B-cell maturation antigen chimeric antigen receptor (CAR) T-cell therapy with ciltacabtagene autoleucel (CiltaCel) has been associated with cytopenias, hypogammaglobulinemia, and increased infection risk, underscoring the need for optimal infection prophylaxis. Intravenous immune globulin (IVIG) replacement is recommended for infection prophylaxis, but optimal IVIG dosing post- CAR T remains undefined. Moreover, IVIG represents an increasingly scarce global resource, with an estimated cost of $140/gram. **Methods:** The first 10 pts treated with CiltaCel at the Vanderbilt University Medical Center were included in the financial analysis on the overall IVIG used via flat-dose (10 g starting, increased in 10 g increments until full weight-based dosing was reached, as needed, based on IgG levels < 400 mg/dL) vs the standard weight-based (0.4 g/kg) approach. **Results:** The median (range) follow up was 10 (7–20) months. Pts received a median of 3 (2–5) prior lines of therapy. All pts were triple-class refractory, 20% and 10% were penta-class and XPO-1 inhibitor refractory, respectively. All but one pt were started on flat-dose IVIG at 10 g after outpatient CiltaCel administration (one began flat-dose IVIG at 20 g following an admission to the ICU for a grade (G) 4 infection). The median weight was 91 (68–117) kg with a median projected weight-based IVIG dose of 36 (26–47) g. Flat-dosed IVIG at 10 g corresponded to a median of 28% (21–38) of standard weight-based dosing. At a median of 12 (3–13) months, IVIG doses were escalated in 4 pts, either due to recurrent infections, persistent IgG levels < 400 mg/dL, or at provider discretion. A total of 21 infectious events were documented: 90% were mild (57% G1, 33% G2). Median time to IgG nadir post- CiltaCel was 164 (6–374) days, and IVIG dose adjustments occurred at a median of 12 (3–13) months post-treatment. Throughout the follow up period, the median total flat-dosed IVIG administered per pt (including dose escalations) was 45 (20–190) g compared to the median projected weight-based dose of 171 (66–554) g. This translated to a median total cost per pt of $6,300 (2,800–26,600) with flat-dosing versus $23,979 (9,217–77,616) with weight-based dosing. The median total cost-savings per pt was $12,712 (2,856–56,616). The cumulative cost-savings across all pts was $176,680. **Conclusions:** Despite an IVIG dose increase in 40% of pts, flat-based dosing resulted in significant cost-savings compared to weight-based dosing. The median flat-dose IVIG was 28% of weight-based dosing, and 90% of infections were < G2. Our data is the first example of using safe and effective flat-dose IVIG prophylaxis post CAR T for RRMM. Larger (preferably randomized) prospective cohort analysis is needed for confirmation of these encouraging results which led to significant reduction in utilization of a critical health-care resource such as IVIG.

PA-118

CoxBoost Six-Gene Proliferation Signature Improves Multiple Myeloma Risk Stratification and Identifies Therapeutic Vulnerabilities: A TP53-Anchored ML Approach

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Introduction: Multiple myeloma (MM) exhibits marked prognostic heterogeneity. Current risk stratification relying on clinical variables (ISS, cytogenetics, age, sex) achieves limited discriminative performance (C-index ~0.63). TP53-mutated (TP53 mt) MM, present in ~5% of newly diagnosed patients and rising to ~25% at progression, confers substantially worse outcomes and may anchor a biologically distinct high-risk gene expression programme. **Methods:**

Differential gene expression (DGE) and gene set enrichment analysis (GSEA) were performed comparing TP53 mt (n = 36) and TP53wt (n = 717) MM from the MMRF CoMMpass cohort. Intersection of DGE and GSEA yielded 46 candidate genes. These, combined with clinical variables, were modelled using Cox regression, LASSO, CoxBoost, XGBoost, and Random Survival Forest (70/30 train-test split). External validation was performed on GSE24080 (n = 559). Drug sensitivity was evaluated across 16 MM cell lines (DepMap, ~192 compounds) using LIMMA, linear regression, permutation testing, and Spearman correlation. Performance was assessed by concordance index (C-index) and hazard ratio (HR). **Results:** CoxBoost selected a 6-gene proliferation signature (UBE2C, STMN1, TK1, DSCC1, PTTG1, CENPF). Combined with clinical variables, it achieved a discovery C-index of 0.742 (95% CI: 0.708–0.776) versus 0.629 for clinical variables alone (+18.0%, $p < 0.001$), with minimal overfitting (train–test gap: 0.006). In multivariable Cox analysis, the CoxBoost risk score was independently prognostic (HR 1.95, 95% CI: 1.51–2.52, $p < 0.001$), adjusting for ISS stage and age. External validation confirmed improved stratification (C-index 0.683, +6.8% over clinical variables). The signature outperformed UAMS-70 (0.742 vs. 0.631) and shared 50% gene overlap with LASSO. Drug sensitivity analysis identified three compounds — MACIMORELIN, MW-150, and BROFAROMINE — with selective activity against high-risk MM cells across all 16 lines ($p < 0.001$). **Conclusions:** A TP53-anchored machine learning approach identified a 6-gene proliferation signature that substantially improves MM risk stratification beyond clinical variables, is robust to overfitting, generalises externally, and exposes actionable therapeutic vulnerabilities. Prospective validation in treatment-stratification trials is warranted.

PA-119

Cumulative Infection Burden Predicts Inferior Outcomes During BCMA-Directed Bispecific Antibody Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: Bispecific antibodies (BiAb) have established a new standard of care in relapsed/refractory multiple myeloma (RRMM), inducing deep and durable responses. However, sustained T cell engagement and on-target, off-tumor killing produce immune impairment, and infections remain a leading cause of morbidity. Whether cumulative infection burden is itself prognostic, rather than merely a toxicity, has not been formally examined. We hypothesized that cumulative infection burden during BCMA BiAb therapy reflects the same immune dysfunction that limits durable response and negatively impacts survival. **Methods:** We conducted a retrospective single-center analysis of BCMA BiAb-treated patients. Baseline characteristics and the timing, type and CTCAE grade of infections were collected. Cumulative infection burden was analyzed separately for all-grade and high-grade (CTCAE ≥3) infections, modeled as a time-dependent linear exposure (primary analysis) and via restricted cubic splines (exploratory analysis). Multivariable Cox proportional hazards models were used to evaluate associations with PFS and OS, adjusting for high-risk cytogenetics, EMD, number of prior lines of therapy (LOT), baseline ALC, prior ASCT and prior CAR-T. A 90-day landmark sensitivity analysis was also performed. Patients were followed from BiAb initiation for up to 3 years. **Results:** Among 117 patients with RRMM (49% HR cytogenetics, 21% EMD, median 5 prior LOT), 62 PFS events and 36 deaths were observed. 235 infections were documented in 90 patients (77%); 220 occurring prior to progression were included in the PFS analysis. Cumulative all-grade infection burden was independently associated with inferior PFS (adjusted HR 1.30 per +1 infection, 95% CI 1.14–1.48, $p < 0.001$), with a pronounced effect for high-grade infections (adjusted HR 1.54, 95% CI 1.29–1.84, $p < 0.001$). Exploratory spline analysis showed no significant deviation from linearity, but suggested the greatest relative hazard increase occurred between 0 and 1 high-grade infections (HR 2.45, 95% CI 1.37–4.35), with attenuated effects thereafter. Cumulative all-grade and high-grade infection burden were similarly associated with inferior OS (HR 1.42, 95% CI 1.20–1.69 and HR 2.01, 95% CI 1.68–2.40, respectively; $p < 0.001$). In an exploratory 90-day landmark analysis (n = 86), the association between early high-grade infection (within first 90 days) and inferior PFS persisted (adjusted HR 1.60 per +1 infection, 95% CI 1.12–2.28, $p = 0.010$). **Conclusions:** Cumulative infection burden during BCMA BiAb therapy is strongly associated with inferior PFS and OS, with the greatest relative increase in hazard occurring after the first high-grade infection. As the same T cell engagement that mediates anti-MM efficacy also drives immune impairment, the ability to avoid infection may reflect the integrity of the same immune compartments required for durable disease control. These findings reframe infections as dynamic clinical surrogates of immune dysfunction, rather than mere toxicities.

PA-120

Cure in Multiple Myeloma Is Age-, Risk- and Treatment-Dependent: Long-Term Analyses from 6,380 Patients Across UK Randomised Trials

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Introduction: Improved survival in multiple myeloma (MM) has renewed focus on the concept of cure. The International Myeloma Society (IMS) has proposed a definition of cure as sustained, treatment-free remission with no detectable disease following finite therapy. However, the proportion of patients achieving such outcomes with current standard of care, and how these vary by demographics and treatment remain poorly quantified. We used long-term follow-up from large UK randomised trials to estimate cure fractions in MM. **Methods:** Individual patient data were analysed from 6380 patients in trials enrolling 2003–16, (Myeloma IX and XI), with median follow-up of 10y (IQR, 8.4–11.4). Primary analyses focused on patients receiving time limited treatment, off maintenance therapy, aligning with the IMS cure definition. Endpoints included relapse-free survival (RFS) and overall survival (OS). Mixture cure models and relative survival methods were used to decompose outcomes into a cured and uncured fraction with ongoing excess risk (compared with age-matched UK population life tables, where appropriate). Pre-specified subgroup analyses included age, transplant-eligibility (TE, TNE), treatment, genetic risk in terms of number of adverse molecular abnormalities (gain(1q), del(17p), t(4;14), t(14;16) or t(14;20); SR = 0, HiR = 1, UHiR≥2), minimal residual disease, and frailty surrogates (WHO PS and UK-MRP). **Results:** Long-term RFS plateaus consistent with cure were observed across trials but showed heterogeneity by patient and treatment factors. Among TNE patients, cure fractions were low (4–6%) with minimal improvement from IMiD-based compared with melphalan-based therapy. In contrast, TE patients undergoing ASCT achieved higher cure fractions (9–21%), and these increased with the incorporation of novel agents (e.g. 16% CVAMP+ASCT vs 13% CTD+ASCT in Myeloma IX and 13% CRD+ASCT vs 21% KCRD +ASCT in Myeloma XI). Among MRD-negative patients post-ASCT, cure estimates were substantially higher (17–40%). Age and genetic risk were the dominant determinants of cure. In Myeloma XI, off-treatment cure fractions declined sharply with age (≤60: 16%; 61–70: 9%; ≥71: 5%) and risk (SR: 17%; HiR: 9%; UHiR: 5%). Relative survival analyses showed younger patients approaching population-matched survival over time, whereas older patients had persistent excess mortality. Maintenance therapy significantly prolonged remission and increased the proportion of patients in sustained disease control ("on-treatment cure") to 28–52%, exceeding off-treatment cure estimates. **Conclusions:** Cure is achievable in a meaningful proportion of MM patients, particularly in those receiving novel agents and ASCT. Cure remains uncommon in older and transplant-ineligible patients. Contemporary quadruplets and immunotherapy approaches may increase disease control rates, but whether they increase cure fractions can only be determined by benchmarking with baselines established in trials with finite therapy and extended follow-up such as those presented here.

PA-121

CUT&Tag Epigenomic Profiling of c-MAF in t(14;16) Multiple Myeloma Reveals a Repressive Chromatin Program Modified by MYC Co-Activation

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Introduction: The t(14;16) translocation in multiple myeloma (MM) fuses IGH to the transcription factor c-MAF, yielding high-risk disease with poor prognosis. c-MAF acts as a pioneer transcription factor, aberrantly opening inactive chromatin and activating oncogenic transcriptional programs. Existing genome-wide c-MAF binding studies employed cell lines that also harbor MYC translocations and RAS mutations. Consequently, the contributions of c-MAF, and its interplay with co-occurring genetic events, remain incompletely characterized. **Methods:** We used CUT&Tag to map c-MAF, H3K4me3, and H3K27me3 genome-wide in ANBL6, a t(14;16) cell line lacking secondary MYC or RAS aberrations. This created a map of MAF binding as well as active (K4+/K27−), repressive (K4-/K27+), bivalent (K4+/K27+), and quiescent (K4-/K27−) chromatin, which we then integrated with single-cell co-CUT&Tag data from normal B-cell development, and RNA-seq from four MAF-family MM cell lines: ANBL6 (14;16/MAF only), MM1S and JJN3 (14;16/MAF plus 8;14/MYC), and SKMM1 (14;20/MAFB plus 8;14/MYC). **Results:** c-MAF bound 11,481 sites across the genome in ANBL6, 36.7% in active chromatin, 7.3% in repressive chromatin, 4.4% in bivalent regions, and the balance (51.6%) in quiescent regions of presumed heterochromatin. Sequence analysis with monaLISA recovered the expected c-MAF binding motif alongside AP-1 and ETS family transcription factor motifs. Most (73%) of the (n = 305) genes where c-MAF bound to active (K4me3-enriched) promoters were already active in normal plasma cells, consistent with c-MAF amplifying existing transcriptional programs. However, 23 c-MAF activated (K4me3-enriched) target genes enriched for repressive K27me3 in healthy plasma cells, showing how and where c-MAF acts as a pioneer factor in t(14;16) MM. Of these, 14 genes (61%) are active in ANBL6, including FGF2, a growth factor implicated in bone marrow niche signaling and treatment resistance. The FGF2 promoter shows higher levels of MAF, and FGF2 transcripts are more abundant, in ANBL6 than in MAF+MYC double-hit lines. ERCC4, a DNA repair gene, is repressed in MAF+MYC double-hit lines but not MAFB-expressing SKMM1, suggesting cooperative repression by c-MAF and MYC with implications for genomic instability. The canonical MAF targets CCND2 and CX3CR1 showed no c-MAF binding in ANBL6, despite high expression of both, suggesting that MYC profoundly alters genome-wide c-MAF binding in double-hit disease. **Conclusions:** These findings reveal that c-MAF aberrantly converts repressed to active chromatin in t(14;16) MM, and MYC co-

activation cooperates in suppressing DNA repair genes at these same loci. Our results reveal key differences between single- and double-hit disease, with implications for subtype-specific therapeutic targeting.

PA-122

Cutaneous Plasmablastic Lymphoma with Rapid Post-PI Progression and Asymptomatic CNS Involvement: A Real-World Therapeutic Sequence in an Elderly, Transplant-Ineligible Patient

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Introduction: Plasmablastic lymphoma (PBL) is a rare, highly aggressive plasma cell–phenotype lymphoma with poor survival and no universally accepted treatment algorithm. In older, comorbid patients, outcomes are shaped by tumour kinetics, feasibility, and timely switching. Importantly, CNS dissemination may be clinically silent, yet immediately redefines treatment intent and priorities. **Methods:** Single-patient case report with clinicopathologic correlation. Cutaneous lesions underwent biopsy with extended immunohistochemistry. PET/CT supported staging and response assessment. Bone marrow biopsy clarified the lymphoma–myeloma differential. Disease evolution was captured by cross-sectional imaging during treatment sequencing. **Results:** A 78-year-old woman presented with two non-ulcerated cutaneous lesions (left cheek nodule 1.5 cm; anterior thoracic-wall tumefaction 3.5 cm, not fixed to ribs) and B symptoms. Histology showed plasmablastic phenotype (CD38+, CD138+, CD20−, CD30−, MUM1+, BCL2+, MYC 100%, Ki-67 70%; CD20/PAX5−). Bone marrow biopsy showed no infiltration, supporting a marrow-negative extranodal PBL phenotype. PET/CT found positive skin lessions and pelvic mass. Comorbidities included COPD, hypertension, hypothyroidism, and longstanding rheumatoid arthritis previously treated with methotrexate; she was not a candidate for autoSCT. Five cycles of dose-adjusted EPOCH induced partial remission, followed by pelvic radiotherapy due to painful osteolytic lessions. Residual disease activity prompted continuation with bortezomib-based RVD (weekly schedule adjusted for age) alongside bisphosphonates. During cycle 7, rapid systemic progression was documented with emergence of a new tumour mass above the left knee, reflecting aggressive relapse kinetics. Despite absence of neurological symptoms, CT brain revealed CNS involvement with an infiltrative mass in the pterygopalatine fossa (31 × 39 mm) and a temporal lobe lesion (20 × 15 mm), fundamentally redefining therapeutic priorities. Given systemic progression, CNS dissemination, transplant ineligibility, and limited access to novel targeted agents, the therapeutic strategy was escalated to a GDP-based backbone with intercalated high- dose methotrexate blocks to address concomitant systemic and CNS disease. **Conclusions:** This case highlights three clinically actionable insights: (1) cutaneous, marrow-negative PBL can obscure early decisional clarity; (2) partial response in PBL may signal aggressive biology and imminent relapse; and (3) CNS involvement may emerge silently and should be considered when progression accelerates, as it immediately changes therapeutic priorities in transplant-ineligible patients. This case highlights the need for clearer treatment strategies and better access to therapies that are active in the CNS for this rare and aggressive disease.

PA-123

Cystatin C Unmasks Hidden Renal Impairment and Independently Predicts Mortality in Newly Diagnosed Multiple Myeloma

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Introduction: Renal impairment is a frequent and clinically relevant manifestation of newly diagnosed multiple myeloma (NDMM) and is associated with morbidity, treatment limitations, and inferior survival. Current IMWG definitions rely mainly on serum creatinine or creatinine-based estimated glomerular filtration rate (eGFR), which may underestimate clinically significant kidney dysfunction. We evaluated whether cystatin C-based renal assessment improves detection of renal involvement and prognostic stratification in NDMM. **Methods:** We conducted a retrospective study of consecutive adults with NDMM. Renal involvement was assessed using three definitions: creatinine-based eGFR according to IMWG criteria, serum creatinine ≥2 mg/dL, and cystatin C-based eGFR. Agreement among definitions was evaluated using Krippendorff's alpha and pairwise Cohen's kappa coefficients. Overall survival (OS) was estimated by Kaplan–Meier method and compared with the log-rank test. A multivariable Cox model including all three renal definitions evaluated independent prognostic value. **Results:** Sixty-two patients were included; median age was 57.5 years and 67.7% were male. ISS stage III disease was present in 66.1%, and high/ultra-high-risk cytogenetics in 35.5%. Renal involvement was identified in 16 patients (25.8%) by creatinine-based eGFR, 19 (30.6%) by serum creatinine ≥2 mg/dL, and 34 (54.8%) by cystatin C-based eGFR, representing more than a twofold increase in detection compared with IMWG creatinine-based criteria. Overall concordance among the three definitions was moderate (Krippendorff's $\alpha = 0.565$; 95% CI, 0.380–0.722). Agreement between cystatin C and creatinine-based definitions was moderate ($\kappa = 0.445$–0.534), whereas agreement between creatinine-based eGFR and serum creatinine ≥2 mg/dL was almost perfect ($\kappa = 0.802$). After a median follow-up of 11 months, cystatin C-defined renal involvement was associated with inferior OS

(12-month OS: 75.0% vs 94.1%; p = 0.0247). Serum creatinine ≥2 mg/dL also predicted worse OS (68.4% vs 90.2%; p = 0.0407), while creatinine-based eGFR showed only a trend toward significance (64.0% vs 89.0%; p = 0.0535). In multivariable analysis, only cystatin C-based renal involvement remained independently associated with mortality (HR 7.28, 95% CI 1.06–143.0; p = 0.043). **Conclusions:** Cystatin C identified a substantially larger population of patients with renal involvement than conventional creatinine-based criteria and was the only renal assessment independently associated with mortality. These findings suggest that reliance on creatinine-based definitions alone may underestimate clinically relevant renal dysfunction in NDMM. Incorporation of cystatin C warrants further evaluation as a tool for renal risk stratification and early identification of high-risk patients.

PA-124

Cytogenetic Characteristics and First-Line Treatment Patterns Among Newly Diagnosed Multiple Myeloma Patients in a Single Chinese Center in 2025: A Cross-Sectional Study

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Introduction: Multiple myeloma (MM) remains incurable with significant heterogeneity. Real-world patients often present with more diverse features, such as advanced age, renal insufficiency, and extramedullary disease, leading to outcomes that may differ from clinical trials. Therefore, real-world cohort studies are essential to complement trial findings. Our center has accumulated a comprehensive NDMM cohort. This single-center, real-world cross-sectional study aims to systematically analyze the clinical characteristics, cytogenetic profiles, first-line treatment patterns, and early responses of NDMM patients at our center in 2025, providing real-world guidance for treatment decisions. **Methods:** This single-center, retrospective, cross-sectional study included NDMM patients treated at our center in 2025. Clinical data were collected from the electronic medical record system. Descriptive statistics were performed for patients with complete treatment and response data. **Results:** This study included 107 NDMM patients, median age 61 years (IQR 52.5–68.0), 58.9% male. Cytogenetic data were available for 91 patients (85.0%): 1q21 amplification was most common (n = 30, 33%), including 24 with 3 copies and 6 with ≥4 copies; t(4;14) and t(11;14) each occurred in 11 patients (12.1%); TP53 mutations in 6 (6.6%). Fourteen patients (13.1%) had confirmed paracortical EMD at diagnosis. Among 95 patients with complete first-line treatment records, 59 (62.1%) received anti-CD38 monoclonal antibody-containing regimens. Of 65 evaluable patients, ORR was 86.2%, CR/sCR rate 32.3%, and ≥VGPR rate 72.3%. In the CD38 antibody group (n = 36), ≥VGPR rate was 86.1%; all 16 evaluable patients receiving CD38 antibody + VRD achieved ≥VGPR. Overall, 31 patients (32.3%) completed autologous transplantation or stem cell collection, 10 (10.4%) were scheduled for transplantation, and 19 received lenalidomide-based maintenance. **Conclusions:** This single-center real-world study revealed key findings of NDMM in Chinese clinical practice in 2025. First, anti-CD38 antibody-containing regimens were widely adopted (62.1%) and showed superior early efficacy (≥VGPR rate 86.1% vs. 72.3% overall). Second, high-risk cytogenetic abnormalities were common, with 1q21 amplification detected in 33% of patients, suggesting a unique genetic background in Chinese patients requiring targeted risk stratification. The 13.1% incidence of extramedullary disease also warrants attention, as these patients often have poor prognosis without standardized escalation therapy. Third, autologous stem cell transplantation remains important, yet only about one-third underwent the procedure, indicating a need for flexible transplant timing and alternative strategies. This single-center retrospective study may have selection bias and limited sample size. Future multicenter prospective studies are needed to optimize risk stratification and individualized treatment for NDMM patients.

PA-125

Cytomegalovirus Reactivation after BCMA CAR T-Cell Therapy Among Relapsed Refractory Multiple Myeloma Patients

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Introduction: Infectious complications remain a major source of morbidity and mortality after CAR T-cell therapy for relapsed refractory multiple myeloma (RRMM). Cytomegalovirus (CMV) reactivation following CAR T is increasingly recognized; however, its incidence, risk factors, and impact on clinical outcomes remains incompletely characterized. We performed a retrospective analysis evaluating CMV detection and CMV reactivation in patients undergoing CAR T for MM. **Methods:** Our single center, retrospective study, included 351 RRMM patients, who had received BCMA directed CAR T from 3/2018 till 1/2026. CMV DNA levels below the quantitation threshold (< 34.5 IU/ml) was categorized as CMV detection whereas CMV DNA levels above the threshold (≥34.5 IU/ml) was categorized as CMV reactivation. Clinically significant CMV infection (csCMVi) was defined as CMV DNAemia requiring treatment or CMV end-organ disease. Time-to-event

analyses were performed using cause-specific hazard models. Overall survival (OS) and progression-free survival (PFS) analyses were conducted using CMV reactivation as a time-dependent covariate. **Results:** The median age at CAR T infusion was 65 years (range, 37–86). With a median of 5 (1–14) prior lines of therapy, 12.5% had received prior BCMA therapy. Median time to CMV detection and reactivation were 70 (12–330) and 26 (9–265) days, respectively. CMV detection was uncommon, with cumulative incidence (CI) rates of 0.85%, 2.0%, 2.6%, and 2.6% at 1, 3, 6, and 12 months post-infusion, respectively. CMV reactivation occurred more frequently, with CI rates of 3.7%, 4.6%, 4.9%, and 5.5% at 1, 3, 6, and 12 months, respectively. With median follow-up of 25 months, csCMVi was seen in 3.4% of the patients. On univariable analysis, higher baseline IgG levels (>500 mg/dL) was associated with lower risk of reactivation (HR 0.31, 95% CI 0.1–1.0). Patients who developed ICANS had a significantly higher cumulative incidence of CMV reactivation compared with those without ICANS (12-month incidence: 7.3% vs 1.5%, $p = 0.037$, 1-month landmark analysis). On multivariable analysis, steroid exposure (HR 34.4, 95% CI 13.8–85.7; $p < 0.001$) and tocilizumab use (HR 60.2, 95% CI 19.9–181; $p < 0.001$) were significantly associated with risk of CMV reactivation. CMV reactivation was not significantly associated with inferior PFS or OS, although numerical trends toward worse outcomes were observed. **Conclusions:** CMV reactivation occurred in 5–6% of RRMM patients during the first year, with most cases in the first 2 months post CAR T. Baseline hypogammaglobulinemia, ICANS, corticosteroids and tocilizumab exposure emerged as strong predictors of CMV reactivation, suggesting that treatment-related immunosuppression play a role in viral reactivation. Although CMV reactivation was not significantly associated with PFS or OS, numerical trends warrant further investigation. These findings provide a framework for risk stratified CMV surveillance and prophylaxis consideration among BCMA CAR T recipients.

PA-126

Daratumumab Based Quadruplet Therapy in Newly Diagnosed Multiple Myeloma: Outcomes from a Tertiary Care Centre in India

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Introduction: Daratumumab based quadruplet regimens have emerged as the new standard of care in first-line treatment of NDMM patients. Landmark trials have established the superiority of the quadruplet regimen with greater depth of response in comparison to the triplet combination. However, data from the Indian setting where higher rates of infections are seen remains limited. This study reports efficacy and safety profile of daratumumab based quadruplet therapy used as frontline treatment of Indian NDMM patients. **Methods:** Electronic medical records of a single tertiary centre were reviewed. All patients receiving at least one complete cycle of daratumumab based quadruplet induction regimens between April 2024 and May 2026 were included. Demographic details, baseline characteristics, RISS, high risk cytogenetics as per IMS-IMWG CGS 2025, type of induction regimen, duration of treatment, depth of response, MRD status and adverse effects as per CTCAE v5.0 criteria were recorded. **Results:** A total of 32 patients were included. Median age was 55 years (range: 27–85) of which 21 (62.5%) were male. At presentation, 24 patients had anemia (75%), 10 had renal dysfunction (31.3%), 4 had hypercalcemia (12.5%) and 27 (84.4%) had lytic bone lesions. Sixteen patients were RISS III (50%), 15 were RISS II (46.9%) and 1 was RISS I (3.1%). High risk cytogenetics as defined by IMS-IMWG CGS 2025 was present in 12 (37.5%). The predominant quadruplet regimen was Dara-VRd (23,71.9%) followed by Dara-VTd (3, 9.4%) and Dara-VCd (4, 12.5%). Daratumumab was administered intravenously in 27 patients (84.4%) while 5 patients received subcutaneously (15.6%). Median cycles of therapy was 5 (range: 1–15). Induction therapy is ongoing in 21 patients (65.6%). Post Induction, 5 underwent ASCT (15.6%) and 6 were put on maintenance therapy (18.8%). Out of 32, response was evaluable in 26 patients; 15 had CR (57.7%) and 8 had VGPR (30.7%) as per the IMWG response criteria. ORR (≥PR) was 96.1%. Of 23 patients achieving ≥ VGPR, 19 (82.6%) achieved ≥ VGPR at the end of 4 cycles indicating early deep response. At the end of 8 cycles, 12 patients underwent MRD assessment (37.5%). Seven (58.3%) were MRD positive and 5 (41.7%) were MRD negative. No treatment discontinuation was observed. Infusion reaction to daratumumab was seen in 3 patients (9.4%). Grade ≥3 haematologic toxicities included neutropenia in 13 (40.6%), anaemia in 7 (21.9%) and thrombocytopenia in 3 (9.4%). Infections occurred in 15 patients (46.9%); 6 (18.8%) required hospitalisation. At a median follow up of 6.5 months PFS and OS data remains immature. **Conclusions:** Daratumumab based quadruplet regimens in treatment of NDMM patients displays efficacy in our setting with the majority achieving ≥ VGPR while also demonstrating early deep response and MRD negativity. Toxicity was manageable with neutropenia and infections as predominant adverse events and no treatment discontinuation. Longer follow up is needed for PFS and OS outcomes.

PA-127

Daratumumab Plus Bortezomib Maintenance After DVMP Induction in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: 3-Year Real-World Outcomes Beyond the ALCYONE Strategy

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Introduction: Outcomes for transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM) patients have significantly improved with daratumumab (D)-based frontline regimens, as demonstrated by the ALCYONE and MAIA trials. However, median progression-free survival (PFS) with DVMP remains shorter than with DRd (≈3 vs. ≈5 years), possibly due to differences in maintenance strategy: D monotherapy in ALCYONE versus continuous DRd in MAIA. To bridge this gap and prevent early relapses during maintenance, the Spanish Myeloma Group investigated the value of extended double maintenance with D and bortezomib (DV) after DVMP induction in a real-world (RW) setting. We present updated results after 3 years of DV maintenance. **Methods:** This multicenter, prospective, observational study enrolled patients after 9 cycles of DVMP induction who planned to receive DV maintenance per usual clinical practice (D 1,800 mg SC every month and V 1.3 mg/m^2 SC every other week) until disease progression or unacceptable toxicity. **Results:** In total 118 patients were recruited, who reflected a frailer real-world population than ALCYONE. Median age was 78 years (66–91), with 36% >80 years old, while ALCYONE's median age was 71 (only 30% ≥75 years old). Notably, 33 (28%) patients would have been excluded from the ALCYONE trial, mainly due to an estimated glomerular filtration rate < 40 ml/min. Thirty-two (27%) patients had ISS III, 20 (17%) had extramedullary disease, and 36 (35%) had high-risk cytogenetics. At the time of inclusion, 56 (48%) patients had achieved VGPR, 24 (20%) CR, and 12% MRD negativity. After 3 years of maintenance, responses continued to deepen, with VGPR stable at 56 (48%), CR rising to 40 (34%); and MRD negativity in 23%. In ALCYONE, we estimated ~45% of patients experienced progression/death during the first 3 maintenance years. In our study 43 (36%) patients progressed/died in the same period, despite having a frailer population. Of 18 (15%) deaths, 9 were unrelated to progression or toxicity. The 3-year PFS and TTP rates were 64% and 72%, respectively. The OS rate was 85%. During maintenance, 94 (80%) patients experienced adverse events (AEs), and 48 (41%) serious adverse events (SAEs). Infections, especially respiratory tract, were the most common (152 [36%] AEs; 46 [51%] SAEs). Nine (2%) AEs and 2 (4%) SAEs of peripheral neuropathy were reported. Only 3 patients were discontinued due to toxicity. **Conclusions:** In real-world practice, the addition of bortezomib to daratumumab maintenance following DVMP induction in transplant-ineligible NDMM patients appears to improve outcomes compared with daratumumab alone, despite inclusion of an older population (average age 7 years higher) and 28% of patients who would not have met ALCYONE trial eligibility criteria. This may represent a valuable alternative for patients intolerant to lenalidomide, though longer follow-up is needed.

PA-128

Daratumumab-Based Therapy Is Associated with Improved Renal Outcomes in Patients with Monoclonal Immunoglobulin Deposition Disease: A Multicenter Retrospective Analysis

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Introduction: Monoclonal immunoglobulin deposition disease (MIDD) is an uncommon plasma celldisorder characterized by deposition of nephrotoxic monoclonal immunoglobulins withinrenal basement membranes, often resulting in progressive chronic kidney disease andeventual end-stage renal disease (ESRD). While bortezomib-based regimens have improved outcomes, durable renal recovery remains challenging in many patients. Daratumumab has demonstrated potent anti–plasma cell activity and significant organresponses in related monoclonal gammopathies, but evidence supporting its use inMIDD is limited. We evaluated outcomes associated with daratumumab-containing therapy in a multicenter cohort of patients with biopsy-proven MIDD. **Methods:** We performed a retrospective

study of patients with biopsy-confirmed MIDD treated at three academic centers. Clinical, laboratory, bone marrow, cytogenetic, and treatment data were collected. Patients were grouped by daratumumab exposure (Dara vs Non-Dara). Outcomes included hematologic response, renal response, and progression to ESRD. The primary endpoint was renal survival, defined as time from initiation of therapy to dialysis or kidney transplantation. **Results:** Forty-two patients were included; median age was 63 years (range 45–72), and 53% were male. Kappa light-chain deposition was present in 83%. All had a detectable plasma cell clone, with median marrow involvement of 7% (range 2–65%). t(11;14) was present in 38%. Median serum free light-chain ratio was 23 (range 2–287), and 54% had monoclonal protein on SPEP. Median creatinine was 2.1 mg/dL and median eGFR was 27 mL/min/1.73 m^2; two required dialysis at baseline. All patients received plasma cell–directed therapy. Ten received daratumumab-based regimens (most commonly Dara-CyBorD), and 32 received non-daratumumab therapy; 7 in the Non-Dara group underwent autologous stem cell transplantation. Baseline eGFR was similar between groups (30 vs 27 mL/min/1.73 m^2; $p = 0.31$). Overall hematologic response rates were 90% vs 75% ($p = 0.31$), with higher CR/VGPR rates in the Dara group (70% vs 40%; $p = 0.10$). Renal response was higher with daratumumab (77% vs 40%; $p = 0.04$). Median eGFR improvement was ~30% in both groups. After a median follow-up of 27 months, ESRD occurred in 10% vs 40% ($p = 0.04$) in Dara and Non-Dara groups, respectively. **Conclusions:** In this multicenter cohort of MIDD, daratumumab-based therapy was associated with improved renal responses and lower progression to ESRD compared with non-daratumumab regimens. Hematologic responses were similar overall, although deeper responses were more frequent with daratumumab. These findings support CD38-targeted therapy as a promising strategy in MIDD and suggest that incorporating daratumumab into clone-directed treatment may improve renal outcomes. Prospective studies are needed to confirm these findings and define optimal management strategies.

PA-129

Daratumumab-Lenalidomide Versus Lenalidomide Maintenance After Transplant in Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: Autologous stem cell transplant (ASCT) followed by lenalidomide maintenance is the established standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM), reducing progression risk and improving survival. Despite these advances, myeloma remains incurable in the majority, underscoring the need for more effective post-transplant strategies. Daratumumab, an anti-CD38 monoclonal antibody, has demonstrated activity across the myeloma treatment continuum, with emerging data suggesting its incorporation into maintenance may deepen responses and improve long-term outcomes in transplant-eligible patients. We performed a systematic review and meta-analysis to quantify the effect of daratumumab-based maintenance compared to standard of care in this population. **Methods:** A systematic literature search was performed across PubMed-MEDLINE, Embase-OVID, and ClinicalTrials.gov through January 1, 2026. Eligible studies were randomized phase II and III trials evaluating daratumumab-based maintenance versus standard-of-care maintenance in transplant-eligible NDMM. The primary outcome was progression-free survival (PFS) expressed as a pooled hazard ratio (HR) with 95% confidence intervals. Secondary outcomes included MRD negativity at 10^{-5} and 10^{-6}, sustained MRD negativity (≥12 months at 10^{-5}), and stringent complete response (sCR) rate. All pooled estimates used a random-effects model with the inverse variance method; heterogeneity was assessed via I^2 statistic. **Results:** Three trials enrolling 1,116 patients were included. D-R maintenance significantly improved PFS compared to lenalidomide alone (HR 0.44; 95% CI 0.34–0.59; $p < 0.05$). Among 558 patients per arm, D-R demonstrated superior MRD negativity at 10^{-5} (OR 3.67; 95% CI 2.84–4.73), at 10^{-6} (OR 3.86; 95% CI 2.94–5.07), sustained MRD negativity (OR 4.44; 95% CI 3.37–5.85), and sCR rates (OR 2.48; 95% CI 1.94–3.17); all $p < 0.05$. Heterogeneity was non-significant across all outcomes. **Conclusions:** D-R maintenance was associated with significant and consistent improvements in PFS, MRD negativity at 10^{-5} and 10^{-6}, sustained MRD negativity, and sCR rates compared to lenalidomide alone in transplant-eligible NDMM. These findings support D-R as a superior post-transplant maintenance strategy and establish daratumumab as an important component of care in this population.

PA-130

Dasatinib and Quercetin in Patients with Relapsed, Refractory Multiple Myeloma Receiving CAR-T Therapy: First Report from the Safety Run-in of the Phase II DART Trial

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Introduction: Ciltacabtagene autoleucel (cilta-cel) produces high and durable response rates in relapsed/refractory multiple myeloma (RRMM), but most patients (pts) relapse. Therapy induced senescent-like (TIS) myeloma cells and T-cell phenotypes have been implicated in limited CAR T-cell expansion, persistence, and durability of response. Dasatinib and quercetin (D+Q) are senolytic drugs that can resensitize TIS MM cells to killing in preclinical

models. We hypothesized that D+Q could improve the durability of CAR T-cell responses, without compromising the established safety profile of cilta-cel. **Methods:** DART (NCT06940297) is an investigator-initiated, single-center, single-arm phase II trial. Eligible pts had received ≥3 prior lines of therapy (pLOT), were triple-class exposed, and had FDA-approved cilta-cel available. Pts receive 100 mg D and 1000 mg Q on Days−7/-6 prior to cilta-cel and on Days 28/29, 58/59 and 88/89 after cilta-cel, in combination with cilta-cel. The primary endpoint is MRD-negativity at 3 months by bone marrow and PET/CT. Secondary endpoints include response, progression-free survival, and adverse events. Correlative research includes longitudinal analysis of TIS. Here, we first report the pre-specified safety run-in. **Results:** Six pts (median age 67 yrs, range 58–72; 3 male/3 female) were included, with median of 3 pLOT. All pts were standard-risk by mSMART and ECOG 0–1. One patient held D for grade 3 neutropenia; no other higher-grade D+Q related toxicities were observed. Immune effector cell-associated adverse events were consistent with the known profile of cilta-cel: CRS occurred in 5/6 pts (no grade ≥3). No ICANS was observed. Median peak absolute lymphocyte count after infusion was 2.85 x109/l (1.02–5.46). CAR expansion and persistence at month 1 was comparable to historical non-D+Q cilta-cel pts. To date, no delayed neurotoxicity has been observed. Post lymphodepletion, all pts had grade ≥3 hematologic toxicity. Grade ≥3 non-hematologic toxicity occurred in 3/6 pts (3/6 Hypertension, 1/6 catheter related infection, 1/6 pneumonia). Primary endpoint, bone marrow MRD and PET/CT negativity rate at month 3, was 67% (BM MRDneg 6/6, PET/CTneg 4/6). With a median follow-up of 5.5 months (range 3–7.3), all pts remain progression-free at data cutoff. In preliminary correlative analysis, TIS (KLRG1+, 2–30%; n = 2) and myeloid signature (CD14/CD16: 2–16%, n = 2) myeloma cells were seen at baseline. Senescent T cells were seen in the bone marrow, but not in the blood (BM, median (range): KLRG1+ 69%, (55–80), n = 4); CD57+ 22% (5–35), n = 6; uPAR+ 6.47% (range, 3–10), n = 6). **Conclusions:** In the safety run-in of the DART trial, D+Q with cilta-cel was feasible and showed a safety profile consistent with cilta-cel alone, and no new signals associated with D+Q. Updated clinical and correlative results including additional TIS analysis in bone marrow biopsy will be reported.

PA-131

Dasatinib for Cranial Nerve Palsy Following Cilta-Cel

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Introduction: Cilta-cel has emerged as a key therapy for RRMM but best practices for management of unique Cilta-cel related toxicities remain limited. Cranial nerve palsies (CNPs) have become an increasingly recognized complication of Cilta-cel therapy with improving characterization of frequency and potential predisposing patient characteristics [Salva et al, ASCO 2025]. To date, there are no consensus recommendations for management of Cilta-cel induced CNPs. Dasatinib has been described as a potential short-term mediator of CAR-T activity via inhibition of lymphocyte-specific protein tyrosine kinase (LCK) [Mestermann et al, Sci Transl Med 2019]. Given the potential for rapid CAR-T cell functional modification with long-term CAR-T functional preservation we incorporated dasatinib into a treatment approach for Cilta-cel induced CNPs. Herein we describe the characteristics and outcomes from a series of patients managed with this approach. **Methods:** We retrospectively reviewed records for patients with RRMM treated with a dasatinib incorporating regimen for Cilta-cel induced CNPs (n = 8). All patients were treated at the Colorado Blood Cancer Institute. Following initial experience, a standard treatment approach was developed utilizing dasatinib 100 mg for 7 days with corticosteroids and IVIg at first recognition of emergent CNP. Data reviewed included demographics, previous lines of therapy, cytogenetic characteristics, CNP symptom duration, CNP recurrence, and laboratory parameters including absolute lymphocyte count (ALC), LDH, ferritin and CRP. **Results:** Patients had a median time from CAR administration to development of CNPs of 22 days. 7 of 8 patients were hospitalized to expedite management and avoid delays in acquiring outpatient dasatinib. Following initiation of dasatinib initial improvement in CNP symptoms was often fairly rapid. Median time to initial CNP resolution was 16 days (range 7–169). Following initial treatment and recovery from CNP 4 of 8 patients (50%) developed recurrence of CNP. CNP recurrences developed a median of 37 days after completion of initial course of dasatinib (range 7–47). 3 of 4 patients with recurrence received a second course of therapy including dasatinib, all achieved eventual full resolution of CNP. One patient developed a facial rash, which was the only adverse event directly attributed to dasatinib administration. **Conclusions:** Dasatinib represents a potentially novel therapeutic option for the management of certain CAR-T related toxicities. We treated 8 patients who experienced Cilta-cel related CNPs with a Dasatinib containing approach. The timing of initial improvement observed gives potential support for dasatinib having CAR T activity modifying effect while high rate of recurrence after initial improvement indicates that dasatinib related modification appeared short lived. Effectiveness of dasatinib may be improved with alternative dosing schedules although difficulty in obtaining urgent outpatient treatment access may impact real-world application.

PA-132

De Novo Anti-BCMA Miniprotein CAR T Cells Enable a Programmable Strategy for Multiple Myeloma Immunotherapy Resistance

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Introduction: B cell maturation antigen (BCMA)-directed immunotherapies have transformed the treatment landscape of multiple myeloma (MM), producing deep responses in relapsed and refractory disease. However, mutations in the BCMA extracellular domain impair efficacy, highlighting the need for binders that engage alternative epitopes. Artificial Intelligence (AI)-guided de novo protein design offers a rational strategy to overcome these limitations by enabling the rapid generation of small, structurally optimized binders with design-specific epitope specificity. Here, we have designed multiple de novo miniprotein-based CAR T cells using AI to overcome resistance. **Methods:** Multiple regions of the extracellular BCMA were selected based on mutation site and accessibility as targets for computational design. Candidates were generated using multiple AI-based approaches, and the selected miniproteins were ranked based on confidence metrics, structural features, and binding regions. Miniproteins were cloned as antigen recognition domains into a second-generation CAR backbone. Recombinant BCMA was used for the binding assays. On-target and off-target activity, as well as tonic signaling, were measured by CD69 surface expression in CAR-positive Jurkat cells. Lead candidates were transduced into primary human T cells for further characterization. Ex vivo cytotoxicity was assessed against multiple myeloma cell lines and K562 cells engineered to express mutated BCMA variants. The efficacy of de novo miniproteins was compared with clinically approved BCMA CAR T cells. **Results:** We ran multiple campaigns and, after applying structural and energetic feature filters across models, selected 30 candidates for experimental screening. Among these candidates, 8 showed positive binding by flow cytometry. Strong BCMA-dependent CAR T activation and cytotoxicity were observed, particularly with 5 miniproteins, comparable to those observed with benchmark BCMA CAR Ts in BCMA wild-type (WT) MM cell lines. We used 5 engineered K562 cell lines, each expressing different clinically relevant BCMA mutations, to test de novo miniproteins against mutated and WT BCMAs. 3 of these miniproteins showed cytotoxic activity comparable to benchmark BCMA CAR Ts. None of the miniproteins showed significant off-target activity or tonic signaling, as assessed by lower CD69 activation when co-cultured with BCMA-negative cells compared to benchmark BCMA CAR T cells, which showed higher activation, suggesting potentially lower toxicity and tonic signaling with miniproteins. **Conclusions:** De novo miniproteins targeting BCMA exhibit cytotoxic activity even when BCMA is mutated, with no off-target effects or tonic signaling. Its rapid design capability with AI-based methods and its smaller size relative to conventional scFvs may provide additional advantages in stability, surface occupancy, and toxicity. We are also in the process of making dual miniproteins to improve activity and translating these miniproteins into other immunotherapy formats.

PA-133

Deep Generative Modeling of Multi-Cohort Flow Cytometry Reveals a T-Cell Exhaustion Signature Predictive of Post-ASCT Outcomes in Myeloma

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Introduction: Autologous stem cell transplant (ASCT) remains standard in myeloma treatment. However, a significant fraction of patients relapse early (i.e., within 2 years). No validated post-treatment biomarker exists to identify patients at high-risk of relapse independent of conventional tumor burden metrics or measurable residual disease (MRD). T-cell reconstitution has been associated with post-ASCT outcomes. High-dimensional flow cytometry is used to phenotype T-cell populations through surface marker co-expression, but cross-cohort integration as a biomarker is challenging, as marker intensities are not directly comparable and manual gating thresholds are subjective. To overcome these barriers, we applied a variational autoencoder (VAE) to day +100 T-cell flow cytometry data to discover a reproducible biomarker of post-ASCT outcome applicable across cohorts. **Methods:** Day +100 post-ASCT PBMCs were analyzed by spectral flow cytometry in two independent cohorts: a single-center cohort (n = 74; 31 markers) and the BMT CTN 0702 randomized trial (n = 96; 25 markers). The 16 shared T-cell markers were z-score normalized and a VAE was trained on the pooled single-cell data. Latent axes were tested for Spearman association with landmark PFS and required to replicate independently in both cohorts. The replicating axis was distilled into a linear marker score and tested by Cox regression. **Results:** In the single-center cohort, 85% received triplet and 15% quadruplet induction; 20% underwent delayed ASCT after first relapse; 30% had high-risk disease (Avet-Loiseau JCO 2025); and 61% were bone marrow MRD-positive (10^{-5}) at day +100. Median follow-up was 5.8 years. CTN 0702 demographics are reported (Stadtmauer JCO 2019). The VAE identified a single latent immune axis predictive of PFS in both

cohorts, consistent with a T-cell exhaustion phenotype. The axis was distilled into a three-marker composite: z(PD-1)+z(TIGIT)-z(CD25). The composite correlated with shorter PFS in both cohorts (single-center $r = -0.29$, $p = 0.013$; CTN $r = -0.28$, $p = 0.007$; combined $r = -0.26$, $p = 6 \times 10^{-4}$) and was independent of CTN treatment arm (partial $r = -0.29$, $p = 0.004$). Simplifying to the patient-level median PD-1/CD25 ratio on CD8+ T-cells strengthened the signal (combined $r = -0.30$, $p = 5 \times 10^{-5}$). Higher median PD-1/CD25 ratio on CD8+ T-cells was associated with shorter PFS in the single-center cohort (HR 4.02, $p = 0.009$) and independently validated in the CTN cohort (HR 4.43, $p = 0.002$). In the single-center cohort, this association remained significant after adjustment for high-risk disease, MRD, and delayed ASCT (adjusted HR 3.83, $p = 0.018$). **Conclusions:** A simple PD-1/CD25 ratio on CD8+ T-cells, discovered by deep generative modeling and validated across two cohorts including a prospective trial, independently predicts PFS beyond established risk factors. Because the signature is easily measurable by routine flow cytometry, it is well-positioned for prospective evaluation as a tool to guide post-ASCT disease monitoring and risk-adapted maintenance.

PA-134

Deep Sustained Response to Belantamab Mafodotin Despite Reversible Grade 4 Ocular Toxicity in Relapsed/Refractory Multiple Myeloma in the Brazilian Public Health System

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Introduction: Belantamab an anti-BCMA antibody-drug conjugate has demonstrated significant efficacy in patients with myeloma across the trials. However, ocular toxicity remains one of the major therapeutic challenges. This case of a Brazilian patient treated through an expanded access program at a fully public hospital (SUS), using exclusively public healthcare resources. Belantamab,bortezomib and dexamethasone (Bela-Vd) and achieved a deep and sustained response after only two infusions, despite developing fully reversible grade 4 ocular toxicity. **Methods:** We report a real-world case from an EAP in Brazil, a patient with R/R MM treated with BVD. Clinical response, ophthalmologic toxicity, management strategies, and outcomes were retrospectively evaluated. Ocular adverse events were assessed through specialized ophthalmologic follow-up, including serial corneal examinations and photographic documentation according to keratopathy and visual acuity (KVA) grading criteria. **Results:** A.B., 64-year male from Brazil, was diagnosed in 2012,IgA/kappa MM, ISS III. Initial treatment VTD in 2012, followed by TMO in 2014. Documentation regarding the depth of response achieved during these prior therapies was unavailable. In March 2023, after clinical PD, initiated treatment VCD achieving a VGPR. Therapy was discontinued after maximal response had been achieved in order to avoid additional cumulative toxicity. In 2024, the patient developed extramedullary relapse, associated with vertebral pain, for which palliative spinal radiotherapy was administered. The most recent biochemical relapse evaluation in 2025, findings included dFLC of 138 mg/L; bone marrow aspirate demonstrating 10% atypical plasma cells. Following the availability of the EAP for belantamab treatment with BVd was initiated on 18/07/25, using dose of 2.5 mg/kg. After the first cycle, the patient did not develop significant ocular toxicity, and a second cycle at the same full dose on 08/08/25. Following the second infusion, the patient developed severe ocular toxicity classified KVA 4, leading to pause of belantamab. Specialized ophthalmologic assessment, including serial photographic documentation of corneal changes. This approach allowed greater precision in both the grading and management of belantamab. Despite early treatment pause, the patient achieved a deep and sustained response. **Conclusions:** This case highlights the remarkable antitumor activity of belantamab even after limited exposure, including in the setting of relapsed disease. The occurrence of KVA4 represents a clinically significant treatment-limiting complication. Nevertheless, the clinical course observed in this patient reinforces that ocular toxicity may be reversible even in severe cases. This case illustrates that belantamab may induce deep and sustained responses even after limited exposure in patients with multiple myeloma. Despite the ocular toxicity, the patient experienced substantial clinical, allowing successful therapeutic reintroduction at a reduced dose (1.9 mg/kg).

PA-135

Deeper Cell-Free DNA Whole Genome Sequencing Improves Recovery of Relapse-Associated BM Variants Ahead of Clinical Relapse in Multiple Myeloma

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Introduction: Clonal evolution is a key driver of progression, relapse, and treatment resistance in multiple myeloma (MM). Reconstructing tumour subclones from bone marrow (BM) is constrained by sampling and invasive concerns, posing a challenge to longitudinal monitoring. Cell-free DNA (cfDNA) from plasma is a minimally invasive alternative that captures tumour fragments. Whether deeper cfDNA whole-genome sequencing (WGS) can recover relapse-driving variants earlier in the disease course remains unclear. Here, we compared recovery of relapse BM variants across longitudinal cfDNA samples using 30X Illumina versus 200X ppmSeq Ultima WGS. **Methods:** We performed WGS of plasma cfDNA and matched germline from 17 newly diagnosed MM cases

using 30 × Illumina and/or 200 × Ultima ppmSeq, with 9 cases sequenced longitudinally and 2 having matched diagnosis and relapse BM. We compared concordance with matched BM, assessed Tumour fraction and somatic copy-number alterations using ichorCNA, and called SNVs using GATK Mutect2 (Illumina), single read SNV (SRSNV Ultima) and SNVFind (Ultima). In cohorts with longitudinal Illumina cfDNA (up to 5 timepoints spanning diagnosis to relapse) and matched relapse BM, we tracked relapse-associated BM SNVs across their cfDNA. Where paired baseline and relapse BM samples were available, we further classified variants as baseline-only, shared, or relapse-only, and recovery of each class was evaluated across cfDNA timepoints and platforms. **Results:** Compared to standard depth, 200X ppmSeq cfDNA sequencing improved SNV recovery (median: 1,385 vs 579, range: 15–3,219 vs 61–2,596), and enhanced detection of low-variant allele frequency (VAF < 0.1) mutations, with an inverse correlation to cfDNA tumour fraction (Spearman's $\rho = -0.88$; $p < 0.01$). In the longitudinal Illumina cohort, relapse-associated BM variants were already detectable in cfDNA at diagnosis, reaching up to 41% (median = 21%, range = 1–41%), before peaking at relapse (median = 41%, range = 1–68%), while background cfDNA from non-matched patients consistently showed minimal recovery (< 1%). In a case study with paired baseline and relapse BM, shared variants were detected in cfDNA, with average recovery increasing from ~30% at baseline to ~70% at relapse. Recovery of baseline-only and relapse-only variants was lower overall, though deeper sequencing combined with SRSNV calling demonstrated approximately 3-fold higher detection across SNVs compared to standard-depth Illumina. **Conclusions:** This pilot study supports cfDNA as a sensitive, minimally invasive approach for longitudinal MM monitoring, with deeper sequencing providing meaningful gains in recovery of low-frequency and clonally distinct tumour variants. Ongoing work will expand variant class profiling across the full cohort and characterize fragmentomic signatures associated with baseline-only, shared, and relapse-only variants to enable earlier detection of relapse-driving clones directly from cfDNA.

PA-136

Deep-Learning Derived 12-Gene Signature Enables Robust Identification of Malignant Plasma Cells in Multiple Myeloma and Its Precursor States

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Introduction: Multiple myeloma (MM) is characterized by significant heterogeneity, making it challenging to distinguish malignant plasma cells (PCs) from non-malignant counterparts in single-cell datasets. Conventional computational approaches use canonical markers and copy number variation, but such approaches are limited by variability in marker expression and reliance on manual interpretation. Reliable automated approaches to identify malignant plasma cells are needed for robust studies of the disease pathogenesis. **Methods:** We developed a supervised deep learning (DL) autoencoder-based model to classify malignant PCs in MM and its precursor states using integrated single-cell datasets from multiple cohorts. Patient-level holdout analysis enabled rigorous dataset-specific validation, complemented by independent external cohorts. Differential gene expression and survival analysis were performed to discover a malignant cell-specific gene signature. Additionally, the generalizability of the malignant PC biomarker was evaluated using an independent, publicly available paired single-cell RNA sequencing (scRNA-seq) and B-cell receptor sequencing (scBCR-seq) dataset with annotated malignant PCs. **Results:** The DL autoencoder model demonstrated superior performance in classifying malignant PCs achieving high mean area under the curve (AUC) scores of 0.80 ± 0.03 on independent test dataset. Notably, the model generalizes well to held-out samples, achieving an AUC of 0.92 ± 0.04 across single-cell platforms. Examining differentially expressed genes between malignant and non-malignant cells, a 12-gene signature specific to malignant PCs was identified. We evaluated the generalizability of the signature across independent datasets, assessing its enrichment in malignant, non-malignant and healthy PCs. The signature showed consistent higher enrichment in malignant cells relative to non-malignant ($P < 0.01$) and healthy counterparts ($P < 0.01$), with no significant differences between non-malignant and healthy populations ($P = 0.059$, $P = 0.47$). Further, validation on CoMMpass single-cell data confirmed the higher enrichment in predicted malignant PCs ($P < 0.01$) compared to their normal counterpart. Survival analysis on the CoMMpass CD138+ RNA-seq data depicted that the higher enrichment of the signature associated with poor survival (HR = 2.7, $P < 0.01$). Independent validation and comparative analysis against existing biomarkers using scRNA-seq and BCR-seq demonstrated that our 12-gene signature exhibits stronger and more consistent alignment with BCR-defined clonal dominance. **Conclusions:** Leveraging DL-based classification, we identified a 12-gene signature that extends existing literature and provides insight into MM pathogenesis. The signature robustly marks malignant plasma cells, including clonal population, and correlates with disease progression. Further, the signature is associated with poor survival highlights its potential as a prognostic biomarker and underscores its clinical relevance in MM.

PA-137

Dendritic Cell Modulation Enhances αCD40 Immunotherapy in Multiple Myeloma

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Introduction: Dendritic cells (DCs) are essential for initiating anti-tumor immunity through antigen presentation and T-cell

priming. Using single-cell RNA sequencing, we previously identified a heterogeneous but low-abundance DC compartment in multiple myeloma (MM), with conventional DCs (cDCs) displaying impaired activation and reduced T-cell priming capacity. While CD40 agonist (αCD40) therapy partially restored cDC function, its anti-tumor effects were transient, highlighting the need for more durable DC-targeting strategies. **Methods:** We investigated the role of Flt3–Flt3L signaling in enhancing DC function using the immunocompetent 5T33MM model. The effects of Flt3L treatment on immune cell composition and tumor burden were evaluated ex vivo and in vivo. In parallel, an immunogenic cell death (ICD)-based screen was performed to identify compounds that promote DC activation. Selected candidates were further assessed alone and in combination with αCD40 therapy. **Results:** Flt3 expression was largely restricted to DC subsets, with minimal expression on MM cells, and Flt3L treatment did not affect MM cell viability or proliferation. Flt3L therapy significantly increased DC abundance in the bone marrow ex vivo. However, this expansion did not translate into reduced tumor burden in vivo. Instead, Flt3L treatment led to an increased frequency of B cells and regulatory T cells (Tregs) in the bone marrow, without enhancing effector cell populations. Interestingly, increased activation of effector cells was observed exclusively in the spleen, indicating compartment-specific immune modulation. Combining Flt3L with αCD40 therapy did not yield additional therapeutic benefit, underscoring limitations of this approach. Through ICD screening, histone deacetylase inhibitor panobinostat was identified as a promising candidate. Panobinostat promoted expansion and activation of cDCs ex vivo, an effect that was further enhanced when combined with αCD40 therapy. **Conclusions:** While Flt3L effectively expands DCs, it fails to translate into therapeutic benefit in MM, underscoring the limitations of DC expansion alone. In contrast, ICD induction using panobinostat enhances cDC activation and synergizes with αCD40, supporting a strategy that combines DC activation with tumor-intrinsic immunogenic modulation to improve anti-tumor immunity in MM.

PA-138

Description of Step-Up Dosing and Adverse Events After Elranatamab Initiation in Patients with Relapsed or Refractory Multiple Myeloma: Results of the Interim Analysis of the Real-World AMbrELA Study

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Introduction: Elranatamab (ELRA) is a bispecific antibody targeting BCMA on plasma cells and CD3 on T cells, inducing cytolysis of myeloma cells. Based on the MagnetisMM-3 study (NCT04649359), ELRA monotherapy was approved in 2023 for the treatment of relapsed or refractory multiple myeloma after exposure to 3 therapeutic classes. ELRA is administered according to a step-up dose (SUD) schedule: 12 mg Day(D) 1, 32 mg D4 and 76 mg D8. This analysis describes the dose escalation patterns and adverse events (AEs) associated with real-world (RW) initiation of ELRA. **Methods:** AMbrELA (EUPAS1000000074) is an ambispective observational study evaluating the RW effectiveness and safety of ELRA in adult patients (pts) included in the early access program in France from May2023 to Sep2025. Retrospectively enrolled pts who received ≥1 dose of ELRA prior to 31Jul2025 were selected for this analysis. This interim analysis includes the description of pt characteristics, disease, prior lines of therapy (LOT), SUD, and cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) incidence. **Results:** At total of 89 pts from 30 centers were enrolled; median follow-up was 13.4 mos (95% CI, 11.5–16.6). Median pt age was 72 yrs (Q1-Q3,66.0–76.0); 29.2% were ≥75 yrs old; 47.2% were male. Median time from diagnosis to initiation of ELRA was 6.8 (3.7–10.9) yrs. At least 1 comorbidity was present in 79.1% of pts; 24.4% had renal failure and 9.3% peripheral neuropathy. ECOG PS was ≥2 in 38.6% of pts; 80.4% had ISS score II/III and 28.2% had extramedullary disease. Among 65 pts with available cytogenetics, 10 had del(17p). Pts received a median of 4 (3–6) prior LOT; 93.3% and 67.4% were exposed to ≥3 and ≥5 therapeutic classes, respectively; 11 (12.4%) had received anti-BCMA therapy, including 9 CAR-T. Most pts (92.1%) completed SUD. The median time between doses 1 and 2, 2 and 3, and 1 and 3 was 3.0 (3.0–4.0), 4.0 (3.0–4.0) and 7.0 (7.0–8.0) days, respectively. Most (69.5%) pts completed SUD on D8 or earlier. All pts had received the recommended premedication. Fifteen (16.9%) pts received ≥1 SUD in the out-patient hospitalization setting, including 8 pts from dose 1. The median time to switch to the out-patient hospital setting during SUD was 1 day (1.0–7.5). During the follow-up period, 35 (39.3%) pts had ≥1 CRS event; 26 (74.3%) after dose 1. No CRS was a serious adverse event (SAE). Six (6.7%) pts developed ICANS; 4 events after dose 1 and 4 events were SAEs, including 2 in the same pt. Median time to onset of CRS and ICANS was 3.0 (2.0–4.5) and 5.0 (3.5–13.0) days, respectively. Median time to resolution was 2.0 (2.0–3.0) and 8.0 (5.5–10.0) days, respectively. **Conclusions:** These interim data from the AMbrELA study provide an accurate picture of ELRA SUD patterns and associated AEs in real life. These data confirm that adapted SUD and premedication favor the management of CRS and ICANS. This analysis will need to be updated as dosing regimens and ongoing medical care may change.

PA-139

Design of the Phase 2 ALANIS Study: Belantamab Mafodotin in Combination with Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in Patients with Newly Diagnosed Amyloid Light Chain Amyloidosis

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Introduction: B-cell maturation antigen (BCMA)-targeting therapies have shown encouraging early results for amyloid light chain (AL) amyloidosis. Belantamab mafodotin (belamaf) is a BCMA-targeting antibody-drug conjugate that has efficacy as monotherapy in relapsed/refractory AL amyloidosis. We present the design of the ALANIS study of belamaf + VCd in newly diagnosed (ND) patients (pts) with AL amyloidosis. **Methods:** ALANIS (NCT07224672) is a phase 2, open-label, multicenter, international, randomized, dose optimization study. Eligible pts are aged ≥18 years with histologically confirmed ND AL amyloidosis, measurable clonal disease, Eastern Cooperative Oncology Group Performance Status 0–2, and adequate organ function, who are ineligible for high-dose chemotherapy with autologous stem cell transplant. Pts will be excluded if they have other plasma cell dyscrasias, significant non-AL amyloidosis-related cardiovascular conditions, Mayo stage 3B disease, or corneal epithelial disease other than mild punctate keratopathy. Pts (N = 40) will be randomized (1:1) to receive 2 different dose levels of belamaf with VCd weekly for 24 weeks during dose optimization. Randomization will be stratified by cardiac stage (I/II vs IIIa). From 24 weeks, pts will receive belamaf monotherapy at a longer planned cycle length for 18 months. Planned interim analysis will determine the optimal belamaf dose from the dose optimization phase. Dose expansion phase will enroll 20 additional pts to receive the selected dose of belamaf (+ VCd for 24 weeks, then monotherapy for 18 months). In both phases, treatment will continue up to 24 months or until progressive disease, death, start of a new anti-AL amyloidosis therapy, unacceptable toxicity, withdrawal of consent, or early study termination, whichever occurs first. Dose modifications (delays/interruptions or reductions) are permitted to mitigate adverse events (AEs). Primary endpoint is efficacy defined by complete hematologic response (CHR) rate. Key secondary endpoints: safety (AEs, serious AEs, ocular findings on ophthalmic examination), organ response rates for kidney, heart, and liver, duration of CHR, and pharmacokinetics. Exploratory endpoints: major organ deterioration progression-free survival (MOD-PFS; a composite endpoint including time to death and clinical manifestation of cardiac/renal failure [whichever comes first]), hematologic progressive disease, and overall survival. No formal hypothesis will be tested on CHR rate. **Results:** n/a. **Conclusions:** The ALANIS trial will determine the role of belamaf in the newly diagnosed AL amyloidosis treatment landscape, where new therapies providing deep responses are needed.

PA-140

Development and Application of a Prognostic Model for Macrofocal Multiple Myeloma

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Introduction: There are few reports on the differences between macrofocal multiple myeloma (MFMM) and classical multiple myeloma, and the prognostic value of the traditional R-ISS staging in this subtype remains unclear. To investigate the clinical characteristics of macrofocal multiple myeloma, evaluate the applicability of R-ISS and R2-ISS staging in this subtype, and establish an improved prognostic model. **Methods:** A retrospective cohort of 28 patients with MFMM and 605 patients with classical multiple myeloma was enrolled. Clinical, imaging, and genetic characteristics as well as survival outcomes were compared between the two groups. Independent risk factors were identified by Cox regression analysis in the MFMM cohort, and an M-ISS scoring system was established. Model discrimination was compared using the C-index. **Results:** Patients with MFMM had lower bone marrow plasma cell percentage, lower beta-2 microglobulin and lactate dehydrogenase levels, but significantly higher rates of extramedullary disease (64.3%), >3 osteolytic lesions (96.4%), and lesion Ki67 index ($P < 0.001$). The median progression-free survival was 108 months in the MFMM group vs. 48.7 months in the classical MM group, and the median overall survival was not reached vs. 94 months ($P < 0.05$). Neither R-ISS nor R2-ISS staging could discriminate survival outcomes in MFMM. Multivariate analysis identified age ≥60 years (HR = 1.636), 1q21 amplification (HR = 2.023), and lesion Ki67 ≥25% (HR = 2.114) as independent adverse prognostic factors. The M-ISS model constructed based on these factors had a C-index of 0.81, outperforming R-ISS (0.66) and R2-ISS (0.76), and significantly stratified survival ($P < 0.05$). **Conclusions:** MFMM is characterized by "severe focal lesions but mild systemic manifestations" and has a better prognosis than classical multiple myeloma. Traditional staging systems have blind spots in evaluating this subtype. The M-ISS model provides more accurate risk stratification.

PA-141

Development and External Validation of the CHEMA65 Score for Predicting Venous Thromboembolism in Chinese Patients with Multiple Myeloma

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Introduction: Venous thromboembolism (VTE) is a common complication of multiple myeloma (MM) and may cause treatment interruption, impaired quality of life, and increased mortality. Current guidelines and consensus emphasize risk-adapted thromboprophylaxis based on VTE risk stratification. However, existing MM-specific VTE risk models have shown only moderate predictive performance and were largely developed in Western populations. **Methods:** We retrospectively recruited newly diagnosed MM patients as a derivation cohort from one tertiary center in China between January 2016 and March 2025 and an independent external validation cohort from another tertiary center in China between April 2013 and October 2022. Incident VTE was defined as objectively confirmed deep vein thrombosis or pulmonary embolism during follow-up. Candidate predictors were selected using bootstrap-assisted LASSO Cox regression. Variables selected in at least 80% of resamples and satisfying the proportional hazards assumption were entered into a multivariable Cox model. Model performance was assessed using the C-index, bootstrap optimism correction, calibration, and Kaplan-Meier risk-group separation. Regression coefficients were converted into an integer point-based score, the CHEMA65 score. **Results:** The derivation cohort included 755 patients, of whom 50 developed VTE; the external validation cohort included 405 patients, of whom 40 developed VTE. The CHEMA65 score consisted of five variables: Cerebral infarction history (2 points), Hypertension (2 points), ECOG performance status ≥2 (2 points), immunomodulatory drug (IMiD) exposure (1 point), and Age ≥65 years (1 point). In the derivation cohort, the original Cox model had an apparent C-index of 0.705 (95% CI, 0.621–0.789), an optimism-corrected C-index of 0.674, and a calibration slope of 0.836; the point-based score showed a C-index of 0.700 (95% CI, 0.618–0.781), an optimism-corrected C-index of 0.700, and a calibration slope of 1.040. VTE occurred in 4.1%, 8.8%, and 12.5% of patients in the low-risk (0–2 points), intermediate-risk (3–4 points), and high-risk groups (≥5 points), respectively (log-rank $P < 0.001$). Compared with the low-risk group, the intermediate- and high-risk groups had hazard ratios of 2.56 (95% CI, 1.36–4.81; $P = 0.003$) and 4.75 (95% CI, 2.16–10.45; $P < 0.001$), respectively. In the external validation cohort, the C-index was 0.648 (95% CI, 0.558–0.737). VTE occurred in 6.1%, 10.3%, and 30.3% of patients in the low-, intermediate-, and high-risk groups, respectively (log-rank $P < 0.001$), with corresponding hazard ratios of 1.72 (95% CI, 0.83–3.58) and 6.10 (95% CI, 2.63–14.12) for the intermediate- and high-risk groups. **Conclusions:** This simple five-variable CHEMA65 score showed good risk stratification and discrimination in both derivation and external validation cohorts, suggesting its potential clinical utility in Chinese MM patients.

PA-142

Development and Validation of a Novel Dynamic Prognostic Scoring System for Patients with Relapsed or Refractory Multiple Myeloma

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Introduction: Existing prognostic systems were designed at diagnosis and may not adequately reflect the dynamic risk evolution in patients with relapsed/refractory multiple myeloma (RRMM). This study aimed to develop a novel dynamic prognostic scoring system for RRMM applicable at the time of second-line treatment. **Methods:** A total of 731 patients who experienced relapse or refractory disease between 2015 and 2021 were included. Using temporal split method, patients with relapse confirmed between 2015 and 2019 comprised the training cohort ($N = 462$), and those from 2020 to 2021 constituted the validation cohort ($N = 269$). Missing data were handled using Multiple Imputation by Chained Equations (MICE; 20 imputed datasets). Candidate variables were screened by univariable Cox regression with respect to second overall survival (OS) refined using LASSO Cox regression, and finally selected through multivariable Cox regression analysis. Scoring was determined by assigning weights based on hazard ratios, rounded to 0.5-point increments. **Results:** The training and validation cohorts were generally well-balanced in baseline characteristics. However, early relapse was more frequent in the training cohort compared to the validation cohort (46.1% vs. 37.9%, $p = 0.038$). Multivariable Cox regression identified five independent prognostic factors assessed at second-line treatment initiation: elevated LDH (HR 1.90), presence of plasmacytoma (HR 1.66), early relapse within 18 months (HR 1.58), low platelet count ($<50 \times 10^9$/L; HR 1.92), and low albumin (<3.5 g/dL, < HR 1.42). Points were assigned as follows: elevated LDH, 2.0 points; low platelet, 2.0 points; plasmacytoma, 1.5 points;

early relapse, 1.5 points; and low albumin, 1.0 point (maximum 8.0 points). Patients were stratified into three risk groups: Low (score 0–1.0), Intermediate (1.5–3.0), and High (≥3.5). In the training cohort, patients were classified into Low (n = 165, 35.7%), Intermediate (n = 208, 45.0%), and High (n = 89, 19.3%), with median OS of 60, 30, and 13 months, respectively ($p < 0.001$). Median progression-free survival (PFS) was 19, 13, and 6 months, respectively ($p < 0.001$). The DPSS-R2 was validated in the validation cohort; median OS was not reached, not reached, and 15 months, respectively ($p < 0.001$), and median PFS was 33, 22, and 7 months across the three groups ($p < 0.001$). This new scoring system demonstrated superior discriminative ability compared to existing staging systems, with a C-index of 0.683 in the training cohort and 0.735 in the validation cohort for OS, outperforming both R-ISS (training 0.543, validation 0.575) and R2-ISS (training 0.588, validation 0.653). **Conclusions:** The new scoring system is a simple and easily applicable scoring system that effectively stratifies survival outcomes in RRMM patients at the time of second-line treatment. By incorporating dynamic risk features, including early relapse and disease burden markers at relapse, it provides superior prognostic discrimination over diagnosis-based staging systems.

PA-143

Development of a Clinical Decision Tool to Guide Outpatient Versus Inpatient Bispecific Antibody Therapy in Patients with Multiple Myeloma

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Introduction: Bispecific T-cell engager antibodies have expanded treatment options for patients with relapsed or refractory multiple myeloma (RRMM). However, cytokine release syndrome (CRS), immune-effector cell-associated neurotoxicity syndrome (ICANS), infection, and unplanned hospitalization remain clinically important barriers to safe step-up dosing. Although inpatient monitoring has traditionally been used for toxicity surveillance, emerging outpatient treatment models require standardized, patient-level risk stratification to guide site-of-care decisions. We developed BTRS-2026, a clinical tool intended to estimate severe CRS, ICANS, and rescue failure risk before bispecific antibody initiation. **Methods:** We performed a literature-derived, AI-assisted model-development study using evidence synthesized from pivotal bispecific antibody trials, real-world outpatient feasibility reports, and consensus oncology guidance. BTRS-2026 was designed for adults with RRMM being considered for teclistamab, talquetamab, or elranatamab step-up dosing. The score uses an additive weighted architecture across seven domains: disease biology and tumor burden, neurotoxicity risk, immune suppression and infection risk, frailty, access and safety, hematologic reserve, and cardiopulmonary comorbidity. Drug-specific modifiers were applied after base score calculation. Weights were assigned based on predictor severity, clinical impact, modifiability, and independence from overlapping variables. Claude Opus 5.7 was used to assist with tool conceptualization, evidence synthesis, and drafting; all score logic and final content underwent investigator review. **Results:** BTRS-2026 stratifies patients into four risk bands: low risk, defined as a score of 0–4; moderate risk, 5–8; high risk, 9–12; and very high risk, 13 or higher. These categories correspond to escalating predicted risk of grade 2 or higher CRS, ICANS, and rescue failure, defined as unplanned hospitalization within 7 days of outpatient step-up dosing. The scoring framework incorporates toxicity signals from MajesTEC-1, MonumenTAL-1, and MagnetisMM-3, including reported CRS rates of 72.1%, 77–80%, and 57.7%, respectively, and infection rates of approximately 76%, 57%, and 70%, respectively. Recommended site of care ranges from outpatient step-up dosing for low-risk patients to inpatient initiation at an ICU-capable facility for very high-risk patients. **Conclusions:** BTRS-2026 provides an interpretable decision-support framework for bispecific antibody site-of-care planning in RRMM. By integrating disease burden, neurotoxicity risk, immune suppression, frailty, access factors, hematologic reserve, and cardiopulmonary comorbidity, the tool may support individualized outpatient versus inpatient treatment decisions. Prospective multicenter validation is required before clinical implementation. Future work should incorporate biomarkers and real-world toxicity outcomes to refine prediction of CRS, ICANS, infection, and outpatient rescue failure.

PA-144

Development of BCMA-Specific TAC-T Cells: Enabling TACtful, a First-in-Human Study in Patients with Relapsed and Refractory Multiple Myeloma (RRMM)

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Introduction: The T cell antigen coupler (TAC) is a made-in-Canada TCR-retargeting synthetic receptor technology that can be

used to engineer anti-tumor T cells. The TAC has previously been evaluated in the HER2 and CLDN18.2 targeting solid tumor setting. The HER-2 and Claudin 18.2 TAC T cells have proven to be safe with early evidence of therapeutic activity in Phase I/IIa trials. TAC-T cells directed against the myeloma-associated B-cell maturation antigen (BCMA) are efficacious against myelomas in vitro and in xenograft models. Importantly, BCMA directed TAC-T cells show equal or greater efficacy in xenograft models than equivalent BCMA CAR-T cells, but with lower levels of cytokine release, suggesting an improved safety profile. Here we describe the development of a BCMA TAC-T cell product and the planned TACtful trial, supported by a pan-Canadian academic multi-institution based team of researchers, clinicians, and patient advocates. **Methods:** Clinical-grade GMP-compliant production of the BCMA TAC-encoding lentiviral vector has been completed. BCMA TAC-T cells will be manufactured using cryopreserved G-CSF-mobilized peripheral blood cells (collected early in the treatment course of patients who received an autologous stem cell transplant) using a proprietary process on a closed manufacturing system. Process development is underway with first cells already manufactured and tested in mice. CTA-enabling in vitro and in vivo preclinical assays have been completed. A first-in-human clinical trial, the TACtful study, is in development to evaluate BCMA TAC-T cells in patients with relapsed and refractory multiple myeloma (RRMM). The proposed study design uses a standard 3+3 dose-escalation. The primary and secondary study objectives include establishing a dose range for future trials, and evaluating safety and efficacy. Exploratory objectives relating to biological and pharmacokinetic correlates are planned. **Results:** The GMP-compliant lentiviral vector production has been completed and the TAC-T cell product is near manufacturing ready for the TACtful trial. A successful Health Canada pre-Clinical Trial Application (CTA) consultation meeting was held in March 2024; CTA submission is targeted for late 2026 with clinical study start anticipated in early 2027. **Conclusions:** A pan-Canadian team of researchers, clinicians, and patient advocates are developing an academic-led pipeline with the goal of establishing a network to advance testing of cost-conscious cell therapies. The TACtful trial is an example that multi-institutional academic collaboration to develop and test such therapies is feasible. Our pre-clinical data suggest that BCMA directed TAC-T cells will have at least equal or greater efficacy than BCMA CAR-T and an improved safety profile.

PA-145

Development of BMS-986453, a Dual-Targeting BCMA × GPRC5D Chimeric Antigen Receptor (CAR) for the Treatment of Multiple Myeloma

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Introduction: T-cell redirecting therapies (TCRTs) targeting BCMA or GPRC5D have demonstrated remarkable efficacy in relapsed/refractory multiple myeloma (RRMM). Both antigens are highly and independently expressed in MM, making them attractive targets for CAR T cell therapy. Despite promising responses, most patients who receive TCRT eventually relapse. Loss or reduced expression of BCMA or GPRC5D after antigen-specific therapy suggests antigen heterogeneity or loss may contribute to resistance. Targeting both BCMA and GPRC5D may overcome this mechanism of resistance and lead to deeper, more durable responses. The objective was to design, optimize, and evaluate dual-targeting BCMA × GPRC5D CAR T cell therapy for MM. **Methods:** To enable dual targeting, we designed a CAR construct library using bicistronic, linear tandem, and loop tandem formats. To identify the optimal design, we compared CAR expression, tonic signaling, in vitro function against single- and dual-positive target cells, and affinity for dual-expressing cells. We evaluated in vivo efficacy in multiple xenograft models, including an antigen-heterogeneity model, to drive selection of BMS-986453. BMS-986453 is under study in a first-in-human, multicenter trial (CA119–0002; NCT06153251). The initial study population includes patients with RRMM who received ≥3 prior lines of therapy (LOT). Baseline BCMA and GPRC5D expression levels were assessed on patient plasma cells. **Results:** Both bicistronic and tandem designs showed robust CAR expression and strong activity against BCMA-positive, GPRC5D-positive, and dual-expressing cells in vitro and in vivo. However, bicistronic constructs showed heterogenous CAR expression due to molecular recombination, whereas tandem designs produced uniform expression of both binding domains without unexpected recombination; loop tandem outperformed linear tandem and bicistronic approaches. The lead loop tandem binding domain had superior in vivo efficacy in an antigen-heterogeneity model and higher affinity for dual-expressing cells than single-antigen domains. Based on these findings, BMS-986453 was selected for further clinical development. We confirmed BCMA and GPRC5D are highly expressed with some patient-to-patient variability in the ongoing phase 1 multicenter trial. Extended follow-up revealed deepening responses, regardless of BCMA or GPRC5D expression levels. **Conclusions:** High BCMA and GPRC5D expression in patients with ≥3 prior LOT confirms their suitability as dual-targeting CAR antigens. The loop tandem design was superior to bicistronic or linear tandem approaches, and the resulting CAR demonstrated potent dual-antigen activity in preclinical studies. These data supported advancement of BMS-986453 into clinical development, where early phase 1 results (NCT06153251)

indicate a highly functional and potent CAR capable of effectively targeting BCMA and GPRC5D in patients.
DJ and RS contributed equally as co-senior authors.

PA-146

Diagnostic Practices and Barriers of High-Risk Multiple Myeloma in England

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Introduction: Across England, there is no consistent definition of high-risk multiple myeloma (HRMM), an absence of a risk-stratified treatment pathway, and variation in the availability and use of diagnostic testing for HRMM (Galley, 2025). We explored the current diagnostic testing landscape for HRMM and identified key barriers to implementing risk-stratified testing and treatment in England. Findings will inform policy recommendations to standardise diagnostic and treatment pathways, supporting equitable access and clinically appropriate risk-stratification for all patients with myeloma. Here, we present final survey findings. **Methods:** A targeted survey was developed to assess current diagnostic testing practices, barriers, and challenges affecting consistent implementation of risk-stratification testing in England. The survey was distributed among consultant haematologists practicing in NHS Trusts in England. Following the final survey, focus groups with clinicians and patients will be subsequently conducted to contextualise and enhance understanding of the survey findings. **Results:** Thirty-four practicing consultant haematologists employed by NHS Trusts in England responded to the survey. They reported 1 – ≥30 years' experience managing and diagnosing myeloma across university/teaching and district/general hospitals. Almost all consultants (n = 33) reported using fluorescent in-situ hybridisation (FISH) to diagnose HRMM; 30 and 32 consultants reported using Serum Free Light Chain (SFLC) and beta-2 microglobulin testing, respectively. Beyond this, the use of additional risk stratification tests was limited. Over half of consultants (59%) performed risk-stratification for HRMM, although one did so occasionally rather than routinely. The primary reasons for conducting risk-stratification were to inform prognosis (n = 12) or inform treatment strategy (n = 4). The most frequently cited barrier to implementing risk-stratification was a lack of clear protocols or guidance (n = 18), followed by a lack of access to testing facilities, or services or funding/reimbursement issues (both n = 17). Most consultants (79.4%) perceived their genetic testing practices to be consistent with NICE NG35 guideline and/or Avet-Loiseau consensus criteria. The primary reasons for ordering genetic tests at diagnosis or relapse were to inform prognosis (n = 27 and n = 13, respectively) and to guide patient counselling (n = 22 and n = 13, respectively). Key challenges affecting the use of genetic testing included delays in sample processing (n = 10) and inappropriate sample collection (n = 5). **Conclusions:** Findings suggest variation in risk-stratification practices across NHS Trusts in England. While all survey respondents agreed that risk-stratification is important, there was no clear consensus on HRMM diagnostic testing practices or how results should be utilised. Survey findings will inform focus group discussions to explore clinician and patient perspectives, to be presented in the poster.

PA-147

Discovering Actionable Steps: Patient Empowerment & the MMRF Patient Navigation Center

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Introduction: Multiple myeloma (MM) is an uncommon and complicated blood cancer. While there have been significant advancements for patients, treatment offerings have scaled tremendously and questions remain for patients including staying up to date with new treatment options, eligibility in clinical trials, and more. This disparity can be potentially magnified in community settings. At The Multiple Myeloma Research Foundation (The MMRF) our goal is to ensure each and every patient is empowered with the knowledge, confidence, and empowerment to navigate through their MM successfully. **Methods:** The Patient Navigation Center (PNC) at the MMRF offers complimentary support to patients and caregivers. Staffed by three oncology nursing professionals, patients may contact the PNC via phone or email and are paired with a nurse navigator who provides personalized, one-on-one support. Each interaction is logged as a case and monitored through the MMRF's CRM platform. PNC nurses work with patients until their needs are addressed, and insights are shared with the broader education team. To measure interactions between patients and nurse navigators, the MMRF distributes surveys across all communication touchpoints. First, individuals receive a satisfaction survey to rate their interaction. Second, patients receive a survey 90 days post-case to identify the positive steps they have taken in managing their MM. **Results:** In 2025, 833 patients and caregivers received a satisfaction survey, yielding a 21% response rate (n = 176), and 827 patients received the longitudinal survey, yielding an 8.7% response rate (n = 72). Respondents completed the satisfaction survey by rating statements on a scale of 1–5, with 5 indicating "strongly agree." Regarding likelihood of using the PNC in the future, respondents averaged 4.9 out of 5, and satisfaction with information received averaged 4.89 out of 5. Among longitudinal survey respondents, 91% reported taking positive steps after speaking with a PNC. Respondents were presented with a list of positive behavioral steps derived from annual learning objectives; top results included communicating treatment goals with their care team (50%), interpreting test results (26%), and seeking a second opinion (21%). **Conclusions:** The 2025 results indicate that patients continue to make positive strides in managing their MM and view

the PNC as a valuable, supportive resource throughout their journey. However, a discrepancy was observed between survey completion rates, suggesting differences in patient engagement that warrant further investigation. 2026 efforts will focus on analyzing engagement patterns and whether positive and negative response patterns correlate with involvement across other areas of the organization, specific disease stages, and/or geographic indicators. These insights will inform how we strengthen and target outreach to ensure equitable resource access for all patients, so that every individual feels empowered in managing their MM at every stage of their journey.

PA-148

Distinct Progression-Free Survival Patterns by Age in Newly Diagnosed Multiple Myeloma

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Introduction: Younger age at diagnosis is often linked to better outcomes in multiple myeloma, but whether this advantage is mainly explained by treatment intensity or reflects additional determinants of disease control remains uncertain. This study evaluated age-associated differences in survival outcomes, treatment exposure, and prognostic factors in newly diagnosed multiple myeloma. **Methods:** Adults with newly diagnosed multiple myeloma treated between 2010 and 2026 were included in a multicenter retrospective cohort. Patients were grouped according to age at diagnosis as < 50 years or ≥50 years. Baseline disease characteristics, cytogenetic risk, first-line treatment, autologous stem cell transplantation (ASCT), response, overall survival (OS), and progression-free survival (PFS) were compared. Survival outcomes were assessed using Kaplan–Meier analysis and Cox proportional hazards models. A 6-month landmark analysis was performed to reduce potential bias related to the timing of ASCT. **Results:** A total of 173 patients were analyzed, including 98 patients aged < 50 years and 75 patients aged ≥50 years. Median age was 44 years in the younger group and 64 years in the older group. IMWG-defined high-risk cytogenetic abnormalities were comparable between groups, whereas advanced ISS and R-ISS stages were more frequent in older patients. ASCT was performed substantially more often in younger patients than in older patients (90.7% vs 39.2%; $p < 0.001$). After a median follow-up of 34 months, median OS was not reached in either group, although 5-year OS was higher among patients aged < 50 years (84.8% vs 61.4%; $p < 0.001$). The difference in PFS was more pronounced: median PFS was 48.0 months in the younger group and 10.0 months in the older group ($p < 0.001$). In multivariable analysis, ASCT remained independently associated with improved OS, while the association between age and OS was attenuated after adjustment. For PFS, age ≥50 years independently predicted shorter survival (adjusted HR 3.03, 95% CI 1.84–5.00; $p < 0.001$), together with absence of ASCT. The 6-month landmark analysis confirmed the consistency of these findings. **Conclusions:** In newly diagnosed multiple myeloma, age-related outcome differences were most evident for disease control rather than mortality. Higher ASCT use appeared to largely account for the OS advantage in younger patients, whereas the persistent independent association between age and PFS suggests that treatment exposure alone may not fully explain age-associated differences in disease control. These findings support further investigation of biological, fitness-related, and treatment-delivery factors influencing outcomes across age groups.

PA-149

DOMMINO-1: A Phase II, Open-Label, Multicenter Study of Inobrodib in Combination with Pomalidomide and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

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Introduction: Treatment outcomes for relapsed/refractory myeloma patients (RRMM) after T-cell redirecting therapy such as bispecific T-cell engagers (TCEs) and chimeric antigen receptor therapy (CAR) T-cell therapy are limited. Available options achieve response in less than 30% of patients with median progression free survival (PFS) of 4 months (Costa, 2025). Alternative treatment options are therefore urgently required, particularly those with a novel mechanism of action. Inobrodib (CSS1477) is a first-in-class, potent, selective, and orally bioavailable inhibitor of the bromodomains of the histone acetyl transferases p300 and CBP. Preclinical studies demonstrated synergistic anti-myeloma activity with immunomodulatory drugs, including pomalidomide, associated with enhanced suppression of IRF4, a key oncogenic driver in MM. A Phase I/II trial (Study CCS1477–02) of inobrodib with pomalidomide and dexamethasone (InoPd) showed high response rates with a manageable safety profile, including patients previously refractory to pomalidomide as well as novel immunotherapies (Searle et al., ASH 2024). A subsequent dose optimisation study in the non-fasted state confirmed 20 mg of inobrodib as the recommended dose (Joseph et al., ASH 2025). **Methods:** DOMMINO-1 (CCS1477–04; NCT07096778) is a Phase II, open-label multicenter trial that will

evaluate the efficacy, safety, and pharmacokinetics of InoPd in patients with RRMM. Approximately 100 patients will be treated with 20 mg inobrodib b.i.d. 4 days on/3 days off for each 28-day cycle in combination with pomalidomide (4 mg; days 1–21) and dexamethasone (20–40 mg depending on age; weekly). **Results:** Eligible patients must have measurable RRMM as per IMWG criteria and be refractory to pomalidomide and an anti-CD38 monoclonal antibody, and refractory or intolerant to at least one proteasome inhibitor, with prior exposure to a T-cell engager required. Patients require adequate hematological and renal function (Hb $\geq$ 8.0 g/dL; plt $\geq$ 75 $\times$ 109/L; neut $\geq$ 1.0 $\times$ 109/L; CrCl $\geq$ 30 mL/min). Exclusion criteria include patients with unresolved toxicities from prior therapies greater than Grade 1 or known severe allergic/anaphylactic reactions to any of the study medications. **Conclusions:** The primary endpoint is ORR per IMWG criteria assessed by IRC. The ORR and 95% confidence intervals will be calculated. Approximately 100 patients will be enrolled to have 90 patients in the efficacy evaluable set to perform the primary analysis. The sample size was justified using the Bayesian optimal Phase 2 dual-criterion design on the primary endpoint ORR. Secondary endpoints include duration of response, time to response, PFS and overall survival. Safety, minimal residual disease, and quality of life measures will also be explored. This is a global study now enrolling across the US and UK.

PA-150

Dose Reduction in Frail Myeloma Patients Does Not Impact Survival Outcomes

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Introduction: Treatment of older MM patients is frequently complicated by increased vulnerability to treatment-related toxicities necessitating dose reduction. However, concerns remain regarding its impact on survival outcomes. This study evaluated OS and PFS trends among older MM patients receiving geriatric intervention and the impact of dose reduction in frailty. **Methods:** This cohort consisted of MM recruited at a tertiary academic centre over 27months. Patients were aged 65 to 99 years and underwent baseline comprehensive geriatric assessment prior to treatment initiation. Patients were then randomised to standard of care or geriatric interventions during their chemotherapy period. Patients who were frail underwent dose reductions of their chemotherapy to reduce chemotoxicity. KM analysis was used to estimate median OS and PFS, with survival differences evaluated using the log-rank test. Multivariable Cox proportional models were constructed to assess the association between survival outcomes and key covariates, including demographic factors, dose reduction status, study arm allocation, BMI and Clinical Frailty Scale (CFS) scores. **Results:** A total of 41 older patients with MM met inclusion criteria. Frailty assessment using the CFS demonstrated that 29 patients (71%) were classified as frail and 70% of frail patients underwent dose reduction. KM analysis demonstrated shorter median OS and PFS among patients who underwent dose reduction compared with those without dose reduction. Within the control arm, patients without dose reduction demonstrated median OS and PFS of 35.1 months and 19.6 months, respectively, compared with 5.5 months for both OS and PFS among those who underwent dose reduction. Similarly, within the intervention arm, patients without dose reduction demonstrated longer median OS and PFS of 54.2 months and 24.3 months, respectively, compared with 8.6 months for both endpoints among patients who underwent dose reduction. Despite these divergent survival trends, formal log-rank testing did not demonstrate statistically significant differences in OS or PFS between dose reduction groups. Furthermore, multivariable Cox proportional hazards regression analysis demonstrated that dose reduction, study arm allocation, BMI, age and CFS were not independently associated with OS or PFS after adjustment. **Conclusions:** In older MM patients, those who are fitter who underwent geriatric interventions demonstrated the most favourable OS and PFS trends. Although frail patients requiring dose reduction exhibited shorter survival outcomes, dose reduction was not independently associated with worse OS or PFS after multivariable adjustment. These findings suggest that worse survival outcomes likely reflect underlying frailty rather treatment-related harm from dose reduction itself. Furthermore, geriatric intervention demonstrated favourable survival trends even among frail patients, supporting the potential role of individualized geriatric-guided management in older myeloma populations.

PA-151

Dose-Optimized Selinexor-Based Regimens in Plasmacytoma-Associated Relapsed/Refractory Multiple Myeloma: Real-World Imaging and Treatment Persistence Outcomes

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Introduction: Plasmacytoma-associated relapsed/refractory multiple myeloma (RRMM), particularly extramedullary disease (EMD), represents a biologically aggressive entity associated with inferior outcomes and limited therapeutic options. Selinexor-based regimens have demonstrated activity in heavily pretreated RRMM; however, real-world data evaluating imaging responses and treatment persistence in plasmacytoma-associated disease remain limited. **Methods:** We performed a retrospective single-center analysis of consecutive RRMM patients treated with selinexor-based regimens between 2024 and 2026. Patients received selinexor combined with proteasome

inhibitor (PI)-based, IMiD-based, anti-CD38-based regimens, or selinexor-dexamethasone according to physician discretion. Clinical, serologic, and imaging data were collected from routine practice. Imaging responses were assessed using available radiologic evaluations. Time to treatment discontinuation (TTD) was defined as the interval between selinexor initiation and treatment discontinuation or last follow-up for ongoing patients. **Results:** Eleven patients had evaluable data available. Median age was 73 years, with a median of 3 prior lines of therapy. Six patients had plasmacytoma-associated disease, including paraskeletal and extramedullary presentations. Selinexor-based regimens included PI-based, IMiD-based, anti-CD38-based, and selinexor-dexamethasone combinations. The overall serologic response rate (≥PR) was 64%, while imaging CR/PR was observed in 73% of evaluable patients. At data cutoff, multiple patients remained on ongoing selinexor therapy, including prolonged responders with treatment exposure exceeding 1–2 years despite prior treatment exposure and dose attenuation strategies. Dose reductions occurred in 91% of patients, whereas permanent treatment discontinuation due to toxicity was uncommon (9%). Toxicities were consistent with the known selinexor safety profile. **Conclusions:** Selinexor-based regimens demonstrated clinically meaningful activity in this real-world RRMM cohort, including encouraging imaging responses in plasmacytoma-associated disease. Despite frequent dose modifications, durable ongoing treatment exposure was observed in selected patients, supporting individualized dose-optimization approaches in difficult-to-treat RRMM populations.

PA-152

Double-Hit Ultra-High-Risk Myeloma Treated with Isa-VRDc Induction and Isa-VRD Consolidation: Subanalysis of the UKMRA RADAR Trial in Newly Diagnosed Transplant-Eligible Patients

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Introduction: RADAR was designed to evaluate an intensive treatment strategy with Isatuximab-VRD- Cyclophosphamide induction, single autologous stem cell transplantation (ASCT), Isa-VRD consolidation, and Isa-R maintenance in patients with double-hit high-risk disease according to recent consensus IMS/IMWG 2025 high risk criteria (Avet-Loiseau, JCO 2025). We recently reported encouraging activity from this treatment pathway. We explored sub analyses aimed at identifying patients with comparatively inferior outcomes despite intensified therapy. **Methods:** UK-MRA RADAR is a prospective, national, multi-centre, risk-adapted phase II/III trial for patients with NDMM eligible for ASCT. Patients enter a high-risk pathway based on the presence of ≥2 HRCA (t(4;14), t(14;16), t(14:20), del(17p), del1p and gain(1q)) defined by standard-of-care NHS cytogenetic (FISH/MLPA) testing. Patients with high-risk disease in v4 of the protocol (HRv4) received 4 × 21 day cycles of Isa-VRDc (Isa: Weekly C2, D1 and D8 C3, D1 and D15 C4; V: Weekly; R:D1–14; D:Weekly; c: D1 and D8). Patients received an ASCT followed by 4 × 21 day cycles of Isa-VRD consolidation (Isa: Weekly C1, D1 and D8 C2, D1 and D15 C3+; V: Weekly; R:D1–14; D: Weekly) and 28 day cycles of IsaR maintenance (Isa: Weekly C1, D1 and D15 C2; R: D1 – D21) until progression. Primary endpoint was progression-free survival (PFS) at 18 months. We undertook exploratory sub analyses of progression-free survival using demographic features, disease characteristics and initial measures of response. For each variable we plotted Kaplan-Meier curves and implemented univariate Cox regression models. **Results:** 70 patients were recruited to the HRv4 pathway between 1Sept22 and 4Sept23. At a median follow up of 24 months, 88% of patients are progression-free at 18 months. Within the ultra-high-risk cohort, variables which were prognostic of progression-free survival included ECOG (0,1,≥2, missing; p = 0.0220), R2-ISS (II,III, IV, missing; p = 0.0039), high LDH levels (≥ULN; p = 0.0097), del17p detected (p = 0.0077), gain 1q21 detected (p = 0.0137), measured at study entry, and achieving a ≥ VGPR at the end of induction (p = 0.0342). In contrast, variables which were not prognostic of PFS included the number of cytogenetic abnormalities (2, ≥3; p = 0.3266), ISS Stage (II, III III; p = 0.0950) and R-ISS Stage (1,2,3, missing; p = 0.1649). **Conclusions:** High-risk definition in newly diagnosed myeloma continues to evolve as more effective therapies are incorporated into frontline treatment. Within the ultra-high-risk, or "double-hit," subgroup, the presence of additional characteristics such as R2-ISS Stage IV and High LDH may identify patients with an even greater unmet need. Ongoing analyses of the full 125 patients recruited in HR v4.0 of the RADAR trial will refine these findings. Novel immunotherapy-based strategies should be specifically explored in these cohorts to determine if they can improve the poor outcomes associated with this biology.

PA-153

DREAMM-15: A Study Assessing the Efficacy and Safety of Extended-Dose Belantamab Mafodotin in Combination with Standard-of-Care Therapies in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Targeting B-cell maturation antigen (BCMA) has demonstrated transformational survival benefits for patients (pts) with RRMM from first relapse. There is an unmet need for accessible anti-BCMA agents at the earliest opportunity across all sites of care. Belantamab mafodotin (belamaf) is an antibody-drug conjugate representing a unique BCMA-targeting modality that provides clinical efficacy with minimal immunosuppression and no evidence of inducing T-cell exhaustion. Belamaf-containing triplet therapies (DREAMM-7/8) have demonstrated superior progression-free survival, improved response rates, and higher minimal residual disease (MRD) negativity vs standard-of-care therapies. Belamaf (B), bortezomib (V), and dexamethasone (d) [BVd] has also demonstrated statistically significant improvement in overall survival (DREAMM-7) vs an anti-CD38–containing triplet, daratumumab + Vd (DVd). Ocular events with belamaf treatment were common and managed through dose and schedule modifications, leading to median belamaf-free intervals of 8–12 weeks while preserving efficacy. These observations, plus additional dose-finding studies and simulations, led to the design of DREAMM-15, which is evaluating the efficacy and safety of proactive extended dosing of belamaf (2.5 mg/kg every 8 weeks [Q8W] in cycle 1, then 1.9 mg/kg Q8W for 2 additional cycles [cycles 2–3], and Q12W thereafter) in combination with pomalidomide (P) + d (BPd), Vd (BVd), or carfilzomib (K) + d (BKd) in pts with RRMM. With a reduced treatment regimen of only 4 doses of belamaf per year after the first 6 months, DREAMM-15 aims to achieve a favorable benefit/risk profile and inform on a harmonized extended dosing regimen for belamaf combinations in multiple myeloma. **Methods:** DREAMM-15 (NCT07227311) is an actively recruiting phase 2, open-label, nonrandomized, multicenter study. Pts aged ≥18 years with confirmed RRMM, 1–2 prior lines of treatment, measurable disease, and Eastern Cooperative Oncology Group performance status of 0–2 are eligible. Notable exclusion criteria include prior exposure to BCMA-targeted therapy and being intolerant/refractory to pomalidomide, bortezomib, or carfilzomib depending on group allocation. Approximately 200 pts will be allocated at a 2:2:1 ratio to the BPd, BVd, or BKd arm. Treatment in each group will continue until progressive disease, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first. The primary endpoint is overall response rate (percent of pts with ≥ confirmed partial response); key secondary endpoints include complete response rate, MRD status, duration of response, and safety. This study will be open in 9 countries: USA, Germany, France, Spain, Netherlands, Greece, China, Japan, and Republic of Korea. **Sponsorship:** GSK (study ID 224317) Copyright statement © 2026 European Hematology Association, Inc. Reused with permission. **Results:** N/A. **Conclusions:** N/A.

PA-154

Dual Proteasome/HDAC Inhibition with I3MV-8b Enhances Memory Formation and Potentiates Antitumor Activity of BCMA CAR-T Cells in Multiple Myeloma

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Introduction: B cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy has emerged as an effective treatment for relapsed/refractory multiple myeloma (RRMM). However, many patients eventually experience disease progression due to insufficient CAR-T persistence and progressive T-cell exhaustion. Emerging evidence suggests that aberrant activation of histone deacetylases (HDACs) contributes to CAR-T dysfunction and exhaustion. Meanwhile, recent studies have identified the proteasome-mediated haem-BACH2 signaling axis as a critical regulator of terminal T-cell exhaustion, supporting transient proteasome inhibition as a promising strategy for CAR-T optimization. In our previous work, we designed and synthesized a series of dual-target inhibitors simultaneously targeting the proteasome and HDAC pathways, among which I3MV-8b demonstrated potent biological activity. We therefore hypothesized that combining I3MV-8b with BCMA CAR-T therapy may enhance antitumor efficacy by promoting memory differentiation and resistance to exhaustion. **Methods:** The cytotoxicity of I3MV-8b on CAR-T cells was evaluated using CCK-8 assays across a range of concentrations to determine the optimal treatment concentration. BCMA CAR-T cells were pretreated with I3MV-8b for 5 days during in vitro expansion.

Flow cytometry was performed to assess memory phenotype (CD45RO, CD62L), exhaustion-associated markers (PD-1, TIM-3, and LAG-3), and apoptosis (Annexin V/DAPI). Antitumor activity was evaluated through co-culture assays with the multiple myeloma cell line ARP1 (E:T = 0.5:1) by flow cytometry. **Results:** Based on CCK-8 assays, 250 nM was selected as optimal pretreatment concentrations for I3MV-8b. Flow cytometric analysis demonstrated that I3MV-8b pretreatment significantly remodeled the differentiation state of BCMA CAR-T cells, characterized by enrichment of a central memory T-cell (Tcm, CD45RO+CD62L+) phenotype. Notably, the proportion of Tcm cells increased from 35% to 83% ($p < 0.01$), accompanied by a slight reduction in apoptosis. In parallel, expression of exhaustion-associated markers, including PD-1, TIM-3, and LAG-3, was decreased by 20%-30% following I3MV-8b pretreatment. Functionally, I3MV-8b-preconditioned CAR-T cells exhibited significantly enhanced cytotoxic activity against ARP1 myeloma cells (48.6% vs 33.6%, $p < 0.01$). **Conclusions:** Our findings support I3MV-8b as a novel pharmacologic strategy to optimize BCMA CAR-T therapy in multiple myeloma. By simultaneously targeting proteasome- and HDAC-associated exhaustion programs, I3MV-8b promotes memory-like differentiation and mitigates T-cell exhaustion, thereby enhancing antitumor activity. This dual-target approach represents a potentially translatable strategy to improve CAR-T durability and therapeutic efficacy in MM, warranting further validation in vivo and through multi-omics profiling.

PA-155

Duffy Null Genotype Modifies Treatment Outcomes in Patients with Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: The ACKR1 (atypical chemokine receptor 1) promoter variant rs2814778 (c.-67T >C) disrupts erythroid expression of the Duffy antigen resulting in the Duffy null phenotype. Often seen in people of African or Middle Eastern descent, its clinical relevance in MM and interaction with standard-of-care frontline treatment strategies is currently an area of active research. **Methods:** We classified NDMM patients from the CoMMpass study with rs2814778 C/C genotype as Duffy C/C (Duffy null) and non-C/C (Duffy non-null). The impact of the Duffy null genotype and self-reported race on the progression-free survival (PFS) was evaluated using Kaplan-Meier survival analyses. Multivariable Cox proportional hazards models adjusted for age, ethnicity, IMS-IMWG 2025 consensus genomics risk score, treatment received, absolute neutrophil count and beta-2 microglobulin levels were also used to determine the prognostic association of Duffy status with PFS. A prespecified genotype-by-treatment interaction term was used to evaluate treatment-specific effect. The resulting p-value was computed from a likelihood ratio test. **Results:** Among 924 evaluable patients, 10.7% (N = 99) were Duffy null and 71.5% (93/130) of African American (AA) patients. Kaplan-Meier (KM) survival analyses showed a significant PFS difference between these Duffy null and non-null groups (HR 1.33, 95% CI 1.04–1.71, $p = 0.025$) and between AA and non AA patients (HR 1.25, 95% CI 1.02–1.53, $p = 0.03$). In a multivariable analysis, the Duffy null genotype was independently associated with PFS (HR 1.43, 95% CI 1.07–1.92, $p = 0.02$). A significant genotype-by-treatment interaction was also observed ($p = 0.025$), indicating variable PFS benefit due to treatment and Duffy null status. However, after adjusting for self-reported race, there was no association between Duffy null and PFS, suggesting partial confounding by population structure. In patients with Duffy null receiving RVd, the addition of transplant appears to improve PFS (HR 0.29, 95% CI 0.15–0.56, $p < 0.001$). Similarly, the addition of transplant to RVd across all self-reported AA patients improved PFS (HR 0.32, 95% CI 0.19–0.53,$p < 0.001$). When transplant followed either doublets or non-RVd triplets, the HR for PFS in Duffy non-null and Duffy null was 0.34 (95% CI 0.25–0.47, $p < 0.001$) and 0.89 (95% CI 0.38–2.08, $p = 0.8$), respectively. **Conclusions:** Exploratory CoMMpass analyses showed that Duffy null was associated with worse PFS, though this effect was partly confounded by its association with self-reported AA race. In CoMMpass, outcomes for AA patients, especially those with Duffy null, improved when transplant was added to RVd. Together with phase 3 DETERMINATION analyses showing a significant PFS benefit with RVd alone over RVd plus transplant in Duffy null patients (Merz L, ASH 2025), these findings suggest Duffy status in MM warrants further study as a potential marker of treatment response.

PA-156

Dynamic Changes in Soluble BCMA (sBCMA) Versus Soluble Free Light Chains (FLC) for the Early Prediction of Therapeutic Response in Multiple Myeloma

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Introduction: This single-center, prospective study compares soluble B-cell maturation antigen (sBCMA) and soluble free light

chains (FLC) assays for predicting short-term therapeutic response in newly diagnosed and relapsed Multiple Myeloma (MM) patients. While FLC is an established biomarker, its clinical utility can be limited by renal function. In contrast, sBCMA reflects clonal proliferation and may overcome FLC's analytical pitfalls. **Methods:** This is a monocentric, longitudinal, and prospective study. The study was approved by the local ethics committee, and all patients gave written informed consent. We evaluated 100 patients: 40 with newly diagnosed MM and 60 relapsed cases. Patients were stratified into 5 cohorts based on transplant eligibility and the number of prior relapses (R1, R2, R3). sBCMA and FLC levels were measured at baseline, 1 month, and 6 months. Response was assessed via IMWG criteria: at 6 months, 6 patients achieved CR, 34 VGPR, 42 PR, 18 PD. sBCMAwas assayed by the Human BCMA/TNFRSF17 DuoSet ELISA, (R&D Systems, BioTechne); FLCs were assayed in all samples by the Freelite® (The Binding Site) reagents, by means of a BNII nephelometer (Siemens). **Results:** At baseline, only sBCMA differed significantly across cohorts ($p < 0.0001$), peaking in newly diagnosed non-transplant-eligible patients. Conversely, the FLC ratio (rFLC) showed no significant baseline differences. Absolute sBCMA, involved FLC, and rFLC values decreased significantly across the cohort at 1 and 6 months ($p < 0.0001$). However, only the 1-month percentage decrease of sBCMA varied significantly among subgroups ($p = 0.0001$). Greater reductions in all biomarkers correlated with superior clinical outcomes (CR/VGPR). While univariate analysis linked early reductions in all biomarkers to favorable 6-month responses, multivariate ordinal logistic regression revealed that only the 1-month sBCMA percentage decrease independently predicted an improved response. A < 50% sBCMA decrease increased the likelihood of poorer 6-month outcomes 5.444-fold ($p = 0.007$). **Conclusions:** Dynamic changes in sBCMA significantly outperform FLC in differentiating baseline disease states and predicting early response. While existing literature primarily links absolute sBCMA to overall survival, this investigation validates the early dynamic percentage change of sBCMA as a rapid, independent indicator of treatment efficacy in a real world differently treated multiple myeloma population.

PA-157

Dynamic Prediction Models in Multiple Myeloma: A Scoping Review of Methods

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Introduction: Survival models aim to model time to death or progression using data available at baseline. These models are used throughout myeloma research, in clinical trials, prognostic factor research, and for prediction. Improved treatments for myeloma mean that patients now survive >10 years from diagnosis. During this time, the value and effect of biomarkers will likely change. Therefore, clinical decision-making requires survival models which are able to account for changes in biomarkers, and update prognosis given a patient's current disease state. This can be done with a variety of statistical methods that can be called 'dynamic.' However, it is not clear how the available methods have been used in myeloma research. **Methods:** We searched Embase, Medline, and Global Health for terms related to "myeloma," "survival," and "dynamic" up to Dec 2025 for relevant studies using dynamic methods. The dynamic method, findings, strengths, and limitations were extracted and summarised. **Results:** 82 relevant studies were identified. The dynamic methods found were landmark models (LM) (n = 67), time varying covariates (TVC) (n = 10), joint models (JM) (n = 10), two-stage models (TSM) (n = 4), multi-state models (MSM) (n = 2), and other (n = 3). Despite all using dynamic methods, 27% still also included a post-baseline measurement, as if it was measured at baseline. Methods papers made up 50% of MSMs, 67% of other, and 100% of TSMs. Research on subgroup analysis and time trends only used LMs. Dynamic methods can also allow different research questions to be answered. For example, studies showed that sustained MRD negativity, 1-year immunoglobulin recovery, and worsening pain scores are all predictive of survival; adjusted for bias from patients starting treatments at different times when assessing treatment effects; and showed that 5-year survival rate is fairly stable when predicting from up to 5 years post diagnosis. **Conclusions:** LMs are useful for updating predictions given a patient's current status but cannot use any measurements taken after the time of prediction. TVCs assume variables do not change between measurements and need to know their future trajectory to make accurate predictions. MSMs can model movement between disease stages but cannot include variables measured after the start of each state. JMs reduce the impacts of measurement error and allow for prediction at any time. TSMs are computationally simpler approximations of JMs but they can overestimate precision or introduce bias. Using the most appropriate dynamic method helps to avoid immortal time bias or measurement error and can allow the most appropriate research question to be answered. Many studies used post-baseline measurements as if they were measured at baseline, or used LMs when JMs, TSMs or MSMs may have been more informative. More complex methods were mostly used in methods papers. So, as modern myeloma therapy extends survival, increasing the need for dynamic methods, more guidance is needed on their use within applied literature.

PA-158

Dysfunctional Mitochondria Underpin T Cell Dysfunction Associated with Frailty in Multiple Myeloma

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Introduction: Frail patients with multiple myeloma (MM) are at higher risk of experiencing adverse events to treatment and are likely to stop treatment early. Poor tolerance of treatment has been associated with "patient factors." However, what these factors are, has yet to be elucidated. Dysfunctional T cells are evident in patients with frailty and MM. However, it is unknown what mechanisms underpin this dysfunction in the frail population with MM and what role mitochondrial dysfunction plays in driving and maintaining T cell dysfunction. **Methods:** The UKMRA FiTNEss study (Myeloma XIV) investigates proactive frailty-adjusted treatments and whether this can improve treatment tolerance and outcomes in the frail population of newly diagnosed myeloma patients. In this cohort, T cell phenotypic distribution, mitochondrial function and cytokine production were investigated by flow cytometry in the peripheral blood of transplant ineligible newly diagnosed MM patients (n = 54, n = 18 per Fit/Unfit/Frail group) and age-matched healthy control (n = 16). **Results:** In frailer and older myeloma patients, there is an increased proportion of CD8+ CD28− T cells (median 37.92% in frail 15.37% in fit), indicating their terminal differentiation (effector memory and/or TEMRA cells). The loss of CD28 strongly and positively correlated with elevated cytotoxic capacity (granzyme B expression) (R2 = 0.73), and elevated degranulation (surface CD107α). Conversely, it negatively correlated with the production of IFN-γ, IL-2 and TNF-α in response to stimulation. This functional state is indicative of T cell senescence in older frailer individuals with myeloma. Mitochondrial dysfunction was evident in this older frailer demographic when compared to healthy age-matched controls and fitter myeloma patients. Older frailer patients accumulated CD8 T cells with depolarised mitochondria (median 2.39% CD8's in frail versus 1.22% CD8's in fit), with normal mitochondrial mass but very low to negative mitochondrial membrane potential (MMP). Also, with increasing frailty, patients accumulated cells with greatly elevated MMP (median 5.58% CD8's in control versus 9.94% in frail, p = 0.048). Elevated MMP was particularly prominent in effector memory and TEMRA CD8+ T cells. **Conclusions:** These data suggest that mitochondrial dysfunction leads to hyperpolarisation of the mitochondrial membrane in order to generate adequate ATP to support T cell function eventually leading to exhaustion of the mitochondrial machinery resulting in mitochondrial depolarisation. This, in turn, may result in reduced ATP availability and a reliance on glycolysis and thus reduced ability to proliferate and secrete cytokines. Greater understanding of the T cell landscape in frailer older myeloma patients will allow greater stratification of patients prior to treatment and potentially elucidate targetable pathways for future immunotherapy discovery in this underserved group.

PA-160

Early Infectious Complications and Hypogammaglobulinaemia in Patients Receiving Bispecific Antibody Therapy for Relapsed/Refractory Multiple Myeloma: A Single-Centre Real-World Experience

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Introduction: Bispecific antibodies (BsAbs) have demonstrated high efficacy in relapsed/refractory multiple myeloma (RRMM) but are associated with hypogammaglobulinaemia, immune dysfunction and increased susceptibility to infection. Despite routine prophylactic measures, real-world data describing the timing and spectrum of infectious complications remain limited. We evaluated infectious complications, IgG nadir and intravenous immunoglobulin (IVIG) utilisation in a single UK tertiary centre cohort of RRMM patients receiving BsAb therapy. **Methods:** We performed a retrospective analysis of 24 consecutive RRMM patients treated with bispecific antibodies between 2024 and 2026. Data collected included bispecific agent, nadir IgG levels, intravenous immunoglobulin (IVIG) utilisation, infectious complications, hospitalisation and intensive care unit (ICU) admission. All patients received standard antiviral and Pneumocystis prophylaxis, with levofloxacin reserved for selected high-risk patients. Early infectious events were defined as occurring within the first three treatment cycles. **Results:** Twenty-four patients received BsAb therapy: elranatamab (n = 17, 70.8%), teclistamab (n = 4, 16.7%), talquetamab (n = 3, 12.5%). IgG nadir was < 3 g/L in 16 (66.7%). IVIG was administered in 15 patients (62.5%), most commonly initiated at cycle 2 (n = 8). Sixteen patients (66.7%) experienced at least one infection; early-cycle infections (C1–C3) occurred in 13 (54.2%), with cycle 1 infections in 11 (45.8%). Bacterial infections affected 9 patients: lower respiratory tract infections (n = 3), UTIs (E. coli n = 2, E. faecium n = 2), S. mitis bacteraemia (n = 1), bacterial sinusitis (n = 1). Viral infections affected eight patients, including CMV reactivation (n = 3), influenza A (n = 2), adenovirus (n = 1), rhinovirus (n = 1) and parvovirus B19 (n = 1); with one case complicated by viral myocarditis and cardiac failure. All CMV reactivations occurred in patients receiving BCMA-targeting therapy. Two patients had both bacterial and viral infections. Hospitalisation occurred in 11 (45.8%); one required ICU admission. Three patients (12.5%) died of disease progression; no infection-attributable mortality occurred. **Conclusions:** This real-world cohort demonstrates a substantial early infectious burden associated with BsAb therapy, with infections occurring from cycle 1 in nearly half of patients despite widespread IVIG use and routine antimicrobial prophylaxis. Both bacterial and viral pathogens contributed significantly to morbidity, and all CMV reactivations occurred in patients receiving BCMA-targeting therapy. No infection-attributable mortality was observed. These findings highlight the need for optimised infection surveillance and prophylactic

strategies, alongside structured early monitoring pathways to support safe treatment delivery. **Funding:** GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa. © 2026 European Hematology Association (EHA). Reused with permission. This abstract was previously accepted for publication at the 2026 EHA Annual Meeting. All rights reserved.

PA-161

Early Relapse Within 6 Months of Idecabtagene Vicleucel Predicts Poor Survival in Relapsed Refractory Multiple Myeloma

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Introduction: We aimed to define early relapse following standard-of-care (SOC) idecabtagene vicleucel (ide-cel) and evaluate associated clinical outcomes in patients with relapsed refractory multiple myeloma (RRMM). **Methods:** We analyzed publicly available registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR), including 821 US patients with RRMM (≥4 prior lines of therapy) who received SOC ide-cel between May 2021 and June 2023 [Sidana et al.]. Multiple progression-free survival (PFS) thresholds (3, 6, 9, and 12 months) were evaluated using receiver operating characteristic (ROC) analysis and Youden's index to determine the optimal cutoff for defining early relapse. High-risk (HR) disease was defined by the presence of ≥1 of the following features: high-risk cytogenetics by FISH (del17p, t(4;14), t(14;16), or 1q21 gain), ISS stage III disease, extramedullary disease (EMD), or plasma cell leukemia. **Results:** As previously reported, 821 patients were included in the analysis, with a median age of 66 years, an overall response rate (ORR) of 73%, and a complete response (CR) rate of 25%. At a median follow-up of 11.6 months, median PFS was 8.8 months. A 3-month landmark analysis was performed to exclude early mortality (7.6%) following ide-cel, resulting in an evaluable cohort of 758 patients. A PFS cutoff of ≤6 months demonstrated the highest discriminatory performance for predicting early relapse (Youden index 0.661), with sensitivity of 79.3% and specificity of 86.7%. Patients with PFS >6 months had an 88.9% 12-month overall survival (OS), whereas those with PFS ≤ 6 months had a 43.1% 12-month OS. Therefore, this was used for further analysis. Overall, 29.7% of patients (n = 225) experienced relapse within ≤6 months of ide-cel. Among these patients, 56.4% (n = 127) had at least one HR feature, whereas 43.6% (n = 98) had no identifiable HR features. There were no statistically significant differences in baseline characteristics, including median age, prior lines of therapy, prior autologous stem cell transplantation, or prior exposure to BCMA-directed therapy, between patients with and without HR features. The median OS among patients with relapse within ≤6 months of ide-cel was 9.4 months (95% CI, 8.5–11.3).On MVA, low baseline hemoglobin (OR 2.07, p = 0.007) was associated with early disease relapse, whereas patients with relapse > 6 months post-CAR T had higher ORR (OR 0.30, p < 0.001) and CR (OR 0.40, p < 0.001). **Conclusions:** In this large real-world cohort of patients treated with SOC ide-cel, relapse within ≤6 months was associated with particularly poor outcomes, with a median OS of less than a year. Notably, nearly half of patients with early relapses lacked conventional high-risk features, underscoring the limitations of current baseline risk stratification approaches.

PA-162

Early Switch to KPD in Multiple Myeloma with Suboptimal Response or Intolerance to First-Line Bortezomib-Based Induction: A Multicenter Real-World Study

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Introduction: Patients with multiple myeloma (MM) who fail to achieve very good partial response (VGPR) after 2 cycles of first-line bortezomib-based induction or develop grade ≥2 adverse events represent a clinically challenging population. Real-world evidence on early switch to carfilzomib, pomalidomide, and dexamethasone (KPd) in this setting remains limited. **Methods:** This multicenter real-world observational study included MM patients who underwent early switch to KPd after first-line bortezomib-based induction between September 12, 2022, and May 1, 2026. Suboptimal early response was defined as failure to achieve VGPR and intolerance as grade ≥2 adverse events per CTCAE. KPd consisted of carfilzomib 20/27 mg/m^2 on days 1, 2, 8, 9, 15, and 16, pomalidomide 4 mg on days 1–21, and dexamethasone 20 mg on days 1, 2, 8, 9, 15, and 16. Best response, stem cell collection, survival outcomes, and adverse events were assessed. **Results:** A total of 77 patients were included. Median age was 63 years (range, 36–80), and 44 (57.1%) were male. Early switch to KPd was due to suboptimal early response in 42 patients (54.5%), intolerance in 22 (28.6%), and mixed reasons in 13 (16.9%). The overall response rate was 92.2% (71/77), with 76.6%

(59/77) achieving at least VGPR and 54.5% (42/77) achieving complete response (CR) or better. Specifically, 42 patients (54.5%) achieved CR or better, 17 (22.1%) achieved VGPR, and 12 (15.6%) achieved partial response (PR); 5 patients (6.5%) had minimal response and 1 (1.3%) had stable disease. Response deepening was observed in 62 of 77 patients (80.5%). Patients who switched because of intolerance achieved higher rates of ≥VGPR (95.5% vs. 64.3%, P = 0.006) and CR or better (77.3% vs. 42.9%, P = 0.016) than those who switched because of suboptimal early response. Fifteen patients successfully underwent autologous stem cell collection, with a median CD34+ yield of 9.84×10^6/kg (range, 4.01–16.87×10^6/kg). In the survival analysis set (n = 67), median progression-free survival (PFS) and overall survival (OS) were not reached; the estimated 12- and 24-month PFS rates were 84.4% and 75.4%, respectively, and the corresponding OS rates were 100.0% and 95.8%. The estimated 12- and 24-month duration of response (DOR) rates were 85.6% and 77.5%, and the corresponding duration of complete response (DOCR) rates were 93.6% and 78.2%, respectively. Any-grade adverse events occurred in 49 patients (63.6%), and grade ≥3 adverse events occurred in 10 (13.0%). The most common hematologic adverse event was anemia (27.3%), while infection (18.2%) and arrhythmia (14.3%) were the most common non-hematologic adverse events. **Conclusions:** This multicenter real-world observational study suggests that early switch to KPd in MM patients with suboptimal early response or intolerance to first-line bortezomib-based induction is associated with high response rates and deep remission. No new safety signals were identified, and the adverse-event profile was consistent with previous clinical reports.

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Effectiveness and Safety of Autologous Stem Cell Transplantation in Multiple Myeloma: A Real-World Single-Center Experience

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Introduction: Multiple myeloma is a clonal plasma cell malignancy characterized by bone marrow infiltration, monoclonal protein production, and end-organ damage. Clinically, the disease manifests through CRAB features (hypercalcemia, renal impairment, anemia, and bone disease). Although a serious condition, multiple myeloma can be managed as a chronic disease, with advances in therapy significantly improving quality of life and survival in the modern treatment of multiple myeloma (immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies). Autologous hematopoietic stem cell transplantation (ASCT) remains the cornerstone of treatment for eligible patients, offering improved survival and durable remission. **Methods:** This retrospective study included 128 patients with hematological malignancies treated at the Clinic of Hematology, Clinical Center of the University of Sarajevo (CCUS) between 2021 and 2024. Among them, 88 patients with multiple myeloma underwent ASCT. Data were obtained from medical records and analyzed with respect to demographic characteristics, disease distribution, and treatment outcomes. **Results:** Multiple myeloma was the predominant hematological malignancy, accounting for 62.5%–73.5% of cases annually and primarily affecting patients aged 51–70 years. Among the 88 transplanted patients, 84 (95.5%) achieved successful treatment outcomes, while 4 patients (4.5%) died, indicating a low transplant-related mortality. These results are comparable to those reported by leading international transplant centers. Infectious complications were most commonly associated with urinary (42.3%) and respiratory sources, reflecting expected patterns in immunocompromised patients. **Conclusions:** ASCT remains a safe and highly effective therapeutic modality for multiple myeloma, with excellent outcomes achievable even in regional centers. The high success rate and low mortality observed at CCUS confirm that appropriate patient selection, modern induction regimens, and comprehensive post-transplant care can yield results comparable to international standards. These findings further support the continued role of ASCT as the gold standard for eligible patients.

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Efficacy and Safety of Aponermin (rhTRAIL)-Kd-Based Regimens in Relapsed/Refractory Multiple Myeloma: A Single-Center Retrospective Analysis

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Introduction: RRMM patients exposed to proteasome inhibitors, immunomodulatory agents, and anti-CD38 antibodies face dismal outcomes. Aponermin (rhTRAIL) engages death receptors DR4/DR5 on plasma cells, triggering apoptosis. Combined with carfilzomib and dexamethasone, aponermin may sensitize resistant clones to DR-mediated cell death. Clinical experience with ApoKd in RRMM remains limited. **Methods:** Between May 2024 and February 2026, we retrospectively analyzed RRMM patients treated with ApoKd-based regimens (±selinexor or chemotherapy). Patients had measurable disease and ≥1 prior line. Responses per IMWG 2016 criteria; toxicity per CTCAE v5.0. **Results:** Thirty-nine patients were enrolled; the median age was 61 years (range, 38–78), with 53.8% being male. Patients were heavily pre-treated, with a median of 5 prior lines of therapy (range, 1–8); 61.5% were triple-class exposed (TCE), 48.7% had high-risk cytogenetics, 28.2% had ISS stage III disease, and 74.4% presented with extramedullary disease (EMD). Prior carfilzomib exposure was documented in 53.8% of patients. The median number of treatment cycles was 4 (range, 2–11), with a

median follow-up of 9.57 months (range, 2.83–23.70). The overall objective response rate (ORR) was 64.1%, with a ≥VGPR rate of 33.3%. In patients with prior carfilzomib exposure versus carfilzomib-naive patients, the ORR was 57.1% versus 72.2%, and the ≥VGPR rate was 23.8% versus 44.4%, respectively. Among TCE versus non-TCE patients, the ORR was 58.3% versus 73.3%; notably, the ≥VGPR rates were identical between these groups (33.3% each), suggesting that depth of response was preserved regardless of triple-class prior exposure. In patients with EMD versus those without EMD, the ORR was 65.5% versus 60.0%, and the ≥VGPR rate was 37.9% versus 20.0%, respectively. The median PFS was 6.8 months (95% confidence interval [CI], 3.30–9.40); 26 patients experienced progressive disease and 6 patients died during the follow-up period. The most frequently reported adverse events included leukopenia (71.8%), thrombocytopenia (69.2%), neutropenia (56.4%), and infections (46.2%). Grade ≥3 adverse events comprised leukopenia (35.9%), thrombocytopenia (30.8%), neutropenia (25.6%), pneumonia, including fungal and bacterial etiologies (12.8%), and tumor lysis syndrome (7.7%). **Conclusions:** In this heavily pre-treated cohort characterized by high rates of EMD and triple-class prior exposure, ApoKd-based regimens achieved an ORR of 64.1% and a median PFS of 6.8 months. Notably, the depth of response appeared independent of triple-class exposure history, and the regimen demonstrated comparable activity in patients with and without EMD. The toxicity profile was predominantly hematologic and manageable. These findings warrant prospective investigation of aponermin-containing combinations as a viable salvage strategy in high-risk RRMM.

PA-165

Efficacy and Safety of Daratumumab Plus VCd in Newly Diagnosed Amyloid Light-Chain Amyloidosis with Cardiac Involvement: A Pooled Analysis of Asian Patients from AMY2009 and AMY3001

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Introduction: Amyloid light-chain (AL) amyloidosis is a rare but life-threatening plasma cell disorder in which misfolded immunoglobulin light chains deposit in vital organs. Cardiac involvement is the leading cause of mortality and occurs in approximately 70% of newly diagnosed (ND) patients. Daratumumab plus bortezomib, cyclophosphamide, and dexamethasone (D-VCd) is the only approved frontline regimen for newly diagnosed AL (ND-AL) amyloidosis. However, no dedicated data exist on its use in cardiac-involved Asian patients. We report a post-hoc pooled analysis of D-VCd in this population. **Methods:** This analysis included 41 cardiac involved Asian patients from China, Japan, and Korea with ND-AL amyloidosis (Mayo cardiac stage II–IIIa) randomized to D-VCd in two studies: AMY2009 (Phase 2; AQUARIUS; n = 24) and AMY3001 (Phase 3; ANDROMEDA; n = 17). Efficacy outcomes included the overall hematologic complete response (HemCR) rate, cardiac and renal response rate at Month 6, and time to HemCR. Safety and long-term outcomes, including treatment-emergent adverse events (TEAEs) and overall survival (OS), were also evaluated. A consistent median follow-up of 11.5 months was applied to both studies to ensure comparability across the pooled cohorts. **Results:** The median age was 61.0 years (range, 37–82), with males accounting for 65.9% of patients and nearly equal proportions of Mayo cardiac stage II (48.8%) and IIIa (51.2%). The overall HemCR rate was 61.0% (95% CI, 44.5–75.8), with 53.7% (95% CI, 37.4–69.3) achieving HemCR by Month 6, while cardiac and renal response rates at Month 6 were 48.8% (95% CI, 32.9–64.9) and 34.1% (95% CI, 20.1–50.6), respectively. The median time to HemCR was 58 days (range, 28–240), and the 12-month OS rate was 87.8% (95% CI, 78.3–98.4), with median OS not reached. Outcomes in the China subgroup (n = 26) were comparable to those in the overall Asian and numerically favorable, with an overall HemCR rate of 65.4% (95% CI, 44.3–82.8) and 61.5% (95% CI, 40.6–79.8) at Month 6. Cardiac and renal response rates at Month 6 were 53.8% (95% CI, 33.4–73.4) and 46.2% (95% CI, 26.6–66.6), respectively. In this subgroup, the median time to HemCR was 60 days (range, 28–240), and the 12-month OS rate was 88.5% (95% CI, 77.0–100.0). All patients experienced ≥1 TEAE; serious and Grade ≥3 TEAEs occurred in 55.0% and 80.0%, respectively. TEAEs leading to death were reported in 3 patients (7.5%); 5 deaths (12.2%) occurred overall, with no patient discontinuing treatment due to TEAEs. Cardiac TEAEs were observed in 30.0%, most commonly cardiac failure (20.0%). **Conclusions:** D-VCd was observed to show deep and durable hematologic responses alongside clinical benefits and manageable safety profile in Asian patients with cardiac-involved ND-AL amyloidosis, consistent with the findings from the individual AMY2009 and AMY3001 studies. These data support D-VCd as an effective frontline option in this high-risk Asian patient population.

PA-166

Efficacy and Safety of Isatuximab Subcutaneous Plus Carfilzomib and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From the Phase 2 IZALCO Study

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Introduction: In combination with conventional doublet and triplet therapy, isatuximab (Isa) provides significant benefit to patients (pts) across the multiple myeloma (MM) spectrum. Subcutaneous (SC) administration of Isa could be a more convenient option for pts and caregivers. The Phase 3 IRAKLIA trial in relapsed/refractory MM (RRMM) pts demonstrated noninferiority in efficacy and pharmacokinetics of Isa SC delivered via a wearable on-body injector (OBI) in combination with pomalidomide and dexamethasone (Pd) vs Isa IV Pd. The Phase 2 IZALCO study (NCT05704049) also showed efficacy and safety of Isa SC plus carfilzomib and dexamethasone (Kd), either by manual or OBI injections, in RRMM pts. Following exposure to both methods, pts showed higher preference for OBI vs manual SC injection. Here we present updated efficacy and safety results from IZALCO. **Methods:** Isa SC 1400 mg was given weekly in Cycle (C)1, then biweekly. In Part 1, pts received Isa injected SC manually. In Part 2, pts were randomized to Isa administered SC via OBI (Isa SC OBI; C1-C3), followed by manual SC injection (C4-C6), or to manual SC injection (C1-C3) followed by Isa SC OBI (C4-C6). Starting at C7, pts could choose either treatment method. All pts were treated with carfilzomib (20 mg/m^2 on Day [D]1–2, then 56 mg/m^2 on D8–9, 15–16 at C1, then D1–2, 8–9, and 15–16) and dexamethasone (20 mg on D1–2, 8–9, 15–16, and 22–23). **Results:** A total of 74 RRMM pts were enrolled (8 in Part 1; 66 in the randomized cohort, Part 2). At the data cut-off of November 10, 2025, 59 pts remained on study. At study entry, pts had median age of 65 (44–85) years, median weight of 75.9 (40.0–129.0) kg, and median of 1 prior line of therapy (1–5), and 56.8% had ISS stage I. The median duration of Isa SC OBI administration was 12 mins and manual SC injection was 6 mins. None of the Isa SC injections, manual or OBI, were interrupted. Median time to best response was 5.3 months (mos) (95% CI: 3.25–6.24). Median follow-up was 21.9 mos. Median PFS was not reached (NR) (95% CI: 16.23-NR). PFS at 18 mos was 61.5% (95% CI: 48.7–72.0). OS at 18 mos was 80.8% (95% CI: 69.8–88.2); median OS was not reached (95% CI: NR-NR). Overall, grade (G) ≥3 TEAEs occurred in 66.2%, and serious TEAEs in 51.4% pts. Infusion reaction (IR) on C1D1 occurred in 2 pts (2.7%) with manual SC injections; no IRs occurred with OBI. Five (6.8%) pts had 13 (0.54%) injection-site reactions (ISRs), all grade 1 and related to isatuximab, out of 2425 Isa SC manual or Isa SC OBI injections. Only 1 ISR was deemed related to OBI. Pt satisfaction with injection method remained consistently high with Isa SC OBI up to C25D15. **Conclusions:** These results continue to support the efficacy and safety of Isa SC delivered via manual injection or OBI, plus Kd. Pt satisfaction with Isa SC OBI remained consistently high after pt choice of injection method at C7D1. These efficacy and safety findings are consistent with those reported in the Phase 3 IKEMA study (Isa IV plus Kd).

PA-167

Efficacy and Safety of Ixazomib-Based Versus Bortezomib/Lenalidomide-Based Maintenance After Autologous Stem Cell Transplantation for Multiple Myeloma: A Multi-Center Retrospective Real-World Study

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Introduction: Post-autologous stem cell transplantation (ASCT) maintenance therapy improves survival in newly diagnosed multiple myeloma (NDMM). However, the optimal maintenance agent of ixazomib, lenalidomide, or bortezomib remains uncertain, particularly for high-risk patients. So we conducted a propensity score-matched retrospective comparison. **Methods:** This multicenter retrospective study included NDMM patients who received ASCT followed by maintenance therapy across four centers (Jan 2020-Dec 2025). Ixazomib-based regimens comprised ixazomib monotherapy (I, 3 or 4 mg orally on days 1, 8, 15 of 28-day cycles), ixazomib plus lenalidomide (IR, R 10–25 mg orally on days 1–14 or 1–21), or ixazomib plus pomalidomide (IP, P 2 or 4 mg orally on days 1–14 or 1–21). Using propensity score matching (PSM) based on demographic characteristics, we selected patients receiving bortezomib and/or lenalidomide-based regimens: bortezomib monotherapy (V, 1.3 mg/m^2 subcutaneous weekly), lenalidomide monotherapy (R, 10–25 mg orally on days 1–21), or bortezomib plus lenalidomide (VR). High-risk NDMM was defined according to the mSMART 4.0 risk stratification system. Treatment continued until disease

progression or unacceptable toxicity. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method ($P < 0.05$ considered significant). Adverse events (AEs) were summarized using descriptive statistics. **Results:** A total of 202 patients were enrolled: 101 received ixazomib-based regimens (IR = 55, I = 37, IP = 9) and 101 received bortezomib and/or lenalidomide-based regimens (VR = 46, R = 50, V = 5). After a median follow-up of 11 months (range 1–64) from maintenance start, the ixazomib-based cohort showed significantly longer median PFS (36 months (95% CI: 30.64–41.36) vs. 12 months (95% CI: 10.38–13.62), $P < 0.05$). Median OS was not reached in the ixazomib-based cohort versus 68 months (95% CI: 54.25–81.75) in the comparator cohort ($P < 0.05$). Among high-risk patients, median PFS was 33 months (95% CI: 17.49–48.51, n = 52) vs. 12 months (95% CI: 10.40–13.60, n = 49; $P < 0.05$), and median OS was 56 months (95% CI: 53.01–58.99) vs. 50 months (95% CI: 30.68–69.32; $P < 0.05$). For the IR versus VR subgroup, median PFS was 36 months (95% CI: 18.92–53.08) vs. 15 months (95% CI: 11.85–18.15; $P < 0.05$); median OS was not reached in the IR group versus 68 months (95% CI: 46.86–89.14) in the VR group ($P < 0.05$). Grade 3/4 adverse events: hematologic toxicities (9.90% in ixazomib-based vs. 40.59% in the comparator cohort), peripheral neuropathy (0 vs. 15.84%), rash (0 vs. 11.88%), diarrhea (3.96% vs. 2.97%), nausea (3.96% vs. 0). Treatment discontinuation due to toxicity occurred in 2.97% vs. 19.80%. **Conclusions:** In this real-world study, ixazomib-based maintenance significantly improved PFS/OS after ASCT in NDMM, including high-risk patients, with lower toxicity and fewer discontinuations (2.97% vs. 19.80%). These findings support ixazomib-based maintenance as an effective, well-tolerated strategy.

PA-168

Efficacy and Safety of Linvoseltamab with Utilization of Outpatient Step-Up Dosing and Prophylactic Tocilizumab

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Introduction: Linvoseltamab (Linvo) is a BCMA-CD3 bispecific antibody approved in RRMM after 4 prior lines. In the phase 1/2 LINKER-MM1 study, linvo demonstrated an ORR of 70% with CRS rate 46% and ICANS 8%. The trial excluded patients with ECOG >1 as well as patients with prior BCMA T-cell redirecting therapies. Here, we present real-world data on the initial cohort of patients that were treated commercially at our center. **Methods:** Pts treated with linvo were identified between Oct 15 2025 and Apr30 2026. Step-up dosing (SUD) was entirely outpatient and prophylactic tocilizumab was administered prior to the initial SUD to reduce CRS as previously published. In contrast to trial dosing, we follow weekly dosing for 2 cycles including SUD, q2w dosing cycles 3–6 and then monthly dosing starting with cycle 7 with plan to de-escalate to monthly sooner if patient has achieved ≥VGPR and/or toxicity concern. Median follow up is 6.5 months for the full cohort and 7.2 months for the BCMA exposed cohort. **Results:** 23 pts were included in this analysis. Notable patient characteristics: 43.5% M, 40.9% black, ECOG 2 + 47.8% and median age is 76 (52–83). R-ISS 1/2/3 40%/50%/10% with 21.7% of pts with extramedullary disease. 39% of pts are high risk by the updated IMS criteria. Median prior lines of therapy for this cohort is 5 (3–18) with 95.7% IMID refractory, 78.3% PI refractory, and 100% anti-CD38 refractory. 65.2% with prior ASCT, 21.7% with prior CAR-T and 26.1% with prior BsAb. In sum, 39.1% BCMA exposed and 21.7% GPRC5D exposed. Median time from prior BCMA agent was 424 days (36–1420). ORR is 60% (12/20) with 40% CR and 50% ≥VGPR. Of patients who completed at least cycle 1, the ORR is 75%. Of the pts who did not complete C1, 3 had early PD and 1 pt self-discontinued treatment. In pts with prior BCMA who had completed at least 1 cycle at data cut off, the ORR was 71% with CR of 57.1%. With the use of prophylactic toci, 2 pts experienced grade 1 CRS (8.7%). There were no ICANS events. Seven pts (30.4%) were hospitalized within 30 days however only one was potentially related to linvo while the rest were due to PD. 5 pts (21.7%) developed infections (2 pneumonia,1 UTI, 1 campylobacter diarrhea, and 1 CMV reactivation). Six patients transitioned to monthly dosing prior to week 24 due to response and/or toxicities per treating physician discretion. **Conclusions:** This is the largest cohort of RRMM patients treated with linvo to date in the real-world setting particularly with incorporation of outpatient step-up dosing and prophylactic tocilizumab. Our data demonstrates the feasibility of outpatient SUD and efficacy of ppx toci in significantly reducing CRS rates, and suggests early de-escalation of dosing maintains durability of response while minimizing toxicity. This real world cohort achieved similar response rates with a frail and older population, and included a large black population compared to the trial. Response was also maintained in pts who were TCR exposed.

PA-169

Efficacy and Safety of Sequenced BCMA-Directed Therapies in Relapsed/Refractory Multiple Myeloma: A Retrospective, Multicenter, International Cohort Study (SEQ-BCMA Study)

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Introduction: BCMA-directed treatments (BCMA-Tx) have improved outcomes of relapsed/refractory multiple myeloma (RRMM), but post-BCMA-Tx relapse represents an unmet need. Real-world data on BCMA-after-BCMA sequencing of the approved modalities CAR T cells, bispecific antibodies (bsAb), and an antibody drug conjugate (ADC) remain limited. We investigated the outcomes of all possible BCMA-after-BCMA treatment strategies. **Methods:** RRMM patients (pts) receiving ≥2 BCMA-Tx were retrospectively included. Characteristics were summarized descriptively; PFS and OS were estimated by Kaplan-Meier (KM) with Benjamini-Hochberg-adjusted log-rank tests and multivariable (age, pLOT, HRCA and EMD); median follow-up (mFU) by reverse KM. **Results:** 180 pts from 21 centers were included. At 2nd BCMA-Tx, median age was 65 years (range 32–86), with 7 (2–15) median prior lines (pLOT). High-risk cytogenetics (HRCA; according to R-ISS) were present in 60/153 (39%) evaluable pt. CAR T was the most frequent 1st BCMA-Tx (n = 104, 58%), followed by ADC (54, 30%) and bsAb (22, 12%). Pts had a median of 1 (0–6) intervening line and 6 months (mo, 0–49.5) between progression on 1stBCMA-Tx to start of 2nd BCMA-Tx. BsAb were the most frequent 2nd BCMA-Tx (101, 56%), followed by CAR T (68, 38%) and ADC (11, 6%). The four most frequent sequences were CAR T→bsAb (72, 40%), ADC→bsAb (29, 16%), CAR T→CAR T (ide cel→cilta cel, 26, 14%), and ADC→CAR T (25, 14%). Overall response rate to 2nd BCMA-Tx was 69% (109/158 ev. pt), and 58% achieved ≥ VGPR/MRD negativity. Median (m)PFS after 2nd BCMA-Tx of all pt was 9.7 mo (mFU 14 mo), mOS 29 mo. 2nd BCMA CAR T yielded a numerically superior mPFS of 15 mo compared to 5.7 mo for bsAb (p = 0.02; Cox HR 0.54, p = 0.02). With regard to how the 1st BCMA-Tx influences CAR T as 2nd BCMA-Tx, most favorable outcomes were seen with CAR T→CAR T (mPFS not reached [NR]), followed by ADC→CAR T (mPFS 15 mo) compared to bsAb→CAR T, which showed diminished survival (n = 17, mPFS 6.2 mo, p = 0.01 and p = 0.08). For pt relapsing after CAR T, 2nd CAR T was superior to bsAb (mPFS NR vs 5.7 mo; BH-p = 0.01). In Cox, CAR T→CAR T (HR 0.23, 95% CI 0.08–0.65, p = 0.01) showed superior PFS vs. CAR T→bsAb, whereas ADC→CAR T (HR 0.57, 95% CI 0.28–1.17, p = 0.12) did not differ significantly. 2nd BCMA-Tx was not affected by the time between 1st and 2nd BCMA-Tx (< 6 vs. >6 mo; p = 0.42) or intervening talquetamab (p = 0.35). 12 pt received a 3rd BCMA-Tx, 5/10 ev. pts achieved a response. After 2nd BCMA-Tx, prolonged neutropenia, infections, CRS, and ICANS (any grade) occurred in 31%, 53% (grade ≥3 32%), 50%, and 3% of pts, respectively; non-relapse mortality among all pts was 8.3%. **Conclusions:** Repeated BCMA-Tx yields high response rates with manageable toxicity, but PFS differs by sequence: CAR T→CAR T provides superior PFS compared to CAR T→bsAb but is attenuated after bsAb. ADC→CAR T appears less detrimental than bsAb→CAR T, though inferior to CAR T→CAR T. These data support CAR T before bsAb and highlight CAR T→bsAb as an unmet need.

PA-170

Efficacy of Venetoclax-Based Therapy in t(11;14)-Positive Relapsed/Refractory Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: Translocation between chromosomes 11 and 14 [t(11;14)] is one of the most common primary cytogenetic abnormalities in multiple myeloma. Venetoclax is a highly selective, oral BH3 mimetic that binds B-cell lymphoma-2 (BCL-2), inducing apoptosis in BCL-2–dependent plasma cells. Early phase studies suggested promising activity of venetoclax-based regimens, particularly in t(11;14) relapsed/refractory multiple myeloma (RRMM). However, venetoclax has not received FDA approval for the treatment of RRMM, in part due to results from two phase III randomized trials. **Methods:** A systematic literature search was performed across PubMed-MEDLINE, Embase-OVID, CENTRAL, ClinicalTrials.gov, and Web of Science databases up to January 1, 2025. Randomized phase III trials evaluating venetoclax-based therapy versus standard-of-care regimens in patients with t(11;14)-positive RRMM were included. Progression-free survival (PFS) was the primary outcome. Overall survival (OS) and time to deterioration in disease-related symptoms (TTDDS) were secondary outcomes. Hazard ratios (HRs) were pooled using a random-effects inverse-variance model with heterogeneity assessed using the I^2 statistic. **Results:** A total of 298 patients from two phase III randomized controlled trials (CANOVA and BELLINI) were included. Venetoclax-based therapy was associated with a directionally favorable improvement in PFS (pooled HR 0.40; 95% CI, 0.08–1.91). No pooled OS benefit was observed (HR 1.15; 95% CI, 0.78–1.71).

Venetoclax-based regimens demonstrated a trend toward prolonged TTDDS (TTDDS HR 0.70; 95% CI, 0.46–1.05). Substantial heterogeneity was observed for PFS (I^2 = 88.8%), while heterogeneity was minimal for OS and TTDDS (I^2 = 0%). None of the pooled efficacy outcomes reached statistical significance. **Conclusions:** Venetoclax-based therapy demonstrates a directionally favorable effect on PFS and TTDDS in t(11;14)-positive RRMM. In BELLINI, despite a small subgroup sample size, venetoclax demonstrated an effect size rarely observed in RRMM, whereas CANOVA was conducted against a highly active comparator. Future trials should prioritize t(11;14) populations and consider non-inferiority or combination-based comparator designs. The lack of statistical significance in pooled outcomes likely reflects differences in trial design and treatment backbone rather than absence of biological activity. Contemporary evidence continues to support venetoclax as a biologically rational, biomarker-directed strategy in t(11;14)-positive RRMM.

PA-171

Efficacy, Safety, and De-escalation Strategies of Teclistamab in Relapsed/Refractory Multiple Myeloma: A Real-World Cohort with 24-Month Follow-up

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Introduction: Teclistamab revolutionized the treatment of triple-class-exposed relapsed/refractory multiple myeloma with high response rates (MajesTEC-1: ORR 63%, CR 39%), but optimal treatment duration remains unknown, particularly whether sustained MRD-negative patients can discontinue therapy. Here, we describe efficacy and safety of de-escalation therapy a real-world cohort. **Methods:** This single-center retrospective study included 24 patients with relapsed/refractory multiple myeloma (RRMM) who received teclistamab from 2023 to 2026. Response was assessed per IMWG criteria and MRD by flow cytometry, and CRS and ICANS by ASTCT criteria. PFS and OS were estimated by Kaplan-Meier. Dosing schedule was systematically recorded. Teclistamab is administered weekly and may be transitioned to every-other-week dosing after 6 months of complete response. Following early infectious events, our institution adopted an earlier dose-spacing strategy, switching to every-other-week dosing after 8 weekly doses in patients who achieved complete response and MRD negativity, followed by monthly dosing if the response was maintained. Median follow-up was 25 months (range, 1.7–40). **Results:** Median age was 75 years (range 50–81), and median prior therapies was 3 prior lines (range 1–9); extramedullary disease in 7/24 (29%). ORR was 79.2% (n = 19); ≥VGPR 71% (n = 17); MRD-negative CR/sCR by flow cytometry in 16/24 (67%). Median PFS and OS were not reached; 2y-PFS was 62%; 2y-OS was 77%; 2-y relapse was 25%; and 2y-NRM was 13%. There were 5 progressions and 6 deaths (2 early toxicity, 1 refractory grade 4 CRS, 2 progression, 1 infection-related). CRS occurred in 16/24 (67%), predominantly G1–2 (n = 13, 54%); CRS ≥G3 in 3 (13%). Tocilizumab in 16 (67%), corticosteroids in 4 (17%). Grade 1 ICANS documented in 1 patient. At cut-off, only 1 out of 24 patients remained on the original weekly schedule. Twelve (50%) were on interval de-escalation: 9 (38%) monthly, 2 (8%) biweekly — all in CR/VGPR. Four patients (17%) had teclistamab permanently discontinued after 2–18 months of treatment while maintaining remission: one planned discontinuation for sustained MRD negativity after 8 cycles, in CR maintained >17 months off therapy; and 3 because of infections. No relapses among patients who discontinued treatment have been noted to date. **Conclusions:** In a real-world cohort substantially older than the pivotal trial, teclistamab achieved an ORR of 79% and MRD-negative CR in 67%, exceeding the MajesTEC-1 benchmark. Half of the cohort is on interval de-escalation and 17% permanently discontinued treatment while maintaining a deep response, including a case of MRD-driven planned discontinuation with >17 months treatment-free. These data support the hypothesis that fixed-duration or MRD-guided discontinuation may preserve anti-tumor benefit while mitigating cumulative immunosuppression. Prospective trials evaluating MRD-driven stopping rules in deep responders are warranted.

PA-172

Elevated APOBEC3B Expression Marks Functionally High-Risk Multiple Myeloma with Early Failure of Frontline PI/IMiD Therapy

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Introduction: A subset of newly diagnosed multiple myeloma (MM) patients develops primary refractory disease or early relapse despite frontline proteasome inhibitor (PI)- and immunomodulatory drug (IMiD)-based therapy. We investigated whether elevated APOBEC3B (A3B) expression at diagnosis identifies a biologically aggressive and clinically high-risk MM subset associated with early treatment failure. **Methods:** RNA-sequencing data from the CoMMpass cohort were analyzed in newly diagnosed MM patients treated with frontline PI/IMiD-based regimens, including bortezomib-, carfilzomib-, or ixazomib-based therapies combined with lenalidomide- or thalidomide-containing backbones, with or without ASCT. Patients were stratified into durable remission (PFS ≥5 years) and early relapse/refractory disease (PFS < 2 years with adequate follow-up). Integrated transcriptomic and functional studies were performed in lentiviral A3B-overexpressing OPM2 cells and A3B-knockdown EJM and MOLP8 cells using three biological replicates.

Results: Across the newly diagnosed CoMMpass MM cohort, elevated A3B expression at diagnosis was associated with inferior progression-free survival (PFS; HR = 2.32, 95% CI 1.76–3.07, P < 0.001) and overall survival (OS; HR = 2.60, 95% CI 1.93–3.51, P < 0.001). Among 650 evaluable patients treated with frontline PI/IMiD-based therapy, early relapse/refractory disease and durable remission occurred in 27.4% and 26.6% of patients, respectively. Early relapse/refractory MM exhibited significantly higher APOBEC mutation enrichment scores at diagnosis compared with durable remission MM (P = 0.0036), with A3B identified as the most significantly upregulated APOBEC family member (log2FC = 0.65, adjusted $P = 7.61 \times 10^{-4}$). Transcriptomic analyses revealed enrichment of chromosomal instability, mitotic progression, checkpoint, and replication stress programs in early relapse/refractory MM compared with durable remission MM (adjusted $P = 10^{-11}$–10^{-5}), with consistent findings across ASCT-treated and non-ASCT-treated subgroups. Concordantly, RNA-seq analyses showed that A3B overexpression enriched, whereas A3B depletion suppressed, these transcriptional programs (adjusted P < 0.05). Functionally, BrdU/7-AAD analyses demonstrated reduced S-phase fraction following A3B depletion, accompanied by decreased γH2AX, p-RPA2(S33), and p-CHK1(S345) levels (P < 0.05), consistent with reduced replication stress and DNA damage signaling in MM cells. **Conclusions:** Elevated A3B expression defines a biologically aggressive, clinically high-risk MM subset associated with early failure of frontline PI/IMiD-based therapy and inferior survival. Convergent transcriptomic and functional analyses identify A3B as a clinically relevant biomarker linked to replication stress and chromosomal instability programs associated with early therapeutic failure in MM, warranting further evaluation in the anti-CD38 era.

PA-173

Elevated circPTK2 Expression Is Associated with Extramedullary Disease and Shows Diagnostic Potential in Multiple Myeloma

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Introduction: Extramedullary multiple myeloma (EMM) is an aggressive subtype of multiple myeloma (MM) associated with poor clinical outcomes and high biological heterogeneity. However, biomarkers for identifying extramedullary progression remain limited. This study investigated the expression and clinical significance of circular RNAs protein tyrosine kinase 2 (circPTK2) in MM patients with and without extramedullary disease. **Methods:** Formalin-fixed paraffin-embedded (FFPE) tissue sections were collected from patients with EMM and MM without extramedullary disease. circPTK2 expressions in FFPE tissue sections were assessed using fluorescence in situ hybridization (FISH). Differences in circPTK2 expression between groups were analyzed via rank-sum test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of circPTK2 to distinguish EMM from MM without extramedullary disease. Progression-free survival (PFS) and overall survival (OS) were further analyzed according to circPTK2 expressions. **Results:** circPTK2 expressions were significantly higher in patients with EMM than in MM without extramedullary disease. ROC curve analysis demonstrated that circPTK2 could discriminate EMM from MM without extramedullary disease with moderate-to-well diagnostic performance (AUC, 0.763; 95% confidence interval, 0.589–0.937). The sensitivity and specificity were 0.563 and 0.929, respectively. After median follow-up of 23.8 months, median PFS and OS in the overall MM cohort were 6.4 and 23.4 months, respectively. Among EMM patients, those with high circPTK2 expression showed trends toward shorter PFS and OS than those with low expression. The median PFS was 5.7 versus 6.4 months, and median OS was 23.4 versus 41.9 months. However, these differences did not reach statistical significance (Log-rank P value = 0.259 and 0.124, respectively), likely due to the limited sample size. **Conclusions:** circPTK2 is significantly upregulated in patients with EMM and may serve as a potential biomarker for distinguishing extramedullary disease in MM. Higher circPTK2 expression may also be associated with inferior survival outcomes in EMM patients. Larger prospective studies are needed to validate its diagnostic and prognostic value.

PA-174

eMMpower-CART: Real-World Insights into Early-Line Cilta-cel Outcomes in Multiple Myeloma (MM)

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Introduction: Cilta-cel, a BCMA-targeted CAR T-cell therapy for RRMM, has demonstrated sustained efficacy in early lines of therapy in clinical trials. However, real-world outcomes among patients (pts) receiving commercial cilta-cel after 1–3 prior lines of therapy (LOT) remain limited. Using the eMMpower multisite retrospective chart review consortium, we characterized baseline characteristics, bridging therapy patterns, and early post-infusion outcomes in US pts receiving cilta-cel in routine practice in earlier lines. **Methods:** This retrospective chart review study included adult pts with RRMM who received commercial cilta-cel in 2–4 LOT. Baseline characteristics, bridging therapy patterns, and post-infusion outcomes (MRD status, ORR) were summarized descriptively. OS and PFS were evaluated using Kaplan-Meier methods. Given limited follow-up, multiple

parametric survival models were used to assess longer-term OS projections. **Results:** In total, 72 pts met study criteria (median age 68 years; 44.4% female; 77.8% White; 63.9% Medicare insured). Cilta-cel was used as 4th line therapy in 48.6% of pts, as 3rd line in 37.5%, and as 2nd line in 13.9%. Overall, 61.1% pts had high-risk cytogenetics, 19.4% had R-ISS stage III disease, 6.9% had ECOG ≥2, 23.6% were frail (SFS score ≥2), and 13.9% had renal impairment. Before cilta-cel infusion, 46 (63.9%) pts received bridging therapy. Among bridged pts, 30.4% received IMiD ± mAb-based regimens, 30.4% PI-based, 26.1% alkylator-based, 4.3% talquetamab, and 8.7% other/unknown regimens. Median time from bridging therapy initiation to cilta-cel infusion was 1.6 months. At a median follow-up of 6.4 months post cilta-cel, ORR was 98.0%, including 73.5% ≥complete response. Among 29 pts with available MRD data, 86.2% achieved MRD negativity at 10^{-5} (median time to MRD negativity: 64 days). Among 3 patients with longitudinal MRD assessments, sustained MRD negativity was observed in all. The estimated 6-month and 12-month PFS rates were 98.4% and 92.2%, respectively. In the overall cohort (N = 72), OS rates were 93.7% at both 6 and 12 months. Exploratory OS extrapolation using the eMMpower consortium data across parametric models projected OS rates of 78.7% at 30 months, 65.8% at 5 years, and 50.8% at 10 years. **Conclusions:** In this real-world cohort of RRMM patients treated with cilta-cel after 1–3 prior lines of therapy, the majority of patients (~86%) received treatment in the 3 L/4 L setting; early-line use was associated with deep responses, high MRD negativity rates, and favorable survival outcomes. Exploratory OS extrapolation suggests the potential for durable long-term benefit with earlier-line cilta-cel in routine clinical practice. Continued longitudinal follow-up within the eMMpower consortium will further characterize the durability of response and long-term survival outcomes in this early-line real-world population.

PA-175

Engineering del(17p) in Multiple Myeloma Reveals TP53-Independent Determinants of Aggressive Disease

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Introduction: Multiple myeloma (MM) is a genetically heterogeneous hematologic malignancy with highly variable clinical outcomes. Among recurrent cytogenetic abnormalities, deletion of the short arm of chromosome 17 [del(17p)] is a well-established high-risk feature associated with poor prognosis. Although del(17p) frequently includes loss of the tumor suppressor TP53, the contribution of additional genes within the deleted region to MM biology remains incompletely understood. Clinical data suggest that larger 17p deletions and loss of multiple genes are linked to inferior outcomes, supporting a broader biological impact beyond TP53 alone. **Methods:** Using the MACHETE genome-engineering approach, we engineered a 21-Mb deletion of 17p in 17p wild-type AMO1 cells and isolated single-cell del(17p) clones. Deletion was confirmed by ultra-low-pass sequencing, FISH, and deep whole-genome sequencing. We performed RNA-seq, cellular proteomics, and quantitative mass spectrometry of conditioned media, together with proliferation, clonogenicity, invasion, and drug-response assays. Candidate drivers were identified by integrating our isogenic data with three independent patient del(17p) MM transcriptomic datasets. SAT2 re-expression and interactome analyses were used for functional validation. **Results:** ATAC-seq and RNA-seq analysis of the isogenic del17p cells revealed a transcriptomic signature consistent with haploinsufficiency, with 73% of 17p-localized genes significantly downregulated (padj < 0.05) relative to the parental line, and these RNA-level changes were corroborated at the protein level by TMT-based quantitative proteomics. Importantly, repeat WGS after four months in culture demonstrated that the del(17p) event remained stable with no detectable changes compared to early time points, and late RNA-seq confirmed sustained suppression of 17p genes, alongside broader expression differences attributable to extended culture. Functionally, del(17p) cells exhibited increased clonogenic capacity, enhanced invasive behavior, and greater resistance to proteasome inhibitors. Multi-omic profiling revealed broad remodeling of metabolic, stress-response, immune, and cell-surface programs, consistent with a major state change induced by 17p loss. Cross-comparison of patient-derived and isogenic transcriptomic datasets identified a core set of genes within the minimal deleted region that were consistently downregulated in del(17p) MM. Among these, reduced SAT2 expression was notably associated with poorer patient outcomes. Re-expression of SAT2 reversed key del(17p)-associated transcriptional, proteomic, and secretory changes and reduced clonogenicity, implicating SAT2 as a functional mediator of the aggressive phenotype. **Conclusions:** This engineered del(17p) MM model shows that 17p loss drives broad TP53-independent cellular reprogramming linked to aggressive behavior. SAT2 emerges as a functional mediator of del(17p) biology and a potential biomarker and therapeutic vulnerability in high-risk MM.

PA-176

Enhanced Efficacy and Differences in Downstream Pathway Modulation with AKT Degradation Versus Inhibition in Myeloma

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Introduction: AKT, also known as Protein Kinase B (PKB), is a set of three serine/threonine-specific protein kinases (AKT1/2/3). It is part of the PI3K/AKT/mTOR signalling axis which is aberrantly activated in multiple myeloma (MM). AKT inhibitors demonstrated significant efficacy in preclinical MM models, but early phase trials showed only modest response rates at tolerable dose levels. We hypothesised that degradation of AKT rather than inhibition may be more potent and potentially overcome resistance mechanisms to inhibitors, enabling a greater therapeutic impact. **Methods:** We designed novel PROTACs based on the AKT inhibitor capivasertib (capi, FDA approved for a subset of metastatic breast cancer), an appropriate linker and a phenyl glutarimide (PG) cereblon binding component. The linker and E3 binding motif were chosen specifically to impart favourable physicochemical properties in the synthesised PROTACs. In vitro analysis in human MM cells lines (MM1s, H929, KMS11) included Western Blots (WB) to assess protein changes and CellTiter-Blue assays for cell proliferation over 5 days of treatment. TMT-labelled mass spectrometry analysis assessed the specificity of degradation. **Results:** The most potent AKT-PROTAC, CCT410766, degraded AKT in a time and concentration dependent manner with a DC50 of 0.02nM at 4hrs in MM1s cells. CCT410766 at 0.1uM reached DC50 after 2hrs, DC90 at 4hrs and Dmax (>95% protein loss) at 7 hrs. Rescue with CRBN knockout (KMS11 vs KMS11-CRBNKO) and short term, low dose, proteosome inhibition confirmed protein degradation as the mechanism of action. There was no evidence of Ikaros/Aiolos degradation. TMT-labelled mass spectrometry analysis (MM1s, 0.1 uM, 4 hrs) demonstrated strong selectivity for all 3 isoforms of AKT with significant reduction in expression (AKT1 Log2FC −2.02, q = 8.48E-04; AKT2 Log2FC −2.8; q = 9.33E-06, AKT3 Log2FC −2.09, q = 5.14E-04). CCT410766 showed greater efficacy in reducing cell proliferation at 5 days in MM1s (% of DMSO at Day 5: 0.04% with 0.1 uM CCT410766 vs 38.3% 0.1 uM capi) and demonstrated a cytotoxic effect vs the cytostasis seen with inhibition (Fold change Day 5 vs Day 0: 0.02, 0.01, −0.012 with CCT410766 vs 4.93, 4.24, 2.27 with capi at 0.05, 0.1 and 0.2uM respectively). Similar results were seen in H929. Capi, as previously reported, led to increased pAKT (1018% of DMSO with 0.1 uM, 24 h, MM1 s) whilst this was downregulated with CCT410766 (1.57%). Similarly, differences in the phosphorylation of downstream pathway proteins were seen, with pS6 and pGSK3B expression maintained after capi but reduced with CCT410766. **Conclusions:** AKT degradation with CCT410766 was associated with a greater effect on cell viability and evidence of cytotoxicity compared to cytostasis seen with AKT inhibition. This enhanced efficacy and the differences in downstream signalling pathway changes may enable greater therapeutic potential for MM than that seen with AKT inhibitors.

PA-177

Enhancing Immunotherapy through Metabolic Modulation in Humanized Multiple Myeloma Mice

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Introduction: Multiple myeloma (MM) is characterized by the proliferation of monoclonal plasma cells. Metabolic disorders with high energy metabolism and glycolysis rates in the bone marrow ensure sufficient energy for the rapid proliferation and growth of MM cells. Phosphatase of regenerating liver-3 (PRL3) inhibitor, a potent modulator of energy metabolism, emerges as an effective drug for MM. However, its limited impact on immune system activation compromises therapeutic efficacy. **Methods:** The study involved synthesizing the target compound TCP and preparing TCP@PRL3 NPs. The effects of TCP@PRL3 NPs on DC activation, T cell function and cell metabolism were verified by flow cytometry, western blot and central carbon metabolism at the cellular and animal levels. **Results:** This study proposes a therapeutic approach utilizing PRL3 inhibitor to enhance photodynamic therapy (PDT) mediated immunogenic cell death (ICD). Mechanically, the metabolomics study results demonstrated that PRL3 inhibition can reduce the produce of L-lactic acid and ameliorate the acidic tumor micro environment to enhance the immune cell function. In addition to conceptual validation in high-energy metabolism CT26 tumors and lowimmunogenicity 4T1 tumors, we co-administered daratumumab (a CD38 antibody) and validated this strategy in humanized multiple myeloma mice, providing a robust potential solution for the clinical treatment of high-energy metabolism and low-immunogenicity tumors. **Conclusions:** The study demonstrated the potential of TCP@PRL3 NPs combined with light irradiation to modulate energy metabolism and enhance immune therapy. This approach led to increased anti-tumor immune responses by regulating tumor proliferation rates, inducing immunogenic cell death (ICD), and reshaping the tumor microenvironment (TME) in humanized multiple myeloma mice. However, challenges such as off-target effects and limited penetration depth remain, suggesting the need for further optimization and development of advanced strategies for effective immunotherapy.

PA-178

Eosinophilia Associated with Elranatamab in Patients with Multiple Myeloma: A Multi-Institutional Analysis

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Introduction: Three commercially available BCMA-directed bispecific T-cell engagers (TCE) have transformed the treatment landscape of multiple myeloma and have been documented to have similar efficacy and toxicity profiles. However, we observed that patients treated with elranatamab developed a unique pattern of hypereosinophilia, frequently occurring independent of rash and occasionally accompanied by organ involvement. We therefore performed a multi-institution analysis comparing eosinophilia across BCMA TCE. **Methods:** We retrospectively evaluated multiple myeloma patients treated with elranatamab (elra; n = 181), teclistamab (tec; n = 138), and linvoseltamab (linvo; n = 44) as monotherapy across three academic centers (n = 363). Eosinophilia was defined as absolute eosinophil count (AEC) >500/μL, hypereosinophilia as AEC >1,500/μL, and severe eosinophilic reaction as AEC >15,000/μL. **Results:** Prophylactic medications, including sulfamethoxazole/trimethoprim, were standard across institutions and BCMA TCE products. Eosinophilia occurred in 29/181 (16.0%) elra-treated patients compared with 8/138 (5.8%; p = 0.003) treated with tec and 1/44 (2.3%; p = 0.013) treated with linvo. Median time to eosinophilia onset ranged from 20 to 26 days with elra, 21–30 days with tec, and 60 days with linvo. Elra-associated eosinophilia frequently occurred independent of rash, with 16/29 (55.2%) cases lacking cutaneous manifestations, significantly more frequent than with tec (16/181 [8.8%] vs. 4/138 [2.9%]; p = 0.024). Severe eosinophilic reactions (AEC >15,000/μL) were observed exclusively with elra (3/181 [1.7%]). Most elra-associated eosinophilia cases were asymptomatic. Among patients with severe hypereosinophilia, two patients had pancolitis: one was successfully rechallenged with elra under corticosteroid support while the other with biopsy-proven morbilliform drug eruption with biopsy-confirmed eosinophilic pancolitis discontinued therapy. A third patient with hypereosinophilia was asymptomatic. In contrast, tec-associated eosinophilia was lower-grade and lacked comparable systemic manifestations. Hematologic evaluation did not identify myeloproliferative neoplasms. Although two patients had positive Strongyloides serologies and received ivermectin, eosinophilia also occurred in serologically negative patients. **Conclusions:** Elra demonstrated a distinct eosinophilic toxicity profile among BCMA-TCE, characterized by higher incidence, greater severity, and infrequent but severe systemic inflammatory manifestations often independent of rash and generally not meeting criteria for DRESS. While the mechanism is unknown, recognition of this syndrome is clinically important. Continued elra dosing with corticosteroids in asymptomatic and/or low-grade cases appears feasible and effective.

PA-179

Epigenetic Upregulation of the H3K36me2 Reader ZMYND8 by the Novel Retinoid WYC-209 Suppresses Multiple Myeloma and Sensitizes to Carfilzomib via CEBPE-Mediated UPR Inhibition

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Introduction: Multiple myeloma (MM) remains incurable due to drug resistance, particularly to proteasome inhibitors like carfilzomib (CFZ). The histone mark H3K36me2 is a key driver of MM progression, yet its readers and downstream effectors are poorly understood. ZMYND8 has been implicated as a potential tumor suppressor, but its role in MM and its relationship with CFZ sensitivity are unknown. **Methods:** We integrated transcriptomic (RNA-seq), epigenomic (CUT&Tag, ChIP-qPCR), and functional analyses in MM cell lines, patient samples, and xenograft models. We identified ZMYND8 as a reader of H3K36me2 via its PWWP domain, and characterized its downstream target CEBPE. We then screened for small molecules that upregulate ZMYND8 and tested their synergy with CFZ in vitro and in vivo. **Results:** ZMYND8 is downregulated in MM and predicts poor prognosis. Mechanistically, ZMYND8 binds H3K36me2 through its PWWP domain, activating CEBPE transcription. CEBPE directly represses ERN1, XBP1, and ATF6, thereby inhibiting the adaptive unfolded protein response (UPR) and suppressing MM cell proliferation and invasion. ZMYND8 overexpression sensitizes MM cells to CFZ. The retinoid WYC-209 (superior to ATRA) epigenetically upregulates ZMYND8 by increasing H3K27ac and reducing H3K27me3 at its promoter via KDM6A. WYC-209 synergizes with CFZ to induce apoptosis, exacerbate ER stress, and suppress tumor growth in NSG mouse models; these effects are abrogated by ZMYND8 knockout. **Conclusions:** We identify ZMYND8 as a H3K36me2 reader that suppresses MM by activating CEBPE and inhibiting adaptive UPR. Pharmacological upregulation of ZMYND8 by the novel retinoid WYC-209 potentiates CFZ efficacy, providing a promising combination strategy for relapsed/refractory MM.

PA-180

Establishment of the First Multiple Myeloma Neomer Catalogue and Evaluation in Cell-Free DNA

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Introduction: Multiple myeloma (MM) remains incurable despite therapeutic advances, with minimal residual disease (MRD) testing important for prognostication. Cell-free DNA (cfDNA) whole genome sequencing (WGS) offers a minimally invasive alternative to bone marrow (BM) aspiration for MRD monitoring, but interpretation can be confounded by mutations arising from clonal hematopoiesis of indeterminate potential (CHIP). Neomers are short k-mer sequences (11–17 bp) absent from the healthy genome but arising from somatic mutations in tumours. We generated the first MM neomer catalogue, evaluated overlap with CHIP-associated mutations, and assessed neomer detection in cfDNA. **Methods:** Somatic variant calls from three datasets were obtained to derive neomers using a previously published pipeline (Georgakopoulos-Soares et al., 2021). The MM neomer catalogue was derived from patients in the MMRF-CoMMpass study (n = 947). For quality control, we excluded variants with sequencing depth < 20x, variant allele fraction < 5%, presence in gnomAD (except known COSMIC cancer hotspot variants), or localization within ENCODE blacklist or RepeatMasker-annotated regions. CHIP-associated mutations were obtained from a curated list of canonical CHIP driver variants (Vlasschaert et al., 2023) and resulting neomers were assessed for overlap with the MM catalogue. For cfDNA validation, we leveraged a dataset of 30 MM patients with matched BM and cfDNA subjected to a 165-gene targeted sequencing panel (Heestermans et al., 2022). **Results:** In newly diagnosed CoMMpass patients, 324,813 somatic variants generated 4,951,208 unique neomers across k = 13, 15, and 17. Most neomers (>98.8%) were patient-private, although recurrent neomers captured key MM driver loci, including frequent mutations within the RAS/MAPK pathway. Among patients with a second BM assessment, those achieving very good partial response or better (n = 13) demonstrated significant within-patient reductions in detectable neomers (median 7,248 to 346 at k = 17; Wilcoxon $p < 0.05$), whereas no significant changes were observed for those with stable/partial response (n = 31, $p = 0.59$) or progressive disease (n = 103, $p = 0.88$). Our CHIP neomer blacklist had minimal overlap (<3.1%) with MM neomers. In cfDNA, 26 patients had detectable somatic mutations and 14/26 (54%) had neomers in the MM catalogue, with higher overlap occurring in relapsed/refractory disease. Six patients harbored neomers derived from CHIP-associated variants, including one case with no MM catalogue overlap. **Conclusions:** This study establishes the first MM neomer catalogue, providing a foundational resource for future neomer-based cancer classification and biomarker development. The observed reduction in neomer burden with treatment response, together with detectable neomers in cfDNA, supports the feasibility of neomer-based cfDNA WGS approaches for non-invasive MRD monitoring in MM. Further evaluation in larger longitudinal cfDNA cohorts will be required to determine clinical utility.

PA-181

Etentamig in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) with Prior Exposure to B-Cell Maturation Antigen (BCMA)-Targeted Therapy

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Introduction: As BCMA-directed therapies move earlier in the treatment pathway, outcomes on sequential BCMA T-cell redirecting therapies are vital to evaluate. However, data availability is currently limited. Etentamig is being developed as a next-generation differentiated BCMA × CD3 bispecific T-cell engager composed of a bivalent BCMA-binding domain with high avidity, low-affinity CD3-binding domain potentially reducing cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life enabling convenient monthly (Q4W) dosing from the start. Phase 1 results of etentamig in heavily pretreated pts with RRMM showed deep and durable responses and potential best-in-class safety. **Methods:** Arm B of the open-label, phase 1b MONVISO study (NCT05650632) evaluated etentamig in pts with RRMM with ≥2 prior lines of therapy (pLoT), including triple-class and prior BCMA exposure (antibody-drug conjugate [ADC] >30 days or CAR-T >6 months [mo] after last exposure). Primary safety endpoints were CRS and immune effector cell-associated neurotoxicity syndrome (ICANS); efficacy endpoints included objective response rate (ORR; IMWG 2016), duration of response (DoR), and progression-free survival (PFS). Pts received etentamig (60 mg IV; no step-up dosing [SUD]) on Cycle 1 Day 1 and Q4W thereafter. **Results:** At cutoff (June 11, 2025), 41 prior BCMA-exposed pts (CAR-T, n = 24; ADC, n = 17) had been treated; 24 (57%) were male, 38 (93%) were White, median (mdn) (range) age was 68 (43–89) years, 37 (88%) had ECOG PS ≤1, and 34 (81%) were triple-class refractory. Mdn (range) pLoT was 6 (3–15), 21 (51%) pts were exposed to BCMA during their last pLoT, and 23

(56%) had previously responded to a BCMA therapy (17/24 [71%] for CAR-T). Mdn (range) time from last prior CAR-T or any prior BCMA to first dose of etentamig was 15 (1–30) and 14 (1–45) mo, respectively. Mdn (range) follow-up was 5.5 (0.2–17.1) mo. With no SUD, CRS and ICANS were reported in 24 (57%) and 3 (7%) pts, respectively (all grade 1/2 events, except 1 grade 3 ICANS). Grade 3/4 neutropenia and infections were reported in 15 (36%) and 17 (41%) pts, respectively. Of 36 efficacy evaluable pts, ORR (95% CI) was achieved by 17 (47% [30–65]) pts with prior BCMA exposure; and 7 (64% [31–89]) whose last pLoT was CAR-T (n = 11). Mdn DoR was 13 (7–not estimable [NE]) mo in pts with prior BCMA CAR-T exposure. Mdn PFS was 9.4 (2–NE) mo in pts who received CAR-T as last pLoT compared with 3.4 (3–11) mo in pts treated with any prior BCMA-directed therapy, and 8.3 [2–NE] mo in pts treated with prior CAR-T at any time. **Conclusions:** Even after prior BCMA exposure, treatment with etentamig led to deep and durable responses, with particularly encouraging responses post-BMCA CAR-T. Consistent with prior data, only low-grade CRS was observed, even without SUD with no new safety signals.

PA-182

Ethnic and Gender Variations in Newly Diagnosed Multiple Myeloma Patients – Israeli Jewish and Arab Patient Cohorts

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Introduction: Multiple Myeloma (MM) symptoms, clinical features, and prognosis can vary between patients. Many studies in recent years demonstrated discrepancies between different ethnic and gender subgroups, however, these differences are still not fully understood, and there is still a need to further investigate the ethnic and demographic influence. Therefore, the main aim of the current study was to reveal the variations between Israeli Jewish and Arab newly diagnosed MM patients. Finally, in this study, we have also compared the differences in the MM diagnosis features among males and females. **Methods:** This study consisted of the available records of 85 newly diagnosed MM Israeli patients (34 (40%) Arab, and 51 (60%) Jewish patients), at the Institute of Hematology at Carmel Medical Center, Israel. The patients included in this study had no significant differences in the Charlson Comorbidity Index (CCI) between the subgroups. In this study, we included the following features – ethnic group, sex, age, CCI, revised international staging system (R-ISS), bone marrow plasma cell percentage (%), Calcium, Creatinine, Hemoglobin, bone lesions - CRAB, M-protein, and Kappa/Lambda ratio. In addition, we compared the two ethnic groups using an independent t-test or Wilcoxon test for continuous features, and Chi-square for categorical features. Finally, we analyzed the correlations between the features using Spearman analysis. **Results:** The results showed that the mean age at diagnosis was slightly higher among Jewish patients 62 (M = 62, SD = 15), compared to a mean age of 61 (M = 61, SD = 13) among the Arab patients. In both ethnic groups, more males were diagnosed. Regarding the MM diagnosis profile, the results demonstrated that the two ethnic groups were diagnosed with almost the same percent of plasma cells (Jewish patients –62%, Arab patients – 61%). Furthermore, the results revealed that the Arab patients had more bone lesions at diagnosis, compared to the Jewish patients, especially when comparing female patients from the two ethnic groups ($P < 0.05$). The results also showed that there was no significant difference in the R-ISS when comparing the two ethnic groups. On the other hand, when comparing the gender effect, the results showed significantly that the majority of the males were diagnosed as R-ISS = 2 (n = 52, 73%), and only one male patient was diagnosed as R-ISS = 3 (n = 1, 1.9%), while 17 (n = 17, 55%) female patients were diagnosed as R-ISS = 2, and 5 female patients were diagnosed as R-ISS = 3 (n = 5, 16%) ($P < 0.05$). Finally, the correlation analysis presented differences between the different subgroups. For example, there were significant variations in the correlation between the R-ISS and the different CRAB symptoms. **Conclusions:** This study revealed that patients can show differences in the MM defining events that are associated with the ethnic and gender subgroups. This study encourages considering these variations when diagnosing and treating MM patients.

PA-183

Evaluating the Association Between Minimal Residual Disease-Negative Complete Response (MRD-Negative CR) and PFS in CAR T-Treated RRMM: A Meta-Analysis of Clinical Trials and Observational Studies

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Introduction: Draft guidance issued in January 2026 by the FDA recognizes MRD-negative CR as a primary endpoint that can be used to support accelerated approval in MM. Evidence supporting this draft guidance, including meta-analyses discussed by the Oncologic Drugs Advisory Committee and published thereafter, did not include trials of CAR T in MM. The applicability of the results of these analyses to this therapeutic class is unknown. The present analysis evaluated the association between MRD-negative CR and progression-free survival (PFS) in RRMM patients (pts) treated with CAR T. **Methods:** A systematic literature review identified clinical trials of CAR T in RRMM published from January 2016 to January 2026.

Trials reporting Kaplan-Meier (KM) plots for PFS at ≥ 12-mo and MRD-negative CR rates at any time point, per IMWG criteria for response and MRD, were eligible. Pts with CR and non-evaluable MRD status were considered MRD-positive. PFS was estimated using reconstructed patient-level data from published KM curves. A stratified KM analysis with a log-rank test was used to compare PFS between studies with a high vs low MRD-negative CR rate relative to the median across studies. Weighted least squares (WLS) linear regression was used to estimate trial-level associations between the log odds of MRD-negative CR rate and log cumulative PFS at 12-mo. Predictive performance was evaluated using leave-one-out cross-validation. **Results:** A total of 21 studies (2 RCTs and 19 single-arm trials) and 1486 pts were included in the analysis. BCMA was the most frequently evaluated CAR T target (14/21 trials; 67%), followed by GPRC5D (3/21; 14%), and various dual targets (4/21; 19%). Across trials, the median number of prior lines of therapy and sample size ranged from 2–8 and 14–254, respectively; median study follow-up ranged from 8.1–67.3 mo. KM analyses stratified by the median MRD-negative CR rate across trials (44.6%) showed that a higher MRD-negative CR rate was associated with significantly longer median (95% CI) PFS (28.3 mo [24.8–32.2] vs 13.4 mo [12.2–15.4] with a lower MRD-negative CR rate, respectively; $P < 0.0001$). Statistically significant, positive associations between MRD-negative CR and 12-mo PFS were observed in the WLS model (slope: 0.12 [95% CI, 0.05–0.18]; R2: 0.43 [95% CI, 0.16–0.69]). Cross-validation confirmed MRD-negative CR rates were predictive of PFS, with 95% predictive intervals for 12-mo PFS encompassing observed values in all studies. **Conclusions:** A higher MRD-negative CR rate was associated with longer PFS in CAR T studies in RRMM, supporting MRD-negative CR as a surrogate endpoint in this setting. Cross-validation supports the predictive value of MRD-negative CR and model robustness.

PA-184

Evaluation of BOLD-100 as a Strategy to Overcome Drug Resistance in Multiple Myeloma

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Introduction: Multiple myeloma (MM) cells are critically dependent on proteostasis machinery, and proteasome inhibitors (PIs) such as bortezomib and carfilzomib exploit this vulnerability, though two significant clinical hurdles limit their efficacy. Acquired PI resistance develops in most patients, driven by GRP78 (HSPA5/BiP) upregulation, the master ER chaperone and regulator of all three UPR branches, enabling stress adaptation and therapy evasion. Bortezomib-induced peripheral neuropathy (BIPN) affects 30–60% of patients and remains a dose-limiting toxicity. BOLD-100, a ruthenium-based metallodrug in clinical evaluation, selectively targets GRP78 and disrupts this adaptive response. A Phase 2 trial with FOLFOX reported reduced oxaliplatin-associated neuropathy, suggesting a potential neuroprotective effect worthy of exploration in MM. This study investigates BOLD-100 to address both challenges: overcoming PI resistance whilst mitigating treatment-associated neuronal injury. **Methods:** Isogenic MM cell lines including PI-sensitive (S), bortezomib-resistant (BR), and carfilzomib-resistant (CR) derivatives of AMO-1, RPMI-8226, U266 and OPM2 were used. BOLD-100 was evaluated with bortezomib and carfilzomib using simultaneous and sequential dosing, with 6-hour pre-treatment before the second drug. Viability was measured by CellTitre-Glo® at 24 and 48 hours and synergy quantified using the Bliss independence model in SynergyFinder+. UPR and apoptotic markers including GRP78, IRE1α, XBP1s, P-eIF2α, ATF4, CHOP, ATF6, and cleaved caspase-3 were assessed by Western blotting at 0, 3, 6, 24, and 48 hours. SH-SY5Y cells were differentiated over 10 days using a retinoic acid/BDNF protocol, and a wound-healing assay monitored neurite regrowth at 72 hours post-injury. **Results:** BOLD-100 exhibited consistent cytotoxic activity across PI-sensitive and resistant cell lines (IC50 125.2–157.2 µM at 24 hours), driving GRP78 downregulation from 6 hours with PERK activation (P-eIF2α, ATF4), IRE1α-XBP1s induction, CHOP upregulation, and cleaved caspase-3, consistent with cells tipping from adaptive UPR into terminal ER stress and apoptosis. Synergistic responses were observed in sensitive and resistant OPM2 cells. Notably, BOLD-100 pre-treatment yielded greater viability reductions than simultaneous dosing, suggesting GRP78 suppression lowers the PI-induced death threshold. Bortezomib impaired neurite regrowth, while BOLD-100 showed improved recovery at 72 hours, suggesting it may attenuate bortezomib-associated neuronal injury. **Conclusions:** Taken together, these findings position BOLD-100 as a clinically relevant strategy in PI-resistant myeloma. GRP78 suppression and UPR collapse provide a mechanistically coherent basis for PI synergy, and persistence in resistant models is important given the unmet need in relapsed/refractory disease. The neuronal findings, while early, are encouraging. Future work will focus on mechanistic evaluation of BOLD-100 across myeloma and neuronal models.

PA-185

Evaluation of Patient-Reported Outcomes and Subgroup Analysis With Subcutaneous Isatuximab Delivered via On-Body Injector Compared With Intravenous Delivery From the Phase 3 IRAKLIA Trial

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Introduction: The phase 3 IRAKLIA trial (NCT05405166) assessed isatuximab (Isa) delivered subcutaneously (SC) via an on-body injector (OBI; Isa SC OBI) vs Isa administered intravenously (Isa IV), with pomalidomide and dexamethasone (Pd), in patients (pts) with relapsed/refractory multiple myeloma (RRMM). Isa SC OBI led to higher satisfaction rates vs Isa IV at Cycle (C)5 Day (D)15 (96.8% vs 70.8%) in pts who completed the questionnaire. Lower proportions of pts reported discomfort and pain, and a higher number reported time savings with Isa SC OBI than with Isa IV. Here, we describe pts' experiences among the satisfied and neutral pt subgroups in the Isa SC OBI and Isa IV arms and the perception of treatment benefits relative to disadvantages and willingness to continue treatment in all pts. **Methods:** 531 pts ≥18 years with RRMM and ≥1 prior line of therapy were randomized to the Isa SC OBI (N = 263) and Isa IV (N = 268; n = 4 did not receive treatment) arms and received 1400 mg (fixed dose) and 10 mg/kg Isa weekly in C1 and every 2 weeks thereafter with Pd, respectively. The satisfied subgroup included pts who answered on the Patient Experience and Satisfaction Questionnaire Follow-Up (PESQ-FU) that they were "satisfied" or "very satisfied" with their injection method at C5D15. The neutral subgroup included pts who were "neither satisfied nor dissatisfied" with their injection method. Discomfort, pain, and side effects of the medication from the PESQ-FU at C5D15 were reported in both subgroups for each treatment arm. At end of treatment (EOT), perception of benefits vs disadvantages and willingness to complete treatment in all pts were assessed using the Patients' Assessment of Treatment (PAT) questionnaire. **Results:** Among satisfied pts at C5D15 (Isa SC OBI, n = 183; Isa IV, n = 143), more Isa SC OBI pts strongly disagreed/disagreed that the injection method was uncomfortable compared with Isa IV pts (78.7% vs 64.3%). A greater proportion of satisfied Isa SC OBI pts strongly disagreed/disagreed that the injection method was painful compared with Isa IV pts (89.1% vs 72.0%) at C5D15. Also, at C5D15, more satisfied pts reported fewer perceived medication side effects with Isa SC OBI vs Isa IV (73.2% vs 55.9%). Trends were similar in the neutral subgroup. Of pts who completed the PAT at EOT (Isa SC OBI, n = 77; Isa IV, n = 70), the proportion of pts who reported high benefits and low disadvantages was slightly higher in the Isa SC OBI arm (45.5%) vs the Isa IV arm (40.0%). At EOT, more pts in the Isa SC OBI arm (50.7%) both expressed willingness to continue treatment and felt benefits outweighed disadvantages than in the Isa IV arm (31.4%). **Conclusions:** In satisfied and neutral pt subgroups, more Isa SC OBI pts reported positive experiences vs Isa IV pts. At EOT, pts perceived more benefits than disadvantages with Isa SC OBI than with Isa IV. Our findings support the feasibility of the OBI as a novel method for SC delivery of Isa, in line with results from the overall IRAKLIA cohort.

PA-186

Evaluation of Routinely Collected National Mortality Data Compared to Trial-Specific Data in UK Multiple Myeloma Clinical Trials: Analysis of the BLISS Project

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Introduction: Using routinely collected healthcare systems data (HSD) to monitor long-term outcomes in myeloma clinical trials could reduce cost, time and resources needed to ascertain outcomes. However, before this approach is adopted evidence is needed that HSD are reported to an equivalent standard to trial-specific collected data. This study examines if national death registries can reliably support long-term survival analyses in UK myeloma trials. **Methods:** The Blood Cancer Long-term Follow-up using Integrated Healthcare SystemS data (BLISS) project, links UK myeloma trial data with HSD via national data providers (NHS England). The database will be used to evaluate the quality and accuracy of HSD in determining clinical trial endpoints, including deaths, cancer registrations, treatment and hospital admissions. Mortality analyses are presented here. Identifiers from 4248 patients across seven phase II and phase III UK myeloma trials coordinated by the Leeds Institute of Clinical Trials Research (2008–2021) have been linked to national mortality data. Analyses were conducted at patient- and trial-levels. Patient-level evaluations examine data completeness, and agreement between trial-collected and registry-derived mortality. Trial-level analyses compare long-term survival estimates from registry data versus trial data alone. **Results:** There was a high linkage success across seven myeloma trials (>98%), and strong patient-level agreement between trial-collected and registry-derived mortality data. Across Phase III trials agreement was excellent (Cohen's Kappa ranging from 0.81 to 0.96) while levels of agreement were lower in Phase II trials (Kappa ranging from 0.50 to 0.61). Dates of death were closely aligned (median difference 0 days; 96% within ± 7 days). Trial-level analyses showed that registry-based survival closely matches trial-derived estimates with similar median overall survival; Myeloma XI trial-derived 74 months (95%CI 71–77)

vs registry-derived 75 months (95%CI 71–78). Ongoing work will examine recorded cause of death and estimate specific treatment comparisons significantly extending follow-up time beyond the original trial period. **Conclusions:** National death data enables estimation of overall survival without the need for trial-specific data collection. Lower levels of agreement were found for early phase studies where the focus is on earlier endpoints. The BLISS project will assess evidence required for additional HSD-derived outcomes including treatment on and post-trial, line of treatment, second cancer incidence, adverse events including infection, fracture, venous thromboembolism and cardiovascular disease. These findings will inform prospective trial design and provide a cost-effective means for clinical trial follow-up.

PA-187

Evaluation of the Hevylite Test as a Prognostic Factor and Its Association with Infections in Patients with Multiple Myeloma

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Introduction: Multiple myeloma is a heterogeneous disease in which evaluation of patient prognosis is essential. Among various variables evaluated, Hevylite, through his ratio (Rhlc) was identified as an independent prognostic factor. In addition, the suppression of the uninvolved light chain (uHLC) is also associated with a higher incidence of infections through the evaluation of uninvolved light chain suppression. The primary aim is to evaluate the impact of Hevylite as an isolated prognostic factor on the median survival of patients. Secondarily, to assess the association between the suppression of the uHLC and the incidence of infections. **Methods:** This is a prospective cohort with 103 patients during the period from February 2022 to December 2024 at three centers:Clínica São Germano, Santa Casa de São Paulo e Hospital Alemão Oswaldo Cruz, with newly or relapsed multiple myeloma of the heavy chain type, with collection time prior to the start of the current line of treatment. A blood sample was collected from all patients included at the time of enrollment. Data collection was carried out through medical record review. **Results:** Of the total patients, 72.8% were newly diagnosed and 27.2% were relapsed. Regarding newly diagnosed patients, rHLC showed a statistical difference, with overall survival not reached in patients below the median ratio and 34.1 months above the median ratio (hazard ratio 0,41). Regarding relapsed patients, there was no statistical difference. Regarding the incidence of infections, among newly diagnosed patients with > = 50% suppression of uHLC, 87.8% had at least one recorded infection, compared to 31.2% without suppression ($P < 0.001$). Among newly diagnosed patients with and without >95% uHLC suppression, the incidence of infection was 100% and 51.7%, respectively. Focusing on bloodstream infections, when evaluating newly diagnosed patients with and without > = 95% uHLC suppression, the incidence was 68.8% and 19%, respectively. **Conclusions:** The isolated prognostic role of rHLC showed a difference in median overall survival, demonstrating its importance as a prognostic fator. Suppression of uHLC was associated with a higher incidence of infections in newly diagnosed multiple myeloma patients, showing the importance of identifying these patients for better management.

PA-188

Evaluation of Triple-Class Exposed Patients in a Brazilian Referral Center

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Introduction: Over the past 20 years, advances in the understanding of disease biology and the development of novel therapies have revolutionized the management of multiple myeloma (MM). Despite these advances, most patients eventually relapse and become refractory to the main drug classes available, including immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies. Patients are defined as triple-class refractory when refractory to all three classes and triple-class exposed when previously exposed but not necessarily refractory. These populations have poor outcomes and represented a major unmet need before the advent of T-cell redirecting therapies. **Methods:** This was a single-center retrospective observational study conducted in São Paulo, Brazil. Data were collected from triple-class exposed MM patients followed at São Germano Clinic between January 2000 and July 2025. The study evaluated demographic and clinical characteristics, subsequent treatments after triple-class exposure, and clinical outcomes. **Results:** A total of 95 patients were included, of whom 67 became triple refractory during follow-up. Median age at diagnosis was 57 years, and 55.8% were female. Triple exposure occurred in the second line in 29.5% of patients, third line in 24.2%, and fourth line in 20%. At triple exposure, 46.3% were triple refractory and 3.2% penta refractory. Median overall survival (OS) from triple exposure was 26.7 months (median follow-up 28 months). Eighty-four patients received subsequent treatment, including 32.1% in clinical trials and 23.8% with novel-target therapies (anti-BCMA ADCs, anti-BCMA bispecific antibodies, and CELMoDs). Median OS from triple refractoriness was 17.8 months (median follow-up 36 months). Among patients receiving further therapy, 44% were treated with agents targeting new mechanisms of action, and 33.9% were enrolled in clinical trials. Among penta-refractory patients, 70.6% were classified as such because of refractoriness to both thalidomide and lenalidomide, reflecting limited access to lenalidomide in the Brazilian public healthcare system. Median OS in this group was 8.1 months,

and 35.6% received therapies with novel targets. **Conclusions:** This study describes the clinical characteristics and outcomes of triple-class exposed patients in a Brazilian referral center. Differences from global reports were observed, particularly those related to limited access to key therapies, including lenalidomide in the public healthcare system.

PA-189

Evolution of Functional Status in Non-Transplant-Eligible Patients with Multiple Myeloma During First-Line Treatment

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Introduction: Multiple myeloma incidence increases with age. Frailty associates with toxicity, treatment discontinuation, and poorer survival. The IMWG developed a frailty score, but functional status is dynamic and changes during treatment due to response, toxicity, or complications. This study evaluated functional status evolution during first-line treatment and identified factors associated with change. **Methods:** This was a Multicenter, retrospective study of NTE patients treated (2020–2025) at two tertiary centers. Functional status was evaluated using the simplified IMWG scale at baseline, 3, and 6 months. Worsening/improvement was defined as any score change between time points. Analysis used SPSS (Fisher's exact test for dichotomous variables; Mann-Whitney U test for continuous variables). **Results:** Analysis included 63 elderly patients (median age 80 [77–83]) with high baseline frailty (median Charlson: 5 [4–6]; ECOG: 1 [0–1]; IMWG: 3 [2–4]); 84.1% were frail at baseline. For treatment comparison, 59 patients were analyzed (4 excluded due to incomplete follow-up): 30 with anti-CD38 regimens and 29 without anti-CD38. No baseline differences existed between groups regarding age, Charlson, ECOG, IMWG score (3 [2–4]), or baseline frailty proportion (83.3%). Worsening from baseline to 3 months was low and similar between groups. From baseline to 6 months, worsening was numerically lower with anti-CD38 ($p > 0.05$). Notably, between 3 and 6 months, IMWG score worsening was significantly less frequent with anti-CD38: 3.3% (1/30) vs. 24.1% (7/29) without anti-CD38 (OR 0.11; 95% CI 0.01–0.95; $p = 0.026$). Discontinuation was similar (36% vs. 40%; $P = 1.000$). A trend toward greater functional improvement was observed with anti-CD38. **Conclusions:** Functional status exhibits a dynamic evolution during first-line therapy. In this elderly, frail cohort, anti-CD38 regimens were not associated with higher discontinuation or greater early IMWG score worsening, particularly between months 3 and 6. Results highlight the importance of longitudinal functional assessments over baseline-only evaluations. Findings require cautious interpretation due to limited sample size, retrospective design, and the availability of more precise alternative scoring systems.

PA-190

Expansion and Identification of Neoantigen-Reactive T Cells in Newly Diagnosed Multiple Myeloma Enrolled in the UKMRA Cardamon Trial

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Introduction: We and others have recently identified a tumour-reactive signature of CD8+ T cells, making up only 1% of bone marrow lymphocytes. Neoantigens from mutations have been predicted in silico, but specific reactivity and cytotoxicity have not been demonstrated ex vivo. The low frequency of reactive T cells together with the subclonality of mutations in myeloma pose technical challenges to identifying antigen-specific responses. We aimed to develop a platform for studying antigen specific T cell responses from myeloma patient material. **Methods:** Cardamon was a Phase II study of deferred ASCT in NDMM. Diagnostic bone marrow cells were selected for CD138+ and sent for whole exome sequencing. Marrow infiltrating lymphocytes (MIL) were obtained from CD138− negative fraction and stimulated with ImmunocultTM anti-CD3/CD28 stimulant and anti-CD137. Cytokines and media were replenished every 2 days for up to 14 days. Flow cytometry was used to assess T cell lineage, activation, and exhaustion markers. Degranulation and cytokine profiles were assessed following 6 hours of artificial stimulation with functional readouts of CD107a+, GZMB+, and IFNg+. To create model antigen-presenting cells, CD19+ B cells from patient peripheral blood were immortalised with BCL-6/BCL-XL and transduced with the sequence of predicted mutated peptides. MILs were co-cultured with immortalised B cells overnight then stained with a T cell reactivity panel, or further cultured for a total of 3 days, after which samples underwent amplicon sequencing and depletion of B cells was measured by fold change from the B cells alone. **Results:** We were able to expand T cells from bone marrow aspirates (40-fold over 10 days, doubling time of 48 hours). Our novel method ensured support for CD8 T cell growth while showing similar rates of CD4 division without outgrowth, allowing a diverse population for downstream assays. Baseline phenotypes showed only 1–3% of CD8+ T cells are double positive for PD-1 and CD39 antigen-experience markers. After expansion, most MILs possessed an effector phenotype, with 80% of MILs positive for activation markers CD69 and CD25. Meanwhile, MILs did not upregulate exhaustion or senescence

markers TIGIT and KLRG1. We observed degranulation (CD107a), IFNg and GZMB production in response to both artificial PHA and antigenic stimulation. Upon co-culture with immortalised B cells expressing mutated neoantigen sequences, MILs were enriched in reactivity and cytotoxic markers by flow cytometry above background to control B cells, and specific cytotoxicity of neoantigen targets was demonstrated in a depletion killing assay (log2FC <−2, log10CPM > 2). **Conclusions:** Our platform expands tumour-reactive MILs that possess an activated effector phenotype with low expression of exhaustion markers, ability to degranulate and specific cytotoxicity of neoantigen targets. This will enable greater understanding of the role of tumour reactivity in disease, with the potential for screening for novel antigens.

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Exploiting a Novel Molecular Glue for High-Resolution Cryo-EM Structural Mapping of the Native Human Immunoproteasome-PA28α/β Activator Complex

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Introduction: Proteasomes are highly sophisticated, protein-degrading machines that execute the selective, efficient, and processive hydrolysis of client proteins. Dedicated tissues involved in immune responses contain a population of proteasome variants, designated immunoproteasomes. The peptide output from immunoproteasomes is strongly influenced by the endogenous activator PA28α/β, a heteroheptameric complex that docks directly on immunoproteasomes and modulates peptide generation. However, until recently isolation and characterization of the native, human immunoproteasome bound to the PA28a/b activator complex has been challenging and limited structural and molecular characterization. Here, we devised a method using molecular glues (MGs) to stabilize the native complex and study the effect on MHC class I (MHC-I) antigen presentation on multiple myeloma (MM) cells. **Methods:** High-throughout screens of a 9,600 HDAC-based compound library identified novel, proprietary molecules that specifically increased immunoproteasome activity in MM cells. Co-immunoprecipitation and gel filtration characterized the effect of MG on the binding of PA28a/b to immunoproteasomes. Mass-spectroscopy immunopeptidomics determined the effect of MG on MHC-I antigen presentation on MM patient tumor cells. Annexin staining and flow cytometry determined the effect of MG on the cytotoxic activity of allogeneic, autologous, and TCR-engineered T cells. Cryogenic electron microscopy (cryo-EM) allowed mapping of the three-dimensional atomic architecture of the immunoproteasome alone and complexed with the PA28a/b activator. **Results:** We identified a novel molecule (compound A) that functions as a MG to increase binding of the PA28a/b activator with immunoproteasomes. Immunoproteasomes affinity-purified from compound A-treated MM cells preferentially cleaved peptides that terminated in Phe, Leu, Tyr, Lys, or Arg. MS-based immunopeptidomics revealed that compound A treatment of MM patient tumor cells increased the relative frequency of MHC-I-bound peptides that terminated in Leu or Lys. Moreover, compound A treatment of MM cells increased the presentation of canonical, non-canonical, and human endogenous retrovirus-derived MHC-I-bound peptides >100-fold relative to untreated cells. Compound A treatment of tumor cells isolated from HLA-A*02:01-restricted patients significantly increased the antimyeloma activity of T-cells engineered to express an NY-ESO-1-specific T-cell receptor. **Conclusions:** Taken together, compound A is a MG that increases immunoproteasome generation of peptides that terminate in large hydrophobic or basic residues to expand the repertoire of MHC-I antigens. Pharmacologics that modulate immunoproteasome-dependent antigen presentation represent a paradigm-shifting strategy to bolster the efficacy of autologous and engineered T-cell engaging immunotherapies. High resolution structural definition of the immunoproteasome-PA28a/b complex active and allosteric sites enables rational optimization of MG analogs.

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Exploiting Synthetic Lethality to Target Proteasomal Adaptations That Trigger p97-Dependent Bortezomib Resistance in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a treatable, but incurable, plasma cell malignancy characterized by unpredictable variability in patient outcomes. The aim of the present study was to analyze genomic profiles from multiple MM patient pre-treatment tumor samples to identify predictive classifiers of clinical response and survival following single-agent bortezomib therapy and to then target key actionable classifiers that underly mechanisms of bortezomib resistance. Proteasomes consist of a 20S catalytic core particle (CP), a 19S regulatory particle (RP) comprised of PSMC and PSMD-encoded subunits, as well as accessory proteins that assist the proteasome in assembly, substrate recognition, and degradation. **Methods:** Gene expression profiles obtained from MM patients enrolled in the APEX and CoMMpass trials were analyzed to identify proteasomal genes that correlated with treatment response, PFS and OS. A pharmacologic screen identified drugs that were synthetic lethal in MM cells engineered to overexpress PSMC2. In vivo efficacy of the p97 ATP active site-directed inhibitor CB-5339 was performed by injected mice with MM cells that overexpressed PSMC2. Tumor volume was determined using bioluminescent imaging. **Results:**

Proteasome PSMC2 messenger RNA were higher in MM cells from bortezomib-resistant patients and PSMC2 expression correlated with progression-free and overall survival after bortezomib therapy. Pharmacologic screens revealed that treatment with of MM cells with CB-5339, an ATP-competitive inhibitor of the molecular chaperone p97/VCP that shuttles ubiquitinated substrates to proteasomes, was synthetic lethal in MM cells engineered to overexpress PSMC2. PSMC2-overexpressing cells were also exquisitely sensitive to CB-5339 upon p97 genetic ablation. Proteasomes affinity-purified from PSMC2-overexpressing cells exhibited higher catalytic activity and reduced sensitivity to bortezomib relative to controls. Bortezomib treatment of PSMC2-KO cells, but not PSMC2-overexpressing cells, followed by in-situ cross-linking revealed K48- and K-63-linkage-specific polyubiquitin chains covalently attached to affinity-purified proteasomes. PSMC2-KO impaired assembly of the mature proteasome complexes, while PSMC2-overexpression promotes association of PSMC2 with PSCM1, PSMD2 and the assembly factor PSMD5. Co-treatment with CB-5339 and bortezomib synergistically targeted myeloma cells obtained from clinically-relapsed patients and reduced the growth of PSMC2-overexpressing myeloma xenografts in mice. **Conclusions:** Taken together, we discovered a genetic vulnerability that provokes proteasome-intrinsic bortezomib resistance and validate the potential of synthetic lethal interactions to guide therapeutic interventions. Efficacy and safety of CB-5339 were validated in multiple MM models and support the clinical testing of CB-5339 in combination with standard of care therapy. Our study affirms that transcriptomic heterogeneity in myeloma cells is a primary driver of prognostic variability.

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Extrachromosomal DNA Shapes Aggressive Transcriptional States in Multiple Myeloma

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Introduction: Extrachromosomal DNA (ecDNA) is increasingly recognized as a key driver of oncogene amplification, intratumoral heterogeneity, and poor clinical outcomes across solid tumors. However, its significance in multiple myeloma remains largely unexplored. Multiple myeloma is characterized by marked genomic instability including hyperdiploidy or IgH translocations, and widespread structural rearrangements that underlie biological heterogeneity and therapy resistance. Defining whether ecDNA contributes an additional layer of genomic complexity in this disease therefore represents an important unmet need. **Methods:** Whole-genome sequencing (WGS) BAM files of patient tumor samples from the Multiple Myeloma Research Foundation (MMRF) CoMMpass study were analyzed using the AmpliconSuite pipeline to identify circularized DNA amplicons indicative of ecDNA. Matched transcriptome (RNA-seq) data and clinical metadata from the same cohort were integrated to evaluate the prognostic impact of gene expression associated with ecDNA-harboring loci. Gene Set Enrichment Analysis (GSEA) was performed using the clusterProfiler R package to assess pathway-level biological signatures linked to ecDNA-positive tumors. **Results:** We identified ecDNA in 28 of 904 patients (3.1%) from the MMRF CoMMpass dataset. Despite the low prevalence, ecDNA-positive myeloma patients exhibited significantly inferior survival compared with patients without ecDNA. Frequently amplified ecDNA loci contained oncogenes such as MYC, TNFRSF17 (BCMA), and SNX29, as well as pro-tumoral lncRNAs including CASC11 and PVT1. GSEA revealed strong enrichment of MYC and E2F targets, oxidative phosphorylation, and PI3K–AKT–mTOR and mTORC1 signaling in ecDNA-positive tumors, highlighting transcriptional addiction and metabolic activation. These pathways align with known mechanisms of proliferation, metabolic rewiring, and treatment resistance in multiple myeloma. **Conclusions:** ecDNA-positive myeloma represents a biologically aggressive subset characterized by oncogene-enriched circular amplicons and hyperactivated proliferative and metabolic programs. Myeloma patients with ecDNA showed significantly worse survival, supporting ecDNA as a previously underrecognized high-risk feature. These findings highlight ecDNA as potential therapeutic vulnerabilities in myeloma and warrant further investigation.

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Extramedullary Disease in Newly Diagnosed Multiple Myeloma: Real-World Evidence from a Latin American Referral Center

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Introduction: Extramedullary disease (EMD) at diagnosis of multiple myeloma (MM) is an uncommon manifestation associated with aggressive disease biology and inferior outcomes. Data regarding the clinical characteristics and treatment outcomes of patients with newly diagnosed multiple myeloma (NDMM) and true extramedullary involvement are scarce, particularly in Latin America. We describe the baseline characteristics and early treatment outcomes of NDMM patients presenting with EMD at a tertiary referral center. **Methods:** We conducted a single-center retrospective cohort study including consecutive adults with confirmed NDMM diagnosed between November 2024 and January 2026 who had evidence of EMD on baseline PET-CT. Patients with paramedullary disease were excluded. Data was extracted from medical records. Responses were classified according to IMWG criteria based on the best documented response after induction therapy. Descriptive statistics were used.

Results: Seventeen patients were included. Median age was 52.3 years (range, 37–78), and 11 patients (64.7%) were male. Lymph node involvement was the most frequent site of EMD, observed in 11 patients (64.7%), followed by lung/pleural involvement in 5 (29.4%) and thyroid involvement in 2 (11.8%). Less common sites included the heart, stomach, testicle, central nervous system, nasopharynx, oropharynx, spleen, and liver (one patient each). Patients presented with 1 to 5 extramedullary sites at diagnosis, with lesion sizes ranging from 8 to 174 mm and SUVmax values ranging from 2.3 to 8.7 on PET-CT. Flow cytometry of bone marrow aspirates demonstrated loss of CD56 expression in 6 patients (35.3%). EMD co-occurred with osteolytic bone disease in all patients (100%), renal impairment in 6 (35.3%), anemia in 7 (41.2%), and hypercalcemia in 1 patient (5.9%). The cohort exhibited several additional high-risk features, including ISS stage III disease in 12 patients (70.6%), high-risk cytogenetics in 4 (23.5%) and bone marrow plasma cell infiltration >60% in 4 (23.5%) of patients. Two patients died before initiation of therapy. Among the 15 patients who received induction treatment, 9 (60%) received a daratumumab-containing regimen. The overall response rate (partial response or better) was 80% (12/15). Despite treatment, 3 patients (20%) experienced primary refractory disease with documented progression after only 2, 3, and 4 months of induction therapy, respectively. **Conclusions:** Patients with NDMM and true extramedullary disease in this real-world Latin American cohort were younger than typically reported for MM and frequently exhibited additional markers of aggressive disease. Although most patients achieved an initial response to induction therapy, a substantial proportion experienced early disease progression, underscoring the unfavorable biology of EMD and the need for optimized treatment strategies and closer disease monitoring in this high-risk population.

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Extramedullary Plasma Cell Dyscrasias Mimicking Solid Tumors: A Single-Center Case Series of Unusual Myeloma Presentations

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Introduction: Extramedullary multiple myeloma (EMM) represents a biologically aggressive form of plasma cell dyscrasia associated with high-risk cytogenetics, treatment resistance, and inferior survival outcomes. EMM frequently presents outside the bone marrow compartment, diagnosis may be delayed when lesions mimic solid tumors or non-hematologic malignancies. **Methods:** We performed a retrospective review of patients diagnosed with plasma cell dyscrasias presenting with unusual extramedullary manifestations at a single tertiary care center. **Results:** Case 1 involved a 68-year-old man presenting with chest pain, weight loss, and an enlarging parasternal mass initially concerning for anterior mediastinal malignancy. CT demonstrated an 8.2 × 6.5 cm mediastinal/chest wall lesion with contiguous sternal involvement. Laboratory evaluation revealed a 6.4 g/dL IgG kappa M-spike, serum viscosity of 5.2 cP, and bone marrow involvement by 72% clonal plasma cells with gain 1q and deletion 13q. Biopsy confirmed IgG4-restricted plasmacytoma. The patient developed dialysis-dependent renal failure and hyperviscosity syndrome requiring emergent plasmapheresis followed by daratumumab-RVd. Case 2 involved a patient presenting with painless jaundice, early satiety, and weight loss secondary to a 4.9 cm pancreatic head mass with biliary obstruction and FDG-avid retroperitoneal lymphadenopathy initially suspicious for pancreatic adenocarcinoma. CA 19-9 was minimally elevated, while SPEP demonstrated an IgA kappa monoclonal protein. Endoscopic ultrasound-guided biopsy revealed CD138-positive kappa-restricted plasmacytoma, and bone marrow biopsy confirmed systemic multiple myeloma with high-risk cytogenetics including t(4;14). Following biliary decompression, the patient initiated daratumumab-CyBorD with partial radiographic response. Case 3 involved isolated CNS relapse following prior BCMA-directed therapy in a patient previously considered in serologic complete remission. The patient developed headaches, diplopia, and gait instability. MRI brain and spine demonstrated diffuse leptomeningeal enhancement without systemic FDG-avid disease on PET/CT. CSF cytology and flow cytometry confirmed clonal plasma cells despite negative SPEP, negative immunofixation, and hypocellular marrow without overt plasma cell progression. The patient required high-dose steroids, intrathecal chemotherapy, and salvage teclistamab-based therapy. **Conclusions:** This series highlights the diverse and deceptive manifestations of extramedullary plasma cell dyscrasias. Recognition of atypical relapse patterns is increasingly important in the era of BCMA-directed therapies, where progression may occur outside the marrow compartment despite apparent systemic remission.

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Extrapolated Progression-Free Survival With Belantamab Mafodotin/Lenalidomide/Dexamethasone (BRd) Exceeds 7 Years in Intermediate-Fit and Frail, Transplant-Ineligible, Newly Diagnosed Multiple Myeloma

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Introduction: Belantamab mafodotin (belamaf) is a BCMA-targeting antibody-drug conjugate that is approved in triplet regimens

for relapsed/refractory multiple myeloma (RRMM) based on robust efficacy vs standards of care (SOC) in the DREAMM-7/DREAMM-8 trials. In a phase 1/2 study (NCT04808037), the tolerability/efficacy of BRd in patients (pts) with transplant-ineligible newly diagnosed MM (TI-NDMM) who were intermediate-fit or frail was evaluated. BRd showed substantial clinical activity (median progression-free survival [mPFS] not reached [NR] at median follow-up [mFU] 28.8 months). Anti-CD38-based regimens (daratumumab + lenalidomide + dexamethasone +/− bortezomib [DRd and DVRd]; isatuximab + VRd [IsaVRd]) are SOC for TI-NDMM based on the MAIA, CEPHEUS, and IMROZ trials. Given the transformational efficacy of belamaf-based regimens in RRMM, including superiority vs DVd, there is interest in understanding long-term PFS of different dose levels in the NDMM setting. **Methods:** At analysis cutoff (March 15, 2026, NCT04808037), individual pt-level data from 66 pts were used to model predicted mPFS of BRd using the overall cohort (2.5/1.9/1.4 mg/kg every 8 weeks [Q8W], mFU 40.7 months) and a 1.9 mg/kg Q8W-only cohort (mFU 37.0 months). Modeling was performed using standard parametric distributions for survival analysis including exponential, Weibull, log-logistic, log-normal, and gamma distributions. Goodness-of-fit was assessed relative to Kaplan-Meier plots, and via standard methods including Akaike Information Criterion and the Bayesian Information Criterion scores. **Results:** A total of 19 PFS events occurred among 66 pts, (4 COVID-19-related). Predicted mPFS overall ranged from 85.5–110.0 months. In the 1.9 mg/kg-only cohort, there were 11 PFS events among 42 pts, (1 COVID-19-related). Predicted mPFS for the 1.9 mg/kg cohort ranged from 87.6–110.7 months. **Conclusions:** Model-predicted mPFS (based on survival extrapolation) of BRd in TI-NDMM (87.6–110.7 months for 1.9 mg/kg-only cohort and 85.5–110.0 months overall) was longer than the reported mPFS for the triplet (DRd: mPFS 61.9 months at 64.5 months mFU) and comparable to that expected for the quadruplets (DVRd: 96–118 months; IsaVRd: 90 months). All pts were intermediate-fit or frail, highlighting the importance of these results in this population with unmet need. Within the analytical limitations (small sample size, small numbers at risk at later timepoints in Kaplan-Meier analyses, and duration of FU), predicted mPFS in the combined cohorts and the 1.9 mg/kg-only cohort was similar, suggesting potential for high efficacy with BRd for TI-NDMM. BRd using a 1.9 mg/kg belamaf dose is being evaluated further for TI-NDMM in the phase 3 DREAMM-10 trial. **Funding:** Supported by GSK.© 2026 European Hematology Association (EHA). Reused with permission. Parts of this abstract were previously accepted and presented at the 2026 EHA Annual Meeting. All rights reserved.

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Feasibility and Efficacy of Intensive Chemotherapy-Based Holding and Bridging Therapy Prior to BCMA CAR-T Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: BCMA-CAR-T cell therapy (CAR-T) is highly effective in relapsed/refractory multiple myeloma (RRMM). Holding and Bridging Therapy (HT/BT) is administered to control disease and reduce tumor burden (TB) prior to infusion. High TB is a driver of severe CAR-T toxicities including CRS, ICANS and movement/neurocognitive disorders. Chemotherapy-based HT/BT (C-HT/BT) has been discussed controversially. While real-world data suggested inferior PFS and increased risk for hematological toxicities with alkylator-based bridging and impairment of CAR-T manufacturing, emerging data indicate that achieving effective disease control is a critical determinant of CAR-T efficacy and toxicity. The role of PACE-like regimens as intensive cytoreductive HT/BT in high-TB patients (pts) remains insufficiently characterized. **Methods:** 88 RRMM pts receiving CAR-T at a single center were retrospectively analyzed. 16 pat. received intensive chemotherapy (IC) with PACE-like regimens as HT and/or BT Responses were separated into deep (≥VGPR) and suboptimal responders (< VGPR) per IMWG criteria. Impact of HT on CAR-T manufacturing and safety outcomes were assessed. **Results:** Of 88 pts who received BCMA-directed CAR-T cell therapy, 18 (19%) received IC as holding and/or bridging therapy. Eight pts received IC as HT and nine as BT alone, with three receiving IC in both settings. Regimens included VdT-PACE (n = 6), Kd-PACE (n = 4), (P)ACE-based combinations (d-ACE, d-PACE, P-PACE, mini-PACE; (n = 5)), IsaKd-PACE and a Selinexor-based regimen (SVd-PACE). ORR to IC-based HT/BT was 76% (≥VGPR 41%, disease control rate 88%), reflecting effective cut-reduction despite high baseline tumor burden. EMD was present in 24% of the overall cohort, markedly enriched in the PACE-like subgroup (53%); 43% of all EMD pts had received IC-based therapy. CAR-T manufacturing was successful in all patients receiving IC as HT (8/8, 100%). Deep response to HT/BT (≥ VGPR) was consistently associated with improved post-CAR-T toxicity. In the IC subgroup, deep responders (n = 7) had lower rates of CRS ≥ grade 2 (14% vs 50%), no CRS grade 3 (0% vs 20%), lower ICAHT ≥ grade 2 (29% vs 40%), and less overall toxicity ≥ grade 3 (14% vs 50%) compared to suboptimal responders (n = 10). CAR-T ORR was 100% in deep responders vs. 80% in suboptimal responders. **Conclusions:** IC with PACE-like regimens was applied preferentially in high-TB/EMD pts and achieved a CAR-T ORR of 90%. Achieving ≥ VGPR was

consistently associated with substantially reduced CAR-T toxicities. IC prior to lymphocyte apheresis did not impair CAR-T manufacturing or CAR-T efficacy. Optimal TB reduction mitigates toxicity, making IC feasible strategy in high TB RRMM pts.

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Feasibility and Safety of Outpatient Bispecific Antibody Administration in Multiple Myeloma: A Single-Center Experience

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Introduction: Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are complications of bispecific antibody (BsAb) step-up dosing (SUD) that require hospitalization. Since 2022, our At-Home Hematology Unit (HHU) has provided support to these patients. The increasing number of procedures performed by the HHU required new alternatives, leading to the implementation in 2025 of an outpatient BsAb administration pathway for multiple myeloma (MM) patients. This pathway allows outpatient administration during SUD and early management of toxicities, without mandatory hospitalization. The aim of this study was to describe our experience with BsAb administration in MM by comparing 3 models used during the SUD phase, focusing on outpatient administration and evaluating its efficacy and safety. **Methods:** Patients with MM treated with BsAbs between February 2022 and May 2026 were analyzed. Patients were classified according to the care model used during the SUD phase: inpatient, outpatient, or mixed. Demographic and clinical variables, type of BsAb, CRS and ICANS characteristics, need for hospitalization, and duration of hospitalization were analyzed. **Results:** Fourteen patients received SUD as inpatient, 5 under a mixed model, and 6 as outpatient. Among the inpatient group, 5 patients were enrolled in a clinical trial (CT) that did not allow outpatient administration; the remaining 9 did not meet the inclusion criteria for the outpatient pathway. In patients in the mixed group, the first two step-up doses were administered as inpatient, whereas the remaining doses were administered in the outpatient setting. CRS rates were similar across the different care models, occurring in 57%, 60%, and 50% of patients in the inpatient, mixed, and outpatient groups, respectively. However, recurrent CRS occurred only in the inpatient group (37.5%), supporting the ability of the outpatient program inclusion criteria to identify patients at higher risk of complications. No patient in the mixed or outpatient groups required readmission due to CRS. Most CRS events occurred after the first step-up dose. Tocilizumab was the preferred treatment for CRS, being administered in 62% of inpatients and 67% of patients in both the mixed and outpatient groups. Dexamethasone was used in 12% of inpatients and 33% of outpatients. This early intervention at the first CRS event likely also contributed to the low readmission rates observed in the mixed and outpatient groups. Shorter hospitalization durations were observed in the mixed group compared with the inpatient group, with median stays of 8 and 11 days, respectively. No patient developed ICANS. **Conclusions:** Our experience with outpatient BsAb administration demonstrates that it is a safe and effective procedure. It requires specific assessment and treatment pathways that enable optimization of hospital resources and improve patients' quality of life.

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First Results of a Noninterventional, Prospective, Postauthorization Safety Study (PASS) of Ciltacabtagene Autoleucel (Cilta-cel) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Cilta-cel is approved (US, EU, Brazil, and other countries) for treating pts with RRMM post ≥1 prior lines of therapy (pLOT). This PASS (EUPAS49370)—a prospective, noninterventional, ongoing study—evaluates safety and effectiveness of cilta-cel in real-world (RW) settings in Europe and Brazil. **Methods:** Pts who have undergone apheresis to receive commercial cilta-cel and provided written informed consent are enrolled consecutively. Follow-up (FU) time is 15 y from infusion. 300 pts will be enrolled to assess short- and long-term safety and effectiveness of cilta-cel. **Results:** This first analysis included 106 pts infused with cilta-cel (24 June 2024–19 November 2025; 86.8% in Germany, 9.4% in Brazil, 3.8% in Austria). At data cut-off (27 February 2026), median (m) FU was 7.95 mo. mAge was 64 y; 29.2% ≥70 y. 22 (20.8%) pts received holding therapy. mpLOT was 2, and 57 (53.8%) pts had 1–2 pLOT. 15/50 (30.0%) pts had high-risk cytogenetics; 29/82 (35.4%) had stage III disease (by International Staging System [ISS] or Revised-ISS); 2/106 (1.9%) had extramedullary disease. 80 (75.5%) pts had bridging therapy (BT; mBT 6.4 wk); common BT agents were

dexamethasone (67.5%), carfilzomib (42.5%), daratumumab (33.8%), talquetamab (26.3%), and pomalidomide (21.3%). 42 pts had post-BT response data, 31 (73.8%) had ≥partial response to BT. 105 (99.1%) pts had ≥1 adverse events (AEs). Most common AEs were cytokine release syndrome (61.3%; grade [G] 3/4 0.9%), infections (47.2%; G3/4 17.0%; G5 2.8%), neutropenia (25.5%; G3/4 20.8%), and hypogammaglobulinemia (19.8%; all G1/2). 38 (35.8%) pts had serious AEs. 11 (10.4%; G3/4 0.9%) pts had immune effector cell–associated neurotoxicity syndrome (ICANS). Cranial nerve palsies occurred in 15 pts (14.2%; G3/4 4.7%); 2 (1.9%) pts with ≥3 pLOT had G3 parkinsonism (both ongoing at data-cut); 1 of the 2 had primary refractory disease. No hematologic second primary malignancies; 1 gastric carcinoma and 2 nonmelanoma skin cancers occurred (each n = 1). 9 (8.5%) pts died, 8 due to AEs and 1 due to disease progression. 6-mo progression-free survival and overall survival were 93.7% (95% CI 85.1–97.4) and 94.9% (88.0–97.8). **Conclusions:** Initial results of this RW PASS demonstrate cilta-cel outcomes in Europe and Brazil were comparable with clinical trial results. Safety was consistent with known cilta-cel safety profile. Half of pts received cilta-cel after 1–2 pLOT, supporting using cilta-cel as standard of care for RRMM in early LOT. **Acknowledgments:** This study was funded by Johnson & Johnson, and Legend Biotech USA Inc. Medical writing support was provided by Shuang Li, PhD, CMPP, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, and funded by Johnson & Johnson and Legend Biotech USA Inc.

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First-in-Human Phase 1 Study of RD140, a Fully Human BCMA/GPRC5D Dual-Targeting FasT CAR-T, in Relapsed/Refractory Multiple Myeloma (RRMM) and Plasma Cell Leukemia (PCL)

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Introduction: RD140 is a novel dual-targeting CAR-T cell therapy incorporating two fully human single-domain antibody fragments directed against BCMA and GPRC5D and manufactured using the FasT CAR-T platform. Here, we report preliminary findings from the first-in-human phase 1 study of RD140 in patients(pts) with RRMM and PCL (NCT06655519). **Methods:** RRMM pts who had received at least three prior lines of therapy and PCL who had received one line therapy with progressive disease were eligible. Pts with extramedullary disease (EMD) or prior exposure to BCMA-targeted therapy were permitted. The FasT CAR-T platform completed cell manufacturing within 3–4 days successfully. Following lymphodepletion with cyclophosphamide 500 mg/m2 and fludarabine 30 mg/m^2 for three consecutive days, RD140 was administered as single infusion at 2 dose levels (DL) of 1 × 10 5 cells/kg (DL1, n = 3) or 3 × 10 5 cells/kg (DL2, n = 6). Primary endpoint was incidence and severity of adverse events. Secondary endpoints included overall response rate (ORR), progression-free survival(PFS), minimal residual disease (MRD)-negative rate by flow cytometry at a sensitivity of 10^{-5}, pharmacokinetics(PK), and pharmacodynamics. **Results:** A total of 9 pts (44.4% male; median aged 65 years [range, 54–72]) received RD140 infusion, comprising 8 with RRMM and 1 with PCL. 6 pts had high-risk cytogenetic abnormalities (per the mSMART 3.0 criteria), including 33.3% with two high-risk cytogenetic abnormalities. 2 pts had EMD and 2 had received prior BCMA targeted therapy. All 9 pts were triple-class exposed, and 6 were penta-class exposed. As of May 6, 2026 data cutoff, with a median follow-up of 6.05 months (range: 3.0–11.5), the overall ORR was 88.9%, and the ORR in DL2 was 100%. Overall stringent complete response (sCR) rate was 55.6%, and sCR rate in DL2 was 66.7%. 8 pts (88.9%) achieved MRD negativity by flow cytometry at a sensitivity of 10–5, of which 6/8 pts achieved MRD negativity by day 28. Median PFS were not reached. The most common treatment-emergent AEs were cytopenia, hypokalemia and hypofibrinogenemia. Cytokine release syndrome (CRS) occurred in all pts; 8 of 9 were grade 1–2, and 1 was grade 3. The median time to CRS onset was 4 days (range, 2–8), and the median duration of 5.3 days (range, 4–13). No neurotoxic effects or ICANS were observed. PK analyses showed the median time to peak expansion was d15 (range, 8–22), and the median peak transgene copy number was 112981.7 copies/μg DNA (range, 48367.13–299955.7). The median AUCd0-d28 was 1362589.91 (range, 351788.0, 2120685.5) Day × Copies/μg DNA. Soluble BCMA was cleared within 1 month post infusion in all 9 pts. **Conclusions:** The current data demonstrated that BCMA/GPRC5D dual-targeting FasT CAR-T RD140 provide deep responses and a very high MRD negativity rate with a favorable safety profile, including in RRMM pts exposed to anti-CD38, PI and IMiDs. Further evaluation in a larger patient population with longer follow-up is warranted.

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First-Line Anti-CD38-Based Quadruplet Induction in Transplant-Eligible Newly Diagnosed Multiple Myeloma: Real-World Results from the Argentine Multiple Myeloma Group (GAMM)

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Introduction: Anti-CD38-based quadruplet regimens have become a standard induction strategy for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). However, real-world data on their use and outcomes in Argentina remain scarce. **Methods:** This retrospective study included NDMM patients from 12 Argentine centers (GAMM) treated with first-line anti-CD38-based induction and planned ASCT. PFS and OS were estimated from anti-CD38 initiation using Kaplan–Meier methods. **Results:** A total of 193 patients were included. Median age was 59 years (IQR, 51–65), 47% were female, and 92% had ECOG PS 0–1. IgG was the most frequent isotype (55%) and kappa the predominant light chain (66%). CRAB features included lytic bone lesions in 154 patients (80%), anemia in 126 (65%), renal failure in 47 (24%), and hypercalcemia in 34 (18%). Elevated LDH was present in 32 patients (17%), R-ISS III in 41 (21%), extramedullary plasmacytomas in 7 (4%), and high-risk cytogenetics in 58 (30%). Daratumumab was used in 183 patients (95%) and isatuximab in 10 (5%). Anti-CD38 antibodies were combined with VRd in 106 patients (55%), VTd in 86 (45%), and KRd in 1 (1%). Median induction was 4 cycles (IQR, 4–6). After induction, ORR was 96.9%, with ≥VGPR in 81.8%, ≥CR in 32.3%, and MRD negativity in 36/72 evaluable patients (50%). High-risk cytogenetics was associated with a higher rate of refractory disease after induction (8.6% vs 0.8%; p = 0.013). Dara-VRd showed a numerically higher post-induction MRD negativity rate than Dara-VTd (22% vs 13%), without statistical significance. The most frequent grade 3–4 induction toxicities were infections (n = 16; 8%) and cytopenias (n = 5; 3%). Induction was discontinued in 11 patients (6%) due to progression/refractoriness (n = 4), infection (n = 3), non-infectious toxicity (n = 2), anaphylaxis (n = 1), or unknown cause (n = 1). ASCT was performed in 182 patients (94%). Median CD34+ collection was 5.1 × 10^6/kg (IQR, 3.5–6.8), plerixafor was required in 112 patients (58%), and collection failure occurred in 2. Post-ASCT ORR was 99.4%, with ≥VGPR in 91.7%, ≥CR in 66.7%, and MRD negativity in 73/123 evaluable patients (59.3%). Consolidation and maintenance were administered to 125 (65%) and 178 patients (92%), respectively. With a median follow-up of 22.6 months (IQR, 16.0–33.3), median PFS was 61.6 months and median OS was not reached; 5-year PFS and OS were 58.6% and 83.5%, respectively. In univariable analysis, lytic bone lesions were associated with inferior PFS (HR, 3.50; p = 0.039), while elevated LDH showed a trend toward inferior PFS (HR, 2.23; p = 0.054). Post-ASCT MRD negativity was associated with superior PFS and OS, and remained independently associated with improved PFS in multivariable analysis (adjusted HR, 0.43; p = 0.037). **Conclusions:** First-line anti-CD38-based induction followed by ASCT achieved high rates of deep response and encouraging survival in this real-world Argentine cohort, with post-ASCT MRD negativity identifying patients with superior outcomes.

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Fixed-Duration Versus Continuous Bispecific Antibody Therapy Regimen for Systemic AL Amyloidosis

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Introduction: Depth and timing of hematologic response in systemic AL amyloidosis correlate with organ recovery and survival. About 50% of patients do not achieve hematologic complete response (hCR) with daratumumab-based therapy, and many relapse. ASCT is restricted to select patients; immunomodulators have renal/cardiac toxicity, and venetoclax benefits t(11;14) cases. T-cell bispecific antibodies (BSAbs) show efficacy, but ideal treatment duration is unknown. We compared fixed-duration vs continuous BSAb therapy for efficacy, safety, and response durability. **Methods:** We retrospectively analyzed 21 patients with systemic AL amyloidosis treated with BSAbs. Baseline demographics, disease characteristics, treatment history, and adverse events were collected. Hematologic and organ responses followed established criteria. Staging used the European modified classification. Variables were summarized as medians/ranges or frequencies/percentages, and compared using the Mann-Whitney U test or Fisher's exact test, respectively. Significance was set at $p < 0.05$. **Results:** Fixed-duration therapy was given to 11 patients, continuous to 10. The fixed cohort (FC) was older (76 vs 67 years, p = 0.02); both had a median of 4 prior therapies. FC had higher NT-proBNP (8884 vs 2288 pg/mL), troponin (0.05 vs 0.03 ng/mL), but lower dFLC (51.6 vs 75.4 mg/dL) and marrow plasma cells (10% vs 20%) than the continuous cohort (CC). Median treatment duration was 3.4 vs 5.9 months (m). The distributions of stages I/II, IIIa, and IIIb were 4, 2, and 5 in FC, and 4, 3, and 3 in CC, respectively. 7 patients in FC had cardiac involvement vs 5 in CC. 9 patients in FC had renal involvement vs 3 in CC. 2 patients in FC had co-existing myeloma vs 8 in CC. 11 patients received Elranatamab vs 9 Teclistamab vs 1 Talquetamab. All FC patients achieved hCR, vs 8 in CC. Median time to hematologic response was 0.6 (0.2–0.9) m in both cohorts, with median duration of response of 9.6 (3–20.2) m in FC vs 7.3 (4.7–32.1) m in CC. Cardiac responses (FC vs CC): complete response (CR) 0/2; very good partial response (VGPR) 2/1; partial response (PR) 2/1; no response (NR) 2/1. Median cardiac response time: 1.5 (1–3) FC vs 3 (2–6) m CC. Renal responses: VGPR 3/0; PR 2/2; NR 1/0; no CR. Median renal response: 2 (2–3.2) FC vs 3 (2–4) m CC. 7 patients in both cohorts had cytokine release syndrome. ICANS occurred in 2 patients in FC vs 4 in CC. Infections occurred in 1 patient in FC vs 4 in CC. None of the patients in FC had neutropenia vs 5 in CC (p = 0.012). At last follow-up, 10 FC and 6 CC patients were alive. **Conclusions:** Fixed-duration BSAb therapy led to rapid, deep hematologic responses comparable to continuous therapy, despite higher baseline risk. Organ responses were seen in both groups, with similar response durability. Fixed-duration therapy had fewer neutropenia and infection events. These

data support further study of fixed-duration BSAb, especially for patients at risk for toxicity.

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FOSL2-ANXA1 Axis Maintains the Survival of Multiple Myeloma Cells with Low BCMA Expression

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Introduction: Antigen-loss escape is a challenge for targeted immunotherapy in patients with multiple myeloma (MM). Our previous work has demonstrated that MM cells with low or no BCMA expression exhibit high ANXA1 levels, which enable the outgrowth of myeloma cells. Here, we investigate a molecular regulator that may induce ANXA1 expression and govern the fate of BCMA-low MM cells. **Methods:** We employed the SMMO cohort of newly diagnosed MM (NDMM) patients recently reported by our group to assess specific gene expression and evaluate clinical outcomes. We also performed a series of biological experiments for mechanistic investigations. **Results:** Using the single-cell transcriptome dataset of 39 NDMM from the SMMO cohort, patients were divided into two groups: ANXA1high group (n = 20) and ANXA1low group (n = 19) by the median ANXA1 level in myeloma cells. We found that the proportion of ANPEP (CD13)- or CD33-positive MM cells in the ANXA1high group was significantly higher than that in the other group (ANPEP: $p = 0.003$, CD33: $p = 0.024$). Consistently, flow-based CD13/CD33 membrane density in the bone marrow myeloma cells of the ANXA1high group was remarkably higher than that in the ANXA1low group ($p = 0.004$). It implies that MM cells with high ANXA1 transcript levels are likely to express myeloid-associated markers. Four transcriptional factors, FOSL2, GATA3, MYC, and FOXM1, have been proven to directly regulate ANXA1 transcription in different contexts. Among them, only FOSL2 displayed a higher expression in the ANXA1high group than that of the counterpart. The correlation analysis showed that FOSL2 transcription was strongly associated with ANXA1 expression in the CD138-enriched plasma cells of 234 SMMO patients subjected to bulk RNA sequencing ($r = 0.55$, $p < 0.001$). The patients with high FOSL2 levels had an unfavorable progression-free survival compared with those with low levels ($p = 0.016$). To verify the relationship between FOSL2 and ANXA1 in MM, FOSL2 was stably knocked down in two MM cell lines (8226, KMS20), both of which had low BCMA expression, high CD33 abundance, and modest ANXA1 levels compared with other myeloma strains at both mRNA and protein levels. As a result, disruption of FOSL2 in either 8226 or KMS20 led to a remarkable reduction in ANXA1 and CD33 expression. Functionally, the proliferative capacity of 8226 and KMS20 cell lines was significantly attenuated with FOSL2 downregulation. An increased proportion of 7-AAD+Annexin V+ population was observed in these two myeloma cell lines with FOSL2 disturbed compared with the controls. For translational purposes, the antagonist inhibiting AP-1 signaling, T-5224, was adopted. With the suppression of FOSL2-involved pathway, ANXA1 and CD33 protein levels in the 8226 and KMS20 cell lines were decreased. **Conclusions:** The data demonstrate that FOSL2 could serve as a key regulator of ANXA1 expression in the MM cells with low BCMA levels and support their survival. Targeting FOSL2 may be a strategy to combat BCMA-low MM cells.

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Frailty Assessment Prior to CAR T-Cell Treatment in Elderly Patients with Multiple Myeloma

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Introduction: Patients with multiple myeloma (MM) often have significant frailty because the median age at diagnosis is 69 years. Traditional performance status measures do not adequately assess frailty in this population. We implemented validated frailty assessment tools in routine clinical practice to better evaluate patient status prior to admission for chimeric antigen receptor T-cell (CAR-T) therapy. **Methods:** All patients with MM > 65 years of age presenting for CAR-T treatment at University of Iowa Hospital and Clinics were assessed with several frailty measurements including Timed Get Up & Go, Grip Strength, and Montreal Cognitive Assessment (MoCA). MoCA assesses cognitive function in multiple domains and is scored out of 30 points, with 26–30 suggestive of normal cognitive function. Timed Get Up & Go assesses functional mobility. Patients stand up from sitting position in a standard chair without using their arms for support, then walk 3 meters at a normal pace, turn at the marked line, walk back to the chair, and return to sitting. Completing testing in < 10 seconds indicates normal mobility. Grip strength was measured using an electric hand dynamometer and scored as weak, medium, or strong with thresholds specific to gender and age. Outcomes were retrospectively assessed. Univariate associations were assessed between the frailty measures and outcomes of interest, including hospitalization length and health care utilization post CAR-T therapy. **Results:** The median age at leukapheresis was 72.3 years (range 65–83.2, SD 4.7) and most were male (72.7%). A total of 22 patients had MOCA assessments performed with a median MOCA 27 (range 18–30, SD 3.5). A total of 14 patients had grip strength performed, and 43% were weak, 43% medium, and 14% measured strong. Get-up and Go testing performed in 13 patients total with only 1 identified patient as abnormal on this assessment. The frailty evaluations were assessed with outcomes including initial hospitalization length of stay, number of visits within 100 days, ED visits within 100 days, re-admissions within 100 days, and discharge disposition from initial hospitalization. Higher MOCA score,

indicating less cognitive impairment, was significantly associated with shorter initial hospitalization duration (beta coefficient –0.28, 95% CI –0.54 to –0.02, p-value 0.03). A low number of events precluded a formal statistical analysis of the other outcomes of interest. **Conclusions:** Performing frailty assessments in the pre-CAR T setting could provide an opportunity for prehabilitation and optimization of initial hospitalization length of stay. The assessments for frailty take minimal clinic time and can reasonably be performed by clinicians and nursing staff. Implementing a standard frailty evaluation prior to CAR T cell therapy could improve patient experience and outcome.

PA-205

Frailty in Newly Diagnosed Multiple Myeloma: Prevalence, Determinants and Prognostic Impact in a Real-World Indian Cohort

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Introduction: Frailty is increasingly recognized as a determinant of treatment tolerance and outcomes in multiple myeloma (MM). Its applicability in India warrants evaluation given younger age at diagnosis, lower life expectancy, and higher comorbidity burden than Western populations. We evaluated the prevalence, determinants, and prognostic impact of frailty using the simplified International Myeloma Working Group (sIMWG) frailty score in a real-world Indian cohort. **Methods:** This single-centre observational study included consecutive newly diagnosed MM patients aged ≥60 years (extended from ≥65 years given India's younger presentation age and high comorbidity burden) from January 2022-December 2025. Patients with prior treatment or missing data were excluded. Frailty was assessed using the sIMWG frailty score (age, Charlson Comorbidity Index, ECOG performance status); scores 0–1 were non-frail and ≥2 frail. Baseline characteristics, treatment outcomes, and survival were analyzed. **Results:** A total of 125 patients with a median age of 66 years (range: 60–85) were evaluated for frailty. The cohort included 86 (68.3%) male patients, with CRAB features in the form of hypercalcemia in 14 (11.2%), renal dysfunction in 42 (33.6%), anemia in 67 (53.6%) and bone lesions in 108 (86.4%) patients. Six (4.8%) and 80 (64%) patients had R-ISS stage I and II, while 39 (31.2%) had R-ISS stage III. High-risk cytogenetics as per IMWG/IMS 2025 were seen in 18 (14.3%) patients. As per the sIMWG frailty score, 78 (62.8%) were classified as frail. The factors responsible for frailty were predominantly poor PS (ECOG-PS ≥2) in 58 (46.2%) and a CCI score ≥2 in 40 (32%); mainly due to high comorbidities [diabetes mellitus (36.8%), ischemic heart disease (26.3%), and chronic kidney disease (18.4%)]. Of note, age 76–80 years (sIMWG score of 1) contributed to frailty in 7 (5.6%) patients, and age >80 years (sIMWG score of 2) was noted only in 2 (1.6%). VRd was the most common regimen (62.4%), followed by VCd (26.4%); 5.9% received doublet therapy. Frail patients had more serious infections (37.3% vs 17.4%, p = 0.020) and all four ICU admissions occurred in this group. Grade ≥3 hematologic toxicity occurred in 34.2% of frail patients. Among 88 evaluable patients, ≥VGPR rates were lower in frail patients (65.4% vs 75%, p = NS). At a median follow-up of 25 months, the 18-month PFS was 84.6% vs 59% in non-frail and frail patients ($\chi^2 = 5.021$, p = 0.025). On univariate analysis, frailty, anemia, hypercalcemia, and eGFR predicted inferior PFS; frailty was the sole independent predictor of PFS on multivariate analysis (HR 1.985, 95% CI 1.020–3.862, p = 0.044). Twenty-six deaths occurred, with 21 (80.7%) in frail patients ($\chi^2 = 4.721$, p = 0.03). **Conclusions:** Nearly half of all frail patients were aged ≤65 years, suggesting Indian myeloma patients accumulate frailty through mechanisms beyond age. Frailty independently predicted inferior PFS and OS, emphasizing the need for routine frailty assessment and frailty-directed therapeutic approaches.

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Frequency and Characteristics of Longer Than 15 Years of Survival Following Triplet-Based Induction and Autologous Stem Cell Transplantation: Prospective Dual-Center Real-World Evidence

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Introduction: With the introduction of novel agents, the concept of "functional cure" has become a reality unlike the earlier misconceptions against its possibility. Here we are presenting the characteristics of long-term survivors recruited from our two-center prospective myeloma databases. As Lenalidomide maintenance treatment approval and reimbursement dates to 2023, this cohort excludes role of post-induction/ASCT treatment strategies. **Methods:** Starting with 2007, all consecutive myeloma patients are recorded prospectively. Among all who underwent autologous stem cell transplantation (ASCT) and diagnosed before 2010 were stratified by overall survival (OS) into four groups: 0–5 years (Group 1), 5–10 years (Group 2), 10–15 years (Group 3), and ≥15 years (Group 4). Baseline characteristics, response to induction treatment, and first progression-free survival (PFS-1) were compared across groups. Kaplan–Meier survival analysis and multivariable Cox regression were performed. Among alive patients Flow-MRD status were additionally characterized. **Results:** Of the 111 patients meeting

criteria, distribution: Group 1: n = 38; Group 2: n = 22; Group 3: n = 18; Group 4: n = 33. Median age at diagnosis 53 years (range 28–72), trend toward younger age among long-survivors (p = 0.006). High-risk cytogenetics was16/104 (15.4%). Induction regimens VCD (n = 80), VRD (n = 23), VAD (n = 5) followed by Mel 200 (n:106) and Mel140 (n:4). Baseline characteristics ISS, high-risk cytogenetics, bone and renal parameters were similar. Post-induction (CR rate 65.8%, 59.1%, 61.1%, and 42.4% and post-ASCT responses (CR rate 36.8%, 18.2%, 16.7%, and 24.2%;) were also similar. Tandem (n:2) or salvage (n:30) ASCT were used. PFS-1 showed a clear stepwise increase across groups: 24.3 months (95% CI 16.3–32.4), 42.0 months (27.3–56.6), 68.6 months (36.9–100.3), and 143.3 months (95% CI 10.6–276.0) for Groups 1 through 4, respectively (log-rank p < 0.001). Pairwise comparisons were significant for all group pairs except Group 3 versus Group 4. In multivariable Cox regression, age at diagnosis was an independent predictor of OS (HR 1.032, 95% CI 1.005–1.060; p = 0.021), while ISS stage was an independent predictor of PFS-1 (HR 1.544, 95% CI 1.119–2.130; p = 0.008). Of the 33 (29.7%) patients who survived at least 15 years, 29 (87.9%) are currently alive with a median OS of 17.5 years (range 16.3–23.8). Among the 29 alive patients, 14 are treatment-free. MRD assessment results are 10/14 MRD-negative. Thirteen of 29 alive patients (44.8%) have never experienced disease progression. **Conclusions:** This dual center prospective RWE demonstrates durable long-term treatment-free and MRD(-) remission is possible following triplet based induction (suboptimal regimen in today's standards) and unmaintained ASCT. Factors associated with long-term survivorship are age and ISS at diagnosis in addition to PFS-1. These results are highly promising as current treatment strategies induce deeper and longer responses.

PA-207

From Niche to Nomad: SEPTIN6-Mediated Syndecan Shedding Drives Plasma Cell Egression and Drug Resistance in Multiple Myeloma

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Introduction: Multiple Myeloma (MM) remains largely incurable despite significant therapeutic advances including proteasome inhibitors, immunomodulatory drugs, and emerging CAR-T and bispecific antibody therapies. The bone marrow microenvironment, particularly BM-mesenchymal stromal cells (BM-MSCs), plays a pivotal role in myeloma progression and therapeutic resistance through immunosuppressive cytokine signalling, metabolic reprogramming, and direct stromal-tumour interactions. While the genetic landscape of myeloma plasma cells has been extensively characterized, stromal niche alterations underpinning therapeutic failure remain poorly understood, representing a critical and underexplored avenue for identifying novel resistance mechanisms and actionable therapeutic targets. **Methods:** BM-MSCs were isolated from newly diagnosed multiple myeloma (NDMM) patients and grouped based on their response to bortezomib-based induction therapy (VCD or VRD) into good responders (GR) and poor responders (PR). High-resolution LC-MS-based proteomic analysis was performed to identify differences in the stromal protein expression between the two groups. Differentially expressed pathways and proteins were analyzed, and key findings were validated in an independent NDMM cohort (n = 37) using Western blotting and confocal immunofluorescence microscopy. Pathway analysis was carried out for validated DEPs. **Results:** Proteomic profiling revealed a distinct stromal signature segregating GR from PR BM-MSCs. PR stromal cells showed enrichment of lipid, cholesterol, and rRNA-processing pathways with suppression of glycosaminoglycan and heparan sulfate metabolism. SEPTIN6 emerged as the most significant differentially expressed cytoskeletal regulator, showing overexpression and aberrant nuclear localization in PR BM-MSCs, strongly associated with poor therapeutic response (p < 0.05). Elevated SEPTIN6 was linked to enhanced CD138/Syndecan-1 membrane redistribution and ectodomain shedding through dysregulated Golgi-dependent syndecan processing, generating soluble CD138 that disrupted CXCL12-mediated BM retention — evidenced by significantly elevated CTPC load in PR patients. PR BM-MSCs further demonstrated TGF-β1 upregulation, nuclear YAP translocation, and marked Collagen VI upregulation, collectively confirming mechanotransduction activation and active ECM remodelling. **Conclusions:** This study identifies a novel SEPTIN6-TGF-β-YAP-Collagen VI stromal resistance axis in MM, wherein PR BM-MSCs acquire a mechanically active, ECM-remodelled phenotype characterized by aberrant SEPTIN6 nuclear localization, YAP mechanosignalling activation, Collagen VI-driven niche stiffening, and CD138 shedding-mediated CTPC mobilization. These findings position SEPTIN6 as a novel biomarker of poor therapeutic response and highlight the stromal microenvironment as a promising therapeutic target for overcoming drug resistance in multiple myeloma.

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Function Tracks Disease, Psychology Tracks Diagnosis: Dissociable Patient-Reported Burden in Smouldering Myeloma: Initial Report from the UK MRA COSMOS Study

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Introduction: Patient experience in smouldering multiple myeloma (SMM) is poorly characterised. Patient-reported outcome (PRO) data across the SMM risk spectrum are sparse, using instruments designed for active disease. With approval of daratumumab the window for PRO in surveillance is closing. **Methods:** COSMOS is a UK-wide multi-centre prospective observational SMM study (30 sites, n = 604). In partnership with SMM patients and public, we developed a bespoke SMM-specific PRO instrument, covering disease-related worry, surveillance burden, adjustment to precancer diagnosis, attitude to treatment trials, for use alongside EORTC-QLQ-C30/-MY20 and EQ-5D-3L. Comparisons against an age-matched UK population (Young et al.) and newly diagnosed MM (NDMM) were made where possible. Of 604 enrolled, 195 had complete baseline PRO data at analysis cutoff; Mayo subcohort:Low/Int/High (n = 25/25/24), ≤4-month progressors (74) excluded. Psychometric evaluation by exploratory factor analysis (EFA), internal consistency, convergent validity, and test-retest were performed. Cross-sectional analyses were stratified by Mayo 20/2/20 and BMPC %; BMPC%-adjusted models isolated risk-labelling from disease-bulk effects. Exploratory logistic regression of trial willingness vs composites, "worry", Mayo risk and sex (uncorrected); reference comparisons used Hedges' g. **Results:** SMM HR-QoL was better than NDMM (median |g| 0.42) and similar to an age-matched UK population (median |g| 0.10). Fourteen bespoke items resolved into two factors with strong reliability: Functional Impact (FI, α = 0.92) and Psychological Burden (PB, α = 0.89), with convergent validity against EORTC and EQ-5D (|r| = 0.46–0.58). The two dimensions showed divergent relationships with disease bulk. FI scaled positively with BMPC% (partial r = +0.22) consistent with EORTC physical functioning and fatigue trends; within SMM, Mayo-FI association was abolished by BMPC% adjustment (p = 0.95), consistent with disease-bulk rather than risk-labelling effect. PB did not scale with disease (BMPC% partial r = −0.23; Mayo KW p = 0.46). Female patients reported higher burden across EORTC and bespoke domains yet were less likely to express willingness to enrol in clinical trials, contrary to the expected burden-engagement relationship. Trial willingness (47.7% baseline) was independently predicted by the disease-coupled FI dimension (OR 1.85 [1.09, 3.30], p = 0.028) and male sex (OR 3.30 [1.60, 7.12], p = 0.002); PB and Mayo risk were non-predictive. **Conclusions:** A SMM-specific PRO instrument resolves patient experience into a bulk-scaled functional dimension and a bulk-dissociated psychological dimension that diverge in both their relationship to disease burden and in predicting patient trial decisions. Findings support individualised, rather than risk-stratified, psychological provision. The sex-burden-willingness inversion is a potential equity signal warranting further study. Cross-sectional findings, longitudinal analyses and validation with the MODIFY interventional study planned.

PA-209

Functional Implications of FCRL5 Mutations for Cevostamab Immune Escape in Multiple Myeloma

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Introduction: Cevostamab, an FCRL5-directed bispecific antibody, has demonstrated strong activity in heavily pretreated multiple myeloma patients, however resistance may emerge from acquired FCRL5 alterations. Here, we modelled patient-derived FCRL5 mutations and investigated their impact on cevostamab-related immune synapse formation. **Methods:** Longitudinal bone marrow aspirates from cevostamab-exposed patients were analyzed by whole genome and exome sequencing. FCRL5 knockout OPM2 cells were reconstituted with wild-type FCRL5, and patient derived FCRL5 mutants. Re-expression was confirmed by RT-PCR and imaging. Nanoscale receptor localization and receptor trafficking after cevostamab engagement were quantified by Direct Stochastic Optical Reconstruction Microscopy (dSTORM) and 3D Lattice light-sheet (LLS) live-cell imaging, respectively. **Results:** An acquired clonal FCRL5E115A missense mutation (VAF = 56%) and a subclonal FCRL5G455Efs*19 frameshift deletion mutation (VAF = 5%) were detected in a patient progressing after two years of cevostamab exposure. To validate the functional impact of these mutations, FCRL5 KO models were generated utilizing CRISPR-Cas9. Cevostamab resistance and complete loss of binding was observed in FCRL5KO models confirming that drug activity is strictly FCRL5-dependent. Re-expression of FCRL5WT (1,987 ± 0,28 clusters/µm2) restored surface expression and cevostamab sensitivity. In contrast, the FCRL5G455Efs*19 did not reach the cell surface. In silico structural modelling using AlphaFold indicated that the frameshift mutation generated a truncated protein lacking the transmembrane domain,

consistent with loss of membrane anchoring. Notably, while FCRL5E115A was detectable (2,949 ± 0,48 clusters/μm^2) on the plasma membrane and retained measurable cevostamab binding, this interaction did not translate into effective cytotoxicity. LLS microscopy showed that FCRL5WT underwent marked receptor polarization after cevostamab exposure, one of indicator of strong T cell engagement. Despite binding with cevostamab, FCRL5E115A failed to undergo comparable polarization. Instead, accelerated internalization of the antibody-receptor complex and increased intracellular signal was observed. These intracellular antibody-receptor complexes were not found in WT cells. This altered spatial behavior provides a mechanistic explanation for why the mutant preserves antigen recognition yet still mediates resistance. **Conclusions:** Here, we describe two mechanistically different modes of resistance arising from acquired FCRL5 mutations upon prolonged cevostamab exposure. FCRL5G455Efs*19 results in loss of FCRL5 surface expression making it inaccessible for cevostamab, whereas FCRL5E115A preserves surface accessibility but rapidly internalizes antibody-receptor complexes, thereby hindering immune synapse formation with T cells. These findings further dissect recently recognized tumor intrinsic mechanisms of resistance to cevostamab.

PA-210

Functional Three-Dimensional Bone Marrow Organoid Provides Native-Like Environment for Multiple Myeloma Cells

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Introduction: Conventional two-dimensional (2D) cell culture fails to adequately support the viability and proliferation of multiple myeloma (MM) primary cells, limiting their utility for drug testing, disease modeling and the analysis of tumor-microenvironment interactions. The bone marrow niche plays a critical role in myeloma cell survival, growth, and therapeutic resistance, therefore in vitro models are needed to better recapitulate the complex cellular and extracellular components of the native microenvironment. Here, we developed an induced pluripotent stem cell (iPSC)-derived three-dimensional (3D) organoid model designed to mimic key features of the bone marrow niche and provide a platform for studying myeloma biology in a more physiologically relevant setting. **Methods:** Whole-organoid immunofluorescence staining was performed to assess key structural components of the bone marrow organoid, including vascular-like networks, immune-like cell populations, and early and late osteogenic compartments. Organoid development was characterized using stage-specific markers (OCT4, TBXT). To evaluate tumor–microenvironment interactions, organoids were co-cultured with the MM cell lines RPMI 8226 and MM1S, and cellular infiltration was monitored over time by light microscopy. At defined time points, organoids were fixed and analyzed by immunohistochemistry (IHC) to determine the localization and distribution of infiltrating myeloma cells. **Results:** The generated organoids recapitulate key components of the bone marrow niche, including vascular-like networks (CD31+), immune-like cell populations (CD45+), and osteogenic compartments at distinct stages of differentiation, ranging from early osteogenic markers (RUNX2+) to mature bone-like cells expressing osteopontin (OPN). Co-culture with multiple myeloma cell lines demonstrated efficient infiltration of the organoid structure and close interactions with niche components, suggesting active tumor–microenvironment crosstalk. Furthermore, the organoid platform might have the potential to support the ex vivo maintenance of primary patient-derived myeloma cells, providing a physiologically relevant model for disease investigation and therapeutic testing. **Conclusions:** In summary, we present a novel organoid-based MM model that recapitulates key features of the bone marrow microenvironment and bridges the gap between conventional 2D culture systems and in vivo conditions. This platform provides a physiologically relevant tool for investigating disease biology, studying tumor–microenvironment interactions, and evaluating emerging therapeutic approaches, including T-cell–redirecting immunotherapies.

PA-211

Gastric Extramedullary Disease as the Initial Manifestation of IgA Kappa Multiple Myeloma with Rapid Fatal Progression

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Introduction: Extramedullary disease in multiple myeloma is associated with aggressive biology and inferior outcomes. Gastrointestinal involvement is uncommon, and gastric infiltration as the initial manifestation of newly diagnosed multiple myeloma is particularly rare (less than 2%). Such lesions may mimic primary gastric malignancy, lymphoma, or benign ulcerative disease, making tissue diagnosis essential. **Methods:** We report a 71-year-old man with coronary artery disease, diabetes mellitus, and hypertension who presented with three months of epigastric pain and weight loss. Upper gastrointestinal endoscopy revealed an ulcerated gastric lesion with bleeding foci. Diagnostic work-up included gastric biopsy, bone marrow biopsy, serum protein electrophoresis and immunofixation, serum immunoglobulins and free light chains, PET/CT, FISH analysis, and next-generation sequencing. **Results:** Gastric biopsy showed diffuse mucosal infiltration by atypical, anaplastic plasma cells with multinucleation, prominent nucleoli, and numerous mitotic figures (Figure 1). The cells were CD138-positive and kappa-restricted by kappa/lambda in situ hybridization. Bone marrow biopsy demonstrated 60% kappa-restricted plasma cell infiltration, and serum studies confirmed IgA kappa monoclonal gammopathy.

Laboratory findings included hemoglobin 9.8 g/dL, creatinine 0.88 mg/dL, calcium 10.3 mg/dL, albumin 2.9 g/dL, beta-2 microglobulin 6.1 mg/L, LDH 374 U/L, IgA 41.1 g/L, and serum free kappa/lambda light chains of 526.2/44.8 mg/L. PET/CT showed widespread lytic bone lesions without other extramedullary disease. FISH revealed t(4;14) and del(1p), while del(17p), gain/amp(1q), t(14;16), and t(14;20) were negative. NGS identified a KRAS mutation. The disease was staged as ISS III, R-ISS III, and R2-ISS IV. VRD therapy was initiated without interruption; however, the patient died from rapid disease progression during cycle 2, week 3, seven weeks after treatment initiation. **Conclusions:** Gastric extramedullary involvement at diagnosis may indicate highly aggressive multiple myeloma biology. In this case, anaplastic morphology, high-risk cytogenetics, KRAS mutation, elevated LDH, and R2-ISS IV disease were associated with rapid fatal progression despite standard first-line VRD therapy.

PA-213

Genomic Determinants of Response to Iberdomide Combination and Monotherapy in Early Relapsed Multiple Myeloma

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Introduction: Most patients with multiple myeloma (MM) develop lenalidomide (Len) resistance at first relapse. Most will receive a second IMiD (e.g., pomalidomide; Pom) during their course. The arrival of cereblon E3 ligase modulators (CELMoD) is imminent. While key studies have investigated the effects of CRBN variants on IMiD/CELMoD binding (Chrisochoidou et al., Blood. 2025) and described chr2q/COP9 signalosome deletions at IMiD relapse (Gooding et al., Blood 2022), genomic determinants of response to CELMoDs in IMiD-resistant settings are underexplored. We performed whole genome sequencing (WGS) for patients on the ReKInDLE study of Iberdomide, Carfilzomib, Daratumumab, and dex (Iber-DKd; n = 32) for Len-exposed early-relapsed MM, with de-escalation to Iber monotherapy after 8 cycles. **Methods:** To compare frequencies of IMiD/CELMoD resistance lesions, baseline 80x WGS of CD138+ marrow tumor (40x germline match) was performed for two cohorts: 1) 16 patients enrolled on ReKInDLE (Len-refractory); 2) 20 unrelated patients with double refractoriness to Len/Pom. **Results:** At this time, 16 patients on Iber-KDd have WGS (Len/single-refractory; median follow up 14.2 months). Nine (56%) achieved MRD- at 10–5 at end-combination (primary endpoint). At the data cut of April 2, 2026, 5/16 (31%) have experienced disease progression (PD). One early progressor had t(14;16) with >70k APOBEC SNV and extramedullary disease. Two patients progressed by end of combination: each with chromothripsis and one with IKZF1 Q156K and the other with DDB1 L631F. IKZF1 Q156 is at the apex of a zinc-finger degron that interacts with CRBN (Sievers et al., Science. 2019) while the DDB1 variant might disrupt CRL4CRBN. The other 2 achieved MRD- at 10–6 and had PD 7 and 11 months after de-escalating to Iber monotherapy. Each had focal deletions of COPS8 and COPS7B, components of the COP9 signalosome that maintains CRL4CRBN, and one had focal deletion of CRBN. Clinically, this suggests response driven by combination tx with clonal regrowth upon de-escalating to Iber monotherapy. For those that remain on monotherapy, three did not achieve MRD- of which one harbored a deletion of COPS7B, COPS9, and COPS8 with COPS8 L71P. Seven others who achieved MRD- have no such aberrations. To contextualize the frequency of IMiD/CELMoD genomic resistance, we compared these events to WGS from IMiD-naïve patients in CoMMpass (n = 752) and unrelated double-refractory patients. The frequency for aberrations in naïve:single:double refractory patients was CRBN 0.9%:8%:43% and COP9 genes 1.9%:23%:48%. None (0%), one (0.1%), and three (0.4%) naïve patients had COPS8, IKZF1, and DDB1 SNV, respectively. **Conclusions:** CELMoDs have activity in IMiD-resistant settings but discrete resistance variants apart from CRBN mutations appear to influence response, arguing for screening in IMiD-resistant scenarios, and for earlier CELMoD integration prior to selection of universal IMiD/CELMoD resistance. Sequencing of additional cases is in progress.

PA-214

Genotype-Informed Single-Cell RNA-Seq Resolves Functional Subclonal Heterogeneity in Multiple Myeloma

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Introduction: Intratumor heterogeneity (ITH) in multiple myeloma (MM) reflects genetic subclones and transcriptional states that are difficult to connect using bulk sequencing or RNA-only single-cell clustering. We developed a genotype-informed single-cell framework integrating gene expression, inferred copy-number alterations (CNA), and single-nucleotide variants (SNV) using

weighted nearest-neighbor (WNN) analysis. **Methods:** Bone marrow mononuclear cells from 10 MM patients were profiled by 5′ scRNA-seq, and matched CD138+ plasma cells and blood were profiled by bulk WES/RNA-seq. Single-cell CNA inference with inferCNV and Numbat, and SNV detection with SComatic and VarTrix, were benchmarked against matched bulk WES. Gene expression, CNA states, and SNV calls were encoded as separate modalities and integrated by WNN. WNN subclones were compared with RNA-only clusters using silhouette score, within-cluster CNA variance, and clone-level signatures, including GEP70 risk, IMiD-resistance, and Selinexor-response as proof-of-principle therapy-associated programs. **Results:** WNN provided a more genotype-coherent view of MM plasma-cell heterogeneity than RNA-only clustering. Across patients, WNN showed improved cluster separation (BH-adjusted $p = 0.01$) and lower within-cluster CNA variance across recurrent MM lesions (median 0.023 vs 0.074; adj $p = 0.008$), indicating coherent grouping of CNA-defined subclones. This was most evident in genetically complex cases, where RNA-only clusters dispersed lesion-bearing cells across multiple groups, whereas WNN localized events such as del (17p13) to defined subclones. WNN also resolved clinically interpretable transcriptional heterogeneity. Across GEP70, IMiD-resistance, and Selinexor-response signatures, WNN produced broader clone-level separation than RNA-only clustering, with significant improvement for Selinexor-response (median dynamic range 2.73 vs 1.53; adj $p = 0.026$). In a patient predicted to be Selinexor-sensitive at bulk level, RNA-only clustering distributed intermediate-to-low response cells across three clusters, whereas WNN concentrated the lowest-response state into one subclone (median z-score -2.20; adj $p < 0.001$ vs all other WNN subclones). Clone-level modeling showed that genomic-risk lesions and transcriptional-risk states were related but not interchangeable: del (17p13) was associated with lower GEP70 ($\beta = -0.61$, adj $p = 1.8 \times 10^{-5}$), lower Selinexor-response score ($\beta = -0.32$, adj $p = 0.029$), and reduced cell-cycle activity, whereas gain(1q21) was associated with higher IMiD-resistance score ($\beta = 0.34$, adj $p = 0.041$). **Conclusions:** WNN integration of scRNA-seq-derived expression, CNA, and SNV features links high-risk genomic lesions to transcriptional-risk and therapy-associated states at single-cell resolution. This approach complements bulk genomics by showing that genomic and transcriptional risk can be partially decoupled within tumors, providing a practical strategy to dissect functional subclonal heterogeneity in MM.

PA-215

Gut Microbiome Dynamics and Associations with Response and Toxicity After BCMA CAR T-Cell Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: The gut microbiome may modulate antitumor immunity and treatment-related toxicity, but its role in relapsed/refractory multiple myeloma (RRMM) treated with B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR T-cell) therapy remains poorly defined. We prospectively evaluated longitudinal changes in gut microbial diversity and explored associations between baseline microbiome features, day 90 response, cytokine release syndrome (CRS), and CAR T-cell expansion. **Methods:** This multicenter prospective observational cohort study enrolled 15 consecutive patients with RRMM receiving BCMA-directed CAR T-cell therapy at three centers. Fecal samples were collected before infusion and at 1 and 3 months after infusion for 16S rRNA gene sequencing. Alpha diversity was assessed using the Shannon index. Longitudinal changes in microbial diversity and community composition were analyzed across time points. Exploratory subgroup analyses were performed according to day 90 response (CR/VGPR vs non-CR/VGPR) and CRS severity (grade 0–1 vs grade ≥2). Associations between baseline microbiome features and peak CAR T-cell expansion (Cmax) were assessed using Spearman correlation. **Results:** BCMA-directed CAR T-cell therapy was associated with marked longitudinal perturbation of the gut microbiome. The Shannon index decreased substantially at 1 month after infusion and partially recovered by 3 months. Paired analyses showed a significant reduction from baseline to month 1 ($P = 3.05 \times 10 - 4$), while diversity at month 3 remained significantly lower than baseline despite partial recovery (baseline vs month 3, $P = 0.0219$), indicating incomplete recovery. At the community level, microbial restructuring was most pronounced at month 1, with partial reversion toward the baseline profile by month 3. Patients achieving CR/VGPR at day 90 ($n = 10$) had significantly higher baseline Shannon diversity than those with inferior responses ($P = 0.0319$). Patients who developed grade ≥2 CRS ($n = 6$) showed numerically lower baseline Shannon diversity, although the difference was not statistically significant ($P = 0.140$). Baseline Shannon diversity showed a positive trend with CAR T-cell Cmax ($\rho = 0.38$, $P = 0.166$). At the genus level, Blautia tended to correlate positively with Cmax, whereas Enterococcus tended to correlate negatively. **Conclusions:** In RRMM patients receiving BCMA-directed CAR T-cell therapy, the gut microbiome undergoes early and substantial disruption followed by partial recovery. Higher baseline microbial diversity and selected genus-level features may be associated with deeper early response and greater CAR T-cell expansion, and may also inform toxicity stratification. These findings support the gut microbiome as a potential predictor of CAR T-cell outcomes in multiple myeloma, the predictive performance of which will be enhanced by integrating muti-omic biomarkers in the future studies.

PA-216

HDP-101, a BCMA-Targeting Antibody-Drug Conjugate with a Novel Amanitin Payload, Establishes the Recommended Phase 2 Dose (RP2D) in a Clinical Phase 1 Trial on Relapsed/Refractory Multiple Myeloma

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Introduction: HDP-101 (INN: pamlectabart tismanitin) is a novel antibody-drug conjugate (ADC) targeting B-cell maturation antigen (BCMA) with a synthetic amanitin payload. In nonclinical studies, it exhibits potent anti-tumor activity against BCMA-positive myeloma cells, including cells with low BCMA expression. **Methods:** HDP-101-01 is a first-in-human, open-label, non-randomized, multicenter phase 1/2a clinical trial in Relapsed/Refractory Multiple Myeloma (RRMM) to evaluate safety, PK/PD, and antitumor activity, and to define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D). Dose escalation (20–218 µg/kg/cycle) was guided by an adaptive Bayesian logistic regression model (BLRM). Patients were dosed every 3 weeks (Q3W) up to Cohort 5 (100 µg/kg). From Cohort 6 (90 µg/kg), based on PK/PD modeling, dosing optimization strategies were introduced including split dosing and/or premedication with corticosteroids and antihistamines, to mitigate the risk of adverse events such as thrombocytopenia and liver enzyme elevations. Safety, efficacy, and PK/PD were evaluated. **Results:** As of May 2026, ten dose cohorts (20–218 µg/kg/cycle) completed the DLT evaluation during dose escalation, with a total of 53 patients (22 female, 31 male; median age 69, range 43–90) included in the analysis. Patients were heavily pretreated (median 6 pre-treatments, range 2–15). HDP-101 showed a manageable safety profile. Tolerability was improved following dose splitting and premedication. No drug-related deaths, infusion reactions, lung, or ocular toxicity were observed. The MTD was not reached. Noncompartmental analysis showed dose-proportional pharmacokinetics (Cmax, AUC) for all analytes, with ~9-day half-life. A two-compartment model with linear clearance best described total antibody PK, with minimal free payload in serum. PK/PD modeling and simulation analyses confirmed that split dosing and/or premedication reduced the impact of HDP-101 on platelets and liver function tests. Clinical responses were observed from ≥90 µg/kg, with increasing efficacy at higher doses. The objective response rate (ORR) across cohorts 5–9 (90–175 µg/kg/cycle) was 39% (13/33 evaluable patients), including 6 PR, 3 VGPR, 1 CR, and 3 sCR. At 175 µg/kg, 2 out of 5 evaluable patients achieved a response (1 VGPR, 1 CR), and 1 patient achieved MR. Notably, responses were also observed in patients previously exposed to BCMA-targeted therapies. Based on the totality of safety, PK/PD, and efficacy data, and considering the balance of exposure, tolerability, and response, 175 µg/kg was selected as the RP2D. **Conclusions:** HDP-101 demonstrates clinical activity with a favorable safety profile in heavily pretreated RRMM patients, supporting the potential of HDP-101 as a novel payload BCMA-targeted ADC therapy. Definition of the RP2D at 175 µg/kg establishes an effective and tolerable dose and enables immediate transition into clinical Phase 2a expansion study, which is started.

PA-217

Health Care Costs in Front-Line Treatment with a CD38 Antibody Versus VRD: A Cost-Effectiveness Analysis

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Introduction: Multiple myeloma (MM) treatment costs are rapidly increasing, due to advent of many effective novel drugs and the resulting increase in MM prevalence. CD38-antibody based therapies are now recommended as first line treatments. The aim of this study was to compare total healthcare resource utilization (HCRU) costs between CD38-based and older first line therapies in MM patients to assess if the higher costs are balanced by improved outcomes in a real word setting. **Methods:** This is a retrospective cohort study of 831 MM patients treated at the Helsinki University Hospital (HUS) in 2018–2025. HUS is the largest healthcare provider in Finland, with a catchment population of 1.7 million inhabitants. We assessed the patient groups divided by eligibility for autologous stem cell transplantation (SCT), and by the use of CD38-antibodies in first line. To control for confounding factors propensity score matching for age and R-ISS status was performed (in a 1:1 ratio) for the two CD38 treatment groups. SCT-eligible patients were treated with CD38-antibody-bortezomib-lenalidomide-dexamethasone (CD38-VRD) or bortezomib-lenalidomide-dexamethasone (VRD), and non-SCT patients with CD38-antibody-lenalidomide-dexamethasone (CD38-RD) or VRD. We compared the total HCRU between the groups. **Results:** 122 MM patients (28 SCT, 94 non-SCT) received

first-line CD38-antibody-based therapy. The SCT group was younger than the non-SCT group (mean 59.9, SD 9.3 years; 73.5, SD 7.6 years). CD38-treatment arms did not differ in age, ISS/R-ISS-scores or comorbidities in either group. The yearly total HCRU/patient of CD38-antibody-treated SCT patients were higher than in non-CD38-treated patients (72 739€ vs. 14 2027€): specific HCRU differences were −1155€ for outpatient visits, −1580€ for procedures and −2132€ laboratory tests, 72761€ for medications and 1519€ for inpatient treatment. For non-SCT patients total costs were 137 739€ vs 38 835€, and differences −1891€ for outpatient visits, 655€ for procedures, 1560€ for laboratory tests, 95 663€ for medications, 2782€ for inpatient treatment. To estimate cost-effectiveness, we examined overall survival (OS) and time to next treatment (TTNT). There was a trend for improved TTNT in the non-SCT group ($p = 0.2$), which was limited by brief follow-up time, median 7.3 months. We could not see any difference in OS $p = 0.72$. In the SCT-group there was no significant difference regarding OS or TTNT. **Conclusions:** In our study we show for the first time the total HCRU costs for patients treated with CD38-antibody therapies as first-line. The increased HCRU costs observed were not linked with apparent OS or TTNT benefit. Further long-term data is required to validate these results, as a key limitation of the current study is the relatively limited follow-up period and sample size. With the advent of many novel MM therapies, balancing HCRU and clinical benefit is crucial and mandates systematic data collection to implement value-based care.

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Healthcare Resource Utilization and Cost Implications of Outpatient Bispecific Antibody Step-Up Dosing in Relapsed/Refractory Multiple Myeloma: A Real-World Experience from a Large Academic Center

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Introduction: Bispecific antibodies (BsAbs) have transformed treatment of relapsed/refractory multiple myeloma (RRMM). Current U.S. FDA labeling recommends inpatient(IP) 48 hour hospitalization during step-up dosing(SUD) for teclistamab(Tec) and talquetamab(Tal). Outpatient(OP) SUD pathways are emerging but remain limited in adoption. We evaluated the feasibility, safety, and healthcare resource utilization associated with OP BsAb SUD at a large academic center. **Methods:** We performed a retrospective analysis among patients (pts) who received Tec or Tal SUD for RRMM at Vanderbilt University Medical Center between May 2023 and January 2026. Clinical, demographic, SUD setting, hospitalization days, cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS) incidence and management data were analyzed. Estimated hospitalization charges were calculated using published National Inpatient Sample multiple myeloma hospitalization data by Solangi, et al. (2024). Medication margin estimates (OP vs IP) were derived using published report by Puttkammer et al. (2025). **Results:** Fifty-one pts underwent 58 BsAb SUD treatments, including 34 Tec (58.6%) and 24 Tal (41.4%); 7 pts received both at different time points. Thirty-four (58.6%) SUD events were IP, 24 (41.4%) were OP (20 fully OP and 4 hybrid). Median (range) hospitalization duration was 8 days (6–12) for IP versus 0 days (0–5) for OP delivery. Overall, 306 hospitalization days were potentially avoidable, including 20 days attributable to grade (G)1 CRS management. Using a cost estimate of $16,240 per hospitalization day for myeloma, this translated to an estimated $4.97 million in potentially avoidable hospitalization cost. Additional healthcare savings were associated with the administration of high-cost medications [Tec, Tal, and tocilizumab (Toci)] in the OP vs IP setting. Overall, 120 IP (78 Tec, 42 Tal) and 13 Toci doses were administered: based on published medication margin methodology, this would have yielded an estimated additional cost margin savings of $1.55 million with full OP delivery. The total estimated potential healthcare savings exceeded $6.5 millions in the study cohort. Overall response rate was 76.4% for Tec and 87.5% for Talq; ≥VGPR was achieved in 67.6% of Tec and 54.2% of Talq. CRS occurred in 31 (53.4%) SUD events, with G2 CRS in 7 (12.1%) and ICANS in 8 (14.3%) SUD events, all G1. No G3 toxicity was observed with OP SUD. **Conclusions:** In this real-world single center analysis, full OP BsAb SUD in RRMM was feasible and safe. Full OP Tec/Tal SUD delivery with OP G1 CRS management yields marked reductions in healthcare utilization. These findings support broader adoption of structured OP SUD pathways and highlight the need for prospective studies to define standardized monitoring strategies and selection criteria as BsAbs continue to expand across myeloma treatment landscape.

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Health-Related Quality of Life (HRQoL) Is Influenced by Clinical Features Rather Than Genetic Risk in Newly Diagnosed Myeloma Patients: Results from the UK Myeloma Research Alliance (MRA) RADAR Trial

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Introduction: Newly diagnosed multiple myeloma (NDMM) is associated with impaired health-related quality of life (HRQoL), but the impact of SLiM-CRAB and other disease features on HRQoL is unclear. Few studies compare HRQoL between NDMM and smouldering myeloma (SMM). We analysed RADAR patient-reported outcomes to assess the influence of disease risk, clinical features and SLiM-CRAB on baseline HRQoL. **Methods:** The UK MRA-RADAR trial is a risk-adapted, phase II/III study in transplant-eligible NDMM. Induction, consolidation and maintenance therapies use combinations of lenalidomide, cyclophosphamide, bortezomib, dexamethasone and isatuximab. High-risk (HR) is defined as ≥2 of: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) and del(1p). COSMOS is a multi-centre prospective observational study in SMM with longitudinal disease, clinical and translational assessments. HRQoL was assessed using EORTC QLQ-C30 and MY20. One-way ANOVA and two-sample unequal variance t-test were used to compare subscales between groups. Hedge's g was used to compare between RADAR and COSMOS patients. P-values were Bonferonni-corrected. Multivariate analysis was done using F-test. Reported differences met statistical and minimally important difference thresholds. **Results:** Baseline HRQoL scores were available for 1160 patients; median age 61(55–66), male 58.1%, ECOG PS 0–1 88%. Clinical features: 12.2% had hypercalcaemia (>2.6 mmol/l), 14% had eGFR < 60 mL/min/1.73 m^2, 23.9% had anaemia (Hb< 100 g/L), 68.3% had ≥1 bone lesion. 20.2% had HR disease. ISSI/II/III were 37.6%/42.8%/7.0%. Younger patients (30–39, n = 21) had inferior HRQoL scores. Hypercalcaemia was associated with worse global health status, physical, role and social functioning ($p \leq 0.003$). Anaemia was associated with more fatigue, dyspnoea, global health status and all functional scales except for emotional functioning ($p < 0.0001$). Bone lesions was associated with more fatigue, pain and insomnia, and worse global health status, physical, role and social functioning ($p \leq 0.002$). Those treated based on SLiM criteria (19.7%) had better HRQoL ($p < 0.0001$ cf CRAB), except for emotional functioning. Genetic risk did not influence HRQoL scores. Higher ISS was associated with more fatigue, appetite loss, dyspnoea and worse global health status and all functional scales except for emotional functioning ($p < 0.0001$). On multivariate analysis, ISS, age, anaemia, and bone lesions are negative predictors of HRQoL. Compared with SMM patients (n = 108), NDMM patients had worse scores across all functional scales, with ≥27points difference in mean scores in pain, role and social functioning. Comparing between NDMM and SMM patients that fulfilled SLiM criteria, NDMM patients had worse social and role functioning and future perspective. **Conclusions:** HRQoL of NDMM patients is largely influenced by clinical features. Patients diagnosed based on SLiM criteria have better HRQoL but similar emotional functioning compared to those with CRAB features. NDMM have worse HRQoL than SMM patients.

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Health-Related Quality of Life with Mezigdomide, Carfilzomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Phase 3 SUCCESSOR-2 Trial

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Introduction: Interim results from the phase 3 SUCCESSOR-2 study showed that adding mezigdomide (Mezi) to carfilzomib-dexamethasone (Kd) significantly prolonged progression-free survival (PFS) versus Kd alone in patients (pts) with relapsed/refractory multiple myeloma (RRMM) previously treated with anti-CD38 monoclonal antibodies (mAbs) and lenalidomide (LEN). To determine whether improved disease control is achieved at the expense of pt-reported functioning, we evaluated health-related quality of life (HRQoL) in SUCCESSOR-2 (NCT05552976). **Methods:** Pts with RRMM who had received ≥1 prior line of antimyeloma therapy, including an anti-CD38 mAb and LEN, and who were naive to Mezi and carfilzomib, were randomized to selected-dose MeziKd or Kd. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Multiple Myeloma Module (-MY20) at baseline, day 1 of cycles 1–7 then every 3 cycles from cycle 8 onward, at end of treatment, and at the 28-day follow-up visit. Analyses were conducted in the stage 2 intent-to-treat (ITT)

population. Constrained longitudinal data analysis estimated between-arm differences in least-squares mean change from baseline. Time to first meaningful deterioration was evaluated using stratified Cox proportional hazards models. Key domains included QLQ-C30 global health status/QoL, physical functioning, role functioning, pain, and fatigue; and QLQ-MY20 disease symptoms and side effects of treatment. **Results:** The stage 2 ITT population included 371 pts (MeziKd, n = 225; Kd, n = 146); HRQoL was similar at baseline across both treatment arms. Throughout the study, pts treated with MeziKd experienced overall HRQoL and daily functioning comparable with Kd; differences were small and suggested no observed meaningful worsening. Outcomes included global health status/QoL (difference 0.63 [95% CI, −2.48 to 3.73]), physical functioning (−0.18 [−3.40 to 3.03]), role functioning (−0.78 [−4.76 to 3.20]), fatigue (−0.65 [−4.11 to 2.82]), pain (−2.99 [−6.76 to 0.78]), and side effects (−1.11 [−3.07 to 0.84]). Disease-related symptoms improved with MeziKd, showing a greater reduction compared with Kd (difference −3.12 [−5.77 to −0.46]; nominal P = 0.022). Pts receiving MeziKd experienced a longer time before worsening of disease symptoms, with deterioration delayed to a median of 41.6 weeks versus 24.3 weeks for Kd (HR, 0.71 [95% CI, 0.51 to 0.99]; nominal P = 0.046). Time to deterioration in other QoL domains was similar between treatment arms, suggesting that MeziKd did not negatively impact pts' day-to-day functioning over time. **Conclusions:** Adding Mezi to Kd in pts with RRMM did not meaningfully compromise pt-reported global QoL, physical or role functioning, pain, fatigue, disease symptoms, or perceived treatment side effects. Together with the reported PFS benefit, these findings support MeziKd as improving disease control without a broad HRQoL trade-off.

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Healthy Individual–Referenced Immune Aging Identifies a Novel Host Fitness Biomarker in Multiple Myeloma

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Introduction: Chronological age incompletely captures host immune fitness in multiple myeloma (MM). Progressive depletion of naïve lymphocyte compartments is a hallmark of immune aging, yet substantial heterogeneity exists among individuals of similar age. We developed a biologically interpretable donor-referenced immune aging model to quantify age-adjusted immune dysfunction and evaluated its association with clinical outcomes in MM. **Methods:** Peripheral blood immunophenotyping data from 216 patients with MM and 152 healthy donors were analyzed. Donor-derived cubic spline models were generated for age-associated trajectories of naïve CD4+ T cells, naïve CD8+ T cells, and naïve CD19+ B cells using log2-transformed absolute counts. For each patient, age-adjusted residuals were calculated as the difference between observed and expected donor values and standardized using donor residual standard deviations. A composite ImmuneAgingScore was constructed from weighted residuals (CD4 naïve 50%, CD8 naïve 25%, naïve B cells 25%), with higher scores indicating greater immune aging. Associations with overall survival (OS) and progression-free survival (PFS) were evaluated using Kaplan-Meier and Cox proportional hazards analyses. **Results:** Patients with MM demonstrated marked depletion of naïve CD4+, CD8+, and B-cell compartments compared with age-matched donors, consistent with accelerated immune aging. The ImmuneAgingScore showed minimal correlation with chronological age, confirming effective age normalization. During a median follow-up of 119 months for OS and 123 months for PFS, 103 deaths and 163 progression events occurred. Higher ImmuneAgingScore was associated with inferior OS as a continuous variable (HR 1.25 per standard deviation increase; 95% CI 1.02–1.53; P = 0.034). When stratified into quartiles, patients in the highest immune-aging quartile experienced significantly worse OS compared with the lowest quartile (HR 1.82; 95% CI 1.12–2.96; log-rank P = 0.021). In contrast, ImmuneAgingScore was not significantly associated with PFS (HR 1.08; 95% CI 0.96–1.21; P = 0.225). **Conclusions:** A donor-referenced ImmuneAgingScore identifies biologically meaningful immune dysfunction that is largely independent of chronological age and is associated with inferior overall survival in multiple myeloma. These findings suggest that immune age represents a novel dimension of host fitness that may complement traditional disease-based prognostic markers and help inform risk stratification in the era of immune-based therapies.

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Hematology-Oncologists' Perspectives on an On-Body Injector for Administration of Large-Volume Subcutaneous Drugs: Implications for Isatuximab Subcutaneous for Multiple Myeloma

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Introduction: Isatuximab (Isa) has been investigated as a subcutaneous (SC) formulation administered through an innovative on-body injector (OBI) in multiple myeloma. Isa SC OBI provides hands-free administration through a small, hidden retractable needle. Here, we assessed physician perspectives on the value of the OBI and their preferences for the OBI vs previous experience with large-volume SC manual injections. **Methods:** This was a qualitative semi-structured cross-sectional double-blinded survey of 50 US hematology-oncologists (heme-oncs). Participants were shipped an unbranded device with a vial of surrogate solution that mimicked the fill volume and viscosity of Isa SC, guided to conduct a hands-on

demonstration, and interviewed remotely one-on-one. Physicians with previous experience with the OBI were excluded. **Results:** Heme-oncs were from private practices (n = 16), academic cancer centers (n = 12), teaching hospitals affiliated with (n = 8) or not affiliated with an academic center (n = 7), and community hospitals (n = 7). Median percentage time in direct patient care was 90% (range 50 to 100%). Most (92%) reported a positive perception of the OBI, and most (90%) thought the OBI was valuable for their practice. Unaided mentions of value included easy to use (n = 45), hands-free for nurses (n = 20), and small needle (n = 15). Among 7 features, those ranked in the top 3 were (1) simple 1-step vial-to-device preparation, (2) hands-free administration, (3) potential to reduce preparation time in the pharmacy compared to large-volume (≥10 mL) SC manual injections. All heme-oncs agreed they would feel confident with treatment by an HCP using the OBI in the clinic. Most (94%) agreed they would feel confident with a pharmacist preparing/loading the OBI outside the sterile hood, and similarly most (92%) agreed they would feel confident with a nurse preparing/loading the OBI by the patient's chairside. The vast majority (98%) thought the OBI required less resources and effort (eg, pharmacist/nurse time) for preparation and administration than large-volume SC manual injections, and most (92%) would choose the OBI over large-volume SC manual injections, assuming no differences in efficacy, safety, and/or cost and that both methods were suitable for the patient. Most (92%) thought it would be feasible for nurses to prepare the OBI in the infusion center at their own practice, and 72% thought it would be feasible to administer the OBI in their own clinic but outside the infusion center. **Conclusions:** Heme-oncs who completed hands-on demonstrations with the OBI recognized clinical value, driven primarily by streamlined preparation workflows and hands-free administration capability. Most had a clear preference for the OBI over large-volume SC manual injections. Most expressed confidence in clinic staff's ability to prepare the OBI outside sterile hood environments or by patient chairside. These findings support the value of the OBI in delivery of Isa SC for multiple myeloma treatment.

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Hepatitis B Virus Reactivation in Multiple Myeloma Patients Treated with Daratumumab-Based Regimens

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Introduction: Daratumumab-based regimens have become the standard first-line therapies for multiple myeloma (MM). Hepatitis B virus reactivation (HBVr) is a potentially fatal complication in patients with resolved hepatitis B infection undergoing anti-CD38 monoclonal antibody therapy. This study evaluated the incidence and clinical outcomes of HBVr in HBsAg-negative/anti-HBc-positive MM patients treated with daratumumab. **Methods:** A retrospective study was conducted in MM patients treated with daratumumab between July 2020 and October 2025 at two Chinese academic centers. HBV serology, HBV DNA, and liver function were monitored during treatment. **Results:** A total of 555 MM patients treated with daratumumab were enrolled, including 336 newly diagnosed MM (NDMM) and 219 relapsed/refractory MM (RRMM) cases, All patients were HBsAg-negative/anti-HBc-positive and did not received any antiviral prophylaxis. Among 142 eligible patients, 7 (4.93%) developed HBVr. The incidence was 1.18% (1/85) in newly diagnosed MM (NDMM) and 10.53% (6/57) in relapsed/refractory MM (RRMM), with a significant difference (P = 0.017). One patient had mild liver dysfunction; no liver failure occurred. Five patients achieved HBV DNA negativity after antiviral therapy and continued MM treatment. Two patients died of progressive MM. **Conclusions:** The risk of HBVr is significantly higher in RRMM than in NDMM among HBsAg-negative/anti-HBc-positive patients receiving daratumumab. Prophylactic antiviral therapy should be considered in RRMM patients to prevent HBVr.

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Hidden Heterogeneity in Multiple Myeloma Outcomes Among Asian American and Pacific Islander Subgroups: A SEER Analysis, 2012–2022

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Introduction: Asian American and Pacific Islander (AAPI) patients are often underrepresented in multiple myeloma (MM) clinical trials and analyzed as a single group in population-level studies. This approach may obscure differences among populations that are genetically, culturally, and socioeconomically (SE) heterogeneous, which could impact real-world care. High-risk cytogenetics (HRC) are associated with inferior outcomes in MM, but it is unclear whether the prevalence differs across disaggregated AAPI groups and contributes to observed survival disparities. We evaluated HRC and survival among disaggregated AAPI groups in the Surveillance, Epidemiology, and End Results (SEER) Research Plus Dataset. **Methods:** Adult patients diagnosed with MM from 2012 to 2022 were identified. HRC was defined by SEER as deletion 17p, t(4;14), and t(14;16). R software (4.5.3) was used to fit Cox proportional hazards models, adjusted for age, sex, race, income, urban status, and HRC. Kaplan Meier (KM) analysis was run with the "survminer" package. **Results:** 18856 patients with MM, including 1554 AAPI, were selected. Filipinos, Chinese, and Hawaiians represented the largest AAPI groups. 54.9% were male, with a median age at diagnosis of 69 years. Koreans and Japanese were the oldest at 72 years, with Pacific Islanders (PIs) the youngest at 60 years. HRC were present in

9.2% of Chinese, 8.1% of Filipinos, 5.1% of Hawaiians, 8.4% of Japanese, 11.4% of Koreans, 15.4% of Pacific Islanders, 19.2% of Samoans, 14% of South Asians, 15% of Vietnamese, and 9.6% in non-AAPI. One-year median survival (OS) in AAPI and non-AAPI patients with HRC was 87.4% and 81.2%, and without HRC, 87% and 87.9%, respectively. KM calculated survival in months was 58 (95% CI: 52, 69) for Chinese, 57 (51, 67) for Filipinos, 61 (53, 72) for Hawaiians, 54 (46, 71) for Japanese, 60 (38, 86) for Koreans, 46 (30, NA) for PI, 32 (28, NA) for Samoans, 46 (39, 64) for South Asians, and 68 (46, 80) for Vietnamese. Compared with non-AAPI, Cox-adjusted hazard ratios were 1.2 for Filipinos (95% CI: 1.0, 1.4), 1.45 for Hawaiians (1.2, 1.8), 1.7 for PI (1.0, 2.6), and 2.2 for Samoans (1.3, 3.4). Adjusted mortality was not significantly different for East Asian, South Asian, or Vietnamese patients. Adding HRC to the model did not significantly change the observed hazard ratios for AAPI. **Conclusions:** Disaggregated analysis of AAPI patients with MM revealed substantial heterogeneity in outcomes. Filipino, Hawaiian, Pacific Islander, and Samoan patients had significantly higher adjusted mortality compared to non-AAPI patients, and these differences persisted after HRC adjustment. These findings suggest aggregating AAPI patients into a single category may obscure these disparities, and larger studies are needed to evaluate whether differences in SE factors, trial accrual, comorbidities, disease biology, or treatment response impact survival in these patients.

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High MRD- Rates and Prolonged PFS with Belantamab Mafodotin Plus Daratumumab, Lenalidomide, and Dexamethasone in Transplant-Ineligible Newly Diagnosed Myeloma: Results of the Phase 1/2 BelaDRd Study

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Introduction: The MAIA trial established daratumumab with lenalidomide, dexamethasone (DRd) as standard therapy for transplant-ineligible (TI) NDMM. Belantamab mafodotin (belamaf) showed high efficacy in relapsed/refractory disease. Quadruplet regimens improved clinical outcomes, providing rationale to evaluate belamaf with DRd in TI NDMM. **Methods:** BelaDRd is a phase 1/2 study, evaluated the combination in TI-NDMM. Part 1 (dose-finding phase) assessed the safety and tolerability of 2 belamaf doses (1.9/1.4 mg/kg Q8W) with DRd. This part established belamaf 1.9 mg/kg Q8W, extended to Q12W as RP2D. Part 2 (dose-expansion phase) evaluates the safety and efficacy of RP2D in Groups A and B, guided by ophthalmologist and hematologist (using Vision-Related Anamnestic tool), respectively. **Results:** In Part 1, 24 patients (pts) (median age:73 years; male:54.2%) entered the study; 12.5% had high-risk cytogenetics (HRC). With median follow-up of 34.3 months, 18 (75%) pts remained on treatment, while 6 (25%) discontinued; one due to AE/SAE, disease progression and withdrew consent each, and three died due to infections. Of 380 planned belamaf doses, 105 doses were skipped due to OAEs. The median dose intensity (MDI) was 0.5 mg/kg/Q4W. The ORR was 91.7%; 70% of pts achieved both ≥CR and ≥VGPR. MRD negativity was achieved in 13 (81.3%) of evaluable pts (n = 16). In Part 2 (n = 12; median age:74 years; male:58.3%), 16.7% of pts had HRC. At a median follow-up of 17.9 months, 11 (91.7%) pts remained on treatment; one pt (8.3%) discontinued due to PD. Of 113 planned belamaf doses 13 (11.5%) doses were skipped due to OAEs. The MDI was 0.8 mg/kg/Q4W. ORR was again 91.7% (11/12 pts), while MRD negativity was achieved in 5 (71.4%) of evaluable pts (n = 7). The median time to ≥PR was 1.1 months for both parts. At 30 months, PFS was 85.9% (95% CI 64.6–94.9) and 87.5% (95% CI 66.1–95.8) in the overall and RP2D populations, respectively; corresponding TTP rates were 90.1% (95% CI 66.2–97.9) and 95.5% (95% CI 71.9–99.4). Fatal TEAEs occurred in 3 pts of cohort 1 and none in part 2. Fatigue was the most common Gr ≥3 non-ocular AE in parts 1 and 2 (13[54.2%] and 6[50.0%] pts, respectively). Gr ≥3 BCVA decline was observed in 74 (10.4%) of ocular assessments in part 1 and 4 (3.9%) and 5 (5.3%) in groups A and B, respectively. Gr ≥2/≥3 keratopathy occurred in 20.2%/0.6% of assessments in Part 1; in Part 2, rates were 6.7%/0% (Group A) and 10.6%/0% (Group B). Median ≥Gr 2 BCVA OAE/keratopathy resolution time was 1.1/1.0 months (Part 1) and 1.9/1.0 months (Part 2). **Conclusions:** The study showed rapid, deep responses and high MRD negativity rates. Low frequency of ≥Gr 3 OAEs occurred and resolved rapidly. Similar frequency of OAEs occurred when dosing was guided by haematologist vs ophthalmologist ocular assessment. The remarkable PFS supports further evaluation of this quadruplet in a phase 3 study versus other novel combinations in NDMM.

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High-Dose Melphalan and Autologous Stem Cell Transplantation in Multiple Myeloma: Updated Real-World Outcomes from India: A Single-Centre Experience of 203 Patients

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Introduction: Background: High-dose therapy followed by autologous stem cell transplantation (HDT-ASCT) remains standard of care for transplant-eligible multiple myeloma (MM). Real-world

long-term outcome data from resource-limited settings, particularly regarding the comparative efficacy of Melphalan 200 mg/m^2 (Mel200) versus Melphalan 140 mg/m^2 (Mel140) conditioning, remain limited. We report updated survival outcomes from our single-centre experience, expanding our previously reported cohort of 186 patients to 203 patients. **Methods:** Methods:Retrospective analysis of 203 patients with MM who underwent HDT-ASCT between 2001 and 2026 was done. Patient characteristics, conditioning regimen, engraftment data, response, and survival outcomes were analysed. Overall survival (OS) and progression-free survival (PFS) estimated using the Kaplan-Meier method. Subgroup comparisons between Mel200 and Mel140 performed using the log-rank test; hazard ratios (HR) estimated by Mantel-Haenszel method. **Results:** Median age was < 60 years in 175 patients (86.2%); 141 (69.5%) were male. Newly diagnosed MM (NDMM) 153 (75.4%) and relapsed/refractory MM (RRMM) 50 (24.6%) patients. Pre-transplant IMWG response ≥VGPR in 155 patients (76.4%): sCR in 18 (8.9%), CR in 34 (16.8%), and VGPR in 103 (50.7%). ISS stage I 52 (25.6%), Stage II 76 (37.4%), and Stage III 54 (26.6%). High-risk cytogenetics i45 (22.2%) patients. Conditioning Mel200 in 164 (80.8%),Mel140 in 39 (19.2%). Median neutrophil, platelet engraftment on Day 11 (range 6–38) Day 13 (range 6–90), respectively. Treatment-related mortality (TRM) was 2.0% (n = 4). Grade ≥3 mucositis in 49 patients (24.1%). At median follow-up of 108.3 months (reverse KM method), median OS from ASCT for the entire cohort was 99.1 months (95% CI: 91.6–131.7). The 1-, 2-, 3-, 5-, and 7-year OS rates were 93.9%, 90.3%, 87.1%, 73.5%, and 63.6%, respectively. Median PFS was 88.8 months (95% CI: 74.8–99.1), with 1-, 2-, 3-, 5-, and 7-year PFS rates of 90.4%, 84.3%, 80.3%, 64.1%, and 52.5%, respectively. Subgroup analysis, Mel200 was associated with numerically superior median OS compared to Mel140 (102.7 vs 89.2 months; HR 1.60 for Mel140 vs Mel200; log-rank p = 0.074) and median PFS (91.6 vs 59.3 months; HR 1.31; p = 0.298). The OS difference trended towards but did not reach statistical significance, likely reflecting patient selection bias with Mel140 preferentially used in older or higher-comorbidity patients. **Conclusions:** Conclusions: In this updated single-centre analysis of 203 myeloma patients undergoing HDT-ASCT, excellent long-term outcomes with a median OS approaching 100 months observed and TRM of only 2%. While Mel200 showed numerically superior OS and PFS, the difference was not statistically significant, consistent with published literature. These data from a real-world setting affirm the durability of HDT-ASCT and support its continued role in transplant-eligible MM, including in resource-constrained environments.

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High-Throughput Single-Cell Structural Lipidomic Profiling Reveals Ether-Phosphatidylethanolamine Remodeling and Ferroptosis Vulnerability Linked to 1q21 Amplification in Multiple Myeloma

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Introduction: Multiple myeloma is characterized by biological heterogeneity, yet phospholipid landscape of plasma cells across disease spectrum remains uncharacterized at single-cell resolution. Ether-linked phosphatidylethanolamines (PE-O/plasmalogens) and polyunsaturated fatty acid-containing PE (PUFA-PE) are linked to ferroptosis, an iron-dependent regulated cell death pathway with emerging therapeutic relevance in hematologic malignancies. Conventional bulk lipidomics obscures cell-to-cell variation and cannot resolve structural isomers. We applied a novel high-throughput single-cell structural lipidomics platform to map phospholipid landscape across MM spectrum and interrogate cytogenetic subgroup-specific remodeling. **Methods:** Plasma cells from 17 patients (1MGUS, 2SMM, 12MM, 2 PCL) were profiled by high-throughput single-cell structural lipidomics, yielding 12,727 single-cell lipidomes. 111 lipid species were retained. Differential abundance was assessed using linear mixed models (LMM) with patient as a random effect. A Ferroptosis Sensitivity Score (FSS = ΣPUFA-PE/ΣPE-O) was computed per cell. Cytogenetic subgroups defined by FISH: 1q21+ (positive /negative, n = 6/6) and t (4;14) (n = 6/6) were compared. **Results:** Disease spectrum and heterogeneity. Plasma cell lipidomes clustered mainly by patient identity rather than disease stage: the median between-patient to between-stage variance ratio was 10.2-fold. Intra-patient coefficient of variation (median 0.330) confirmed extensive cell-to-cell variation invisible to bulk approaches. PE-O composition was elevated in SMM and MM (27%) relative to MGUS (20%) and PCL (21%). Ferroptosis sensitivity and PE-O as primary driver. FSS ranged from 0.21 to 1.27 across 12,727 cells (stage medians: MGUS 0.75, SMM 0.51, MM 0.55, PCL 0.58). Per-patient median FSS was strongly inversely correlated with PE-O abundance (p = 0.0001), indicating ether-PE depletion, but not PUFA-PE accumulation, is principal determinant of ferroptosis vulnerability. Amplification 1q21 elevates FSS via selective PE-O depletion. 1q21+ patients showed significantly higher FSS than non-1q21+ ones (0.62vs.0.52, p = 0.018), driven by a 5.5 percentage-point reduction in PE-O composition (p = 0.010). 19 of 22 PE-O species were reduced. The magnitude of PE-O reduction correlated with FSS elevation across species (Spearman r = 0.683, p = 0.0005). Translocation (4;14). LMM identified 2 significantly upregulated lipids in t(4;14) vs. non-t(4;14). The t

(4;14)/1q21+ co-occurring subgroup(n = 5)showed highest median FSS among cytogenetic subgroups, consistent with additive ether lipid remodeling in this combination. **Conclusions:** High-throughput single-cell lipidomics reveals profound inter- and intra-patient phospholipid heterogeneity in MM that eclipses disease-stage effects. 1q21+ is associated with selective PE-O depletion, elevating ferroptosis sensitivity. These findings establish a cytogenetic-lipidomic axis in MM and nominate PE-O biosynthesis as a potential vulnerability in high-risk subgroups.

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Hitting Two Birds with One Stone: CD85k-BCMA Dual-Targeted CAR-T Cells in Relapsed/Refractory Multiple Myeloma

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Introduction: Despite the remarkable efficacy of BCMA CAR-T therapy in multiple myeloma (MM), however, the durability of response is frequently limited by antigen escape and the emergence of antigen-negative clones. To address this challenge, we identified CD85k as a strategic target for combinatorial immunotherapy. CD85k expression is not only restricted to aggressive early myeloma cells but also prominent on myeloid-derived suppressor cells (MDSCs). Here, we report the development of a novel bispecific CD85k-BCMA CAR T-cell construct. By concomitantly targeting tumor cells and ablating the immunosuppressive MDSC compartment, this approach delivers a synergistic "one-stone-two-birds" effect. We hypothesize that this strategy will mitigate antigen escape and sustain anti-tumor immunity, thereby improving progression-free survival (PFS) in relapsed/refractory multiple myeloma (RRMM). **Methods:** To elucidate CD85k's clinical significance, we analyzed single-cell RNA-seq datasets correlating expression with DARA-KRD responsiveness and PFS post-BCMA CAR-T therapy. CD85k surface expression was profiled via flow cytometry in MM cell lines and primary samples (newly diagnosed vs. relapsed). Functional roles were assessed in CRISPR/Cas9 CD85k-knockout MM cells via proliferation and colony-formation assays. Therapeutically, CD85k-targeting and bispecific CD85k-BCMA CAR-T cells were engineered. In vitro cytotoxicity, cytokine secretion, and MDSC depletion were evaluated, alongside antitumor efficacy in patient-derived bone marrow co-cultures and ARP1 xenograft NSG mice. **Results:** CD85k overexpression significantly correlated with DARA-KRD regimens and shorter PFS post-BCMA CAR-T. Flow cytometry confirmed CD85k upregulation in relapsed and post-BCMA CAR-T patients versus newly diagnosed cohorts. CD85k knockout impaired clonal expansion and colony formation. In vitro, CD85k CAR-T cells exhibited potent cytotoxicity and cytokine release, efficiently clearing patient-derived MDSCs. In xenograft models, CD85k CAR-T cells substantially reduced tumor burden, achieving efficacy comparable to BCMA CAR-T cells. Furthermore, in bone marrow co-cultures, CD85k-BCMA CAR-T cells demonstrated superior malignant plasma cell elimination compared to single-target controls, underscoring the robust therapeutic potential of this dual-targeting strategy. **Conclusions:** Our findings identify CD85k as a key mediator of relapse, we demonstrate that bispecific CD85k-BCMA CAR-T cells provide superior efficacy compared to monotherapies. By efficiently clearing both malignant clones and immunosuppressive MDSCs, this approach offers a potent strategy to circumvent antigen escape and microenvironment-mediated resistance, paving the way for improved outcomes in RRMM. **Funding support:** Key International Cooperation Projects of Tianjin #25YFGKHZ00100; Key Projects of Tianjin Natural Science Foundation #25JCZDJC00530; Noncommunicable Chronic Diseases-National Science and Technology Major Project #2023ZD0501300.

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Home-Based Subcutaneous Therapy in Elderly and Frail Patients with Multiple Myeloma: A Single-Centre Real-World Experience from India

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Introduction: Elderly and frail myeloma patients face significant logistical and clinical challenges in accessing hospital-based therapy, particularly in resource-limited settings. Home-based subcutaneous (SC) drug administration, supervised by trained nurses, offers a safe and patient-centric alternative. Real-world data from the Indian subcontinent on this approach remain limited. Aims To evaluate the feasibility, safety, efficacy, and patient satisfaction of home-based SC therapy in elderly and frail MM patients at a single centre in Mumbai, India. **Methods:** A retrospective observational study of 9 MM patients receiving home-based SC therapy (2020–2026). Eligibility was assessed using IMWG frailty score, KPS, caregiver availability, drug storage feasibility, and distance from hospital. Regimens included SC Daratumumab and SC Bortezomib, combined with Pomalidomide, Lenalidomide, or Dexamethasone. Trained nurses administered therapy in 8 patients; 1 patient self-administered. Outcomes included treatment completion rates, IMWG-defined responses, CTCAE-graded adverse events, unplanned hospital visits, and patient-reported satisfaction. **Results:** Median age was 74 years (range 55–83); 5 male, 4 female. By IMWG criteria, 5 patients were frail, 3 intermediate-fitness, and 1 fit. ECOG ranged from 0–3. Myeloma isotypes included IgG Lambda (n = 3), IgA Kappa

(n = 3), IgA Lambda (n = 2), and IgG Kappa (n = 1). Six patients received maintenance therapy; 3 received active treatment (1st–3rd line). A total of 158 SC home administrations were delivered, constituting 71–100% of planned treatment time in evaluable patients. Treatment responses were encouraging: 7 patients (78%) achieved VGPR, 1 (11%) achieved CR, and 1 (11%) maintained stable disease, with a median time to best response of 2 months. No infusion-related reactions, anaphylaxis, or DVT were recorded. Grade 1–2 adverse events included neutropenia (n = 2), peripheral neuropathy (n = 2), anemia (n = 2), and one episode of UTI. Dose reductions were required in 1 patient. Each home visit saved ~90 minutes, with >180 cumulative OPD visits avoided. All evaluable patients strongly preferred home therapy (satisfaction 5/5), citing reduced travel and preserved daily activities. Caregiver burden was low in all cases. One patient expired from disease progression; one was lost to follow-up after TB-related hospitalization. **Conclusions:** Conclusions Home-based SC therapy is feasible, safe, and well-tolerated in elderly and frail MM patients in India, offering substantial reduction in hospital burden while preserving quality of life. Prospective studies are warranted to establish standardized protocols for home-based MM therapy in India Keywords: Multiple Myeloma · Home-based therapy · Subcutaneous Daratumumab · Bortezomib · Elderly · Frailty · Quality of Life · India. **Methods:** A retrospective observational study of 9 MM patients receiving home-based SC therapy (2020–2026). Eligibility was assessed using IMWG frailty score, KPS, caregiver availability, drug storage feasibility, and distance from hospital. Regimens included SC Daratumumab and SC Bortezomib, combined with Pomalidomide, Lenalidomide, or Dexamethasone. Trained nurses administered therapy in 8 patients; 1 patient self-administered. Outcomes included treatment completion rates, IMWG-defined responses, CTCAE-graded adverse events, unplanned hospital visits, and patient-reported satisfaction. **Results:** Median age was 74 years (range 55–83); 5 male, 4 female. By IMWG criteria, 5 patients were frail, 3 intermediate-fitness, and 1 fit. ECOG ranged from 0 to 3. Myeloma isotypes included IgG Lambda (n = 3), IgA Kappa (n = 3), IgA Lambda (n = 2), and IgG Kappa (n = 1). Six patients received maintenance therapy; 3 received active treatment (1st–3rd line).

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How to Select ASCT Candidates in Patients with Suboptimal Stem Cell Mobilisation: A Case Study

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Introduction: ASCT deepens the induction response and prolongs progression-free survival, and is standard care in the UK for transplant-eligible patients with multiple myeloma. Patients with suboptimal stem cell collection have poorer outcomes. Poor mobilisers typically have stem cell yields of < 2.0 × 106 CD34+ cells/kg. At our centre, we also assess the stem cell colony (GM-CFC). GM-CFC < 20 × 104/kg is insufficient for ASCT. Common risk factors are prolonged prior chemotherapy or lenalidomide use, prior radiotherapy to the pelvis, bone marrow infiltration by disease and bone marrow failure. Careful investigation of the causes of poor mobilisation is essential for a safe ASCT procedure. **Methods:** We retrospectively reviewed the electronic patient record and the laboratory record of a case with suboptimal stem cell mobilisation. **Results:** A 59-year-old female presented with mild anaemia, neutropenia, an IgG lambda paraprotein of 28 g/L and a frontal bone lytic lesion. Her bone marrow showed 15% clonal plasma cells. CD138 cell FISH showed 1q gain. She was diagnosed with IgG lambda myeloma, standard cytogenetics risk. She was treated with DaraVTD induction chemotherapy to partial response (paraprotein 4 g/L), and the plan was to proceed to ASCT. Two million CD34+ cells/kg were collected with G-CSF mobilisation, but the GM-CFC was borderline at 20 × 104/kg. Post-induction, she remained cytopenic (Hb 102 g/L, WBC 3.2 × 109/L, neutrophils 1.9 × 109/L, platelets 133 × 109/L). A bone marrow biopsy showed erythroid and megakaryocyte dysplasia without blast excess and 4% lambda-restricted plasma cells. Extended NGS identified three pathogenic variants (TET2 p.His682IlefsTer18 (VAF 17%), U2AF1 p.Gln157Pro (VAF 16%) and TET2 p.Lys1720Ter (VAF 16%)). Her mild cytopenia persisted despite correcting haematinics deficiency and holding off further chemotherapy. A repeat bone marrow biopsy two months later showed persistent dysplasia, which supported the diagnosis of myelodysplastic syndrome with multilineage dysplasia (IPSS-M low risk) rather than chemotherapy-related temporary atypical changes in morphology. On balance, given the risk of AML progression post-ASCT and the benefit of ASCT for myeloma disease control, the myeloid MDT and myeloma MDT's consensus was not to proceed to ASCT. This case highlighted the importance of thorough pre-ASCT investigation in patients with suboptimal stem cell mobilisation. Early MDS diagnosis is challenging in patients post-chemotherapy and with bone marrow residual disease, as both cytopenia and atypical morphology in this setting are common. With the easy access to fast-turnaround NGS in our centre, the routine, timely MDS investigation is now possible for this group of patients. **Conclusions:** Careful investigation and risk-benefit assessment pre-ASCT is essential in patients with suboptimal stem cell mobilisation.

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Iberdomide Drives Effector T Cell Expansion and Increases Immune Activation in Combination with Daratumumab and Dexamethasone in Multiple Myeloma Patients

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Introduction: Iberdomide (Iber) is a cereblon E3 ligase modulator (CELMoD) with demonstrated clinical activity in relapsed/refractory multiple myeloma (RRMM). Iber dynamically remodels the bone marrow immune microenvironment by expanding and activating effector T cells, NK cells, and NKT cells while reducing markers of T cell exhaustion and senescence. Recently, the phase 3 EXCALIBER-RRMM trial demonstrated superior minimal residual disease (MRD) negativity rates with Iber+Dara+Dex versus Bortezomib Dara+Dex. These findings suggest that Iber may provide enhanced immunologic synergy with daratumumab (Dara) relative to proteasome inhibitor–based backbones. Here, we comprehensively define the immunophenotypic changes induced by Dara+Iber+Dex triplet therapy in peripheral blood (PB) and bone marrow (BM) of RRMM patients to define immune mechanisms that may drive the observed combinational synergy. **Methods:** Paired bone marrow mononuclear cells were collected at baseline and cycle 2 day 15 (C2D15) from RRMM patients receiving Iber+Dex (n = 16) or Dara+Iber+Dex triplet therapy (n = 28). PB samples were collected at the same timepoints from RRMM patients receiving Iber monotherapy (n = 19), Iber+Dex (n = 126), or Dara+Iber+Dex triplet therapy (n = 36). A custom high-dimensional spectral flow cytometry panel was used to comprehensively profile dynamic changes across innate and adaptive immune compartments, including T-cell differentiation states, activation markers, checkpoint receptor expression, and senescence markers. **Results:** Most observed effects aligned with Iber's pharmacologic activity, supporting Iber as the primary driver of the immune responses in the combination. B and NK cell depletion was dose-dependent across cohorts and was observed in both PB and BM with the addition of Dara increasing the reduction in triplet therapy. Within the T-cell compartment we see increases in CD8+ and gamma delta T cells with a reduction of CD4+ T cells. T cells shifted from TEMRA and Naive populations to effector and central memory in the triplet therapy at a higher percentage compared to doublet therapy. Dara+Iber+Dex treatment significantly increased activated T cells with CD69+ and HLA-DR+ expression at greater frequencies compared to doublet therapy which was coupled with a depletion of CD38+ CD4+ and CD8+ T cells. Significant alterations in CD14+ monocyte populations were additionally observed in the BM with triplet therapy. **Conclusions:** ber functions as the primary immunomodulatory agent driving therapeutic activity in this combination, with Dara inducing CD38+ cell depletion in NK cells and T-cells. Immunomodulatory changes observed in BM that are absent in PB with Dara addition—particularly alterations in central memory T-cells—provide compelling rationale for comprehensive BM tumor microenvironment analysis in future mechanistic studies. These findings support the biological basis for superior MRD negativity observed with triplet therapy in EXCALIBER-RRMM.

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Identification and Characterisation of the Long Non-Coding RNA SNHG25 in Gain(1q)-Positive Multiple Myeloma

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Introduction: Multiple Myeloma (MM) is characterised by the malignant transformation of plasma cells in the bone marrow, with over 6000 people diagnosed in the UK each year. MM has high levels of genetic complexity which evolves during the disease course and following therapy to promote therapeutic resistance and relapse. An important genetic abnormality is gain(1q); a chromosomal aberration where part of or the whole chromosome 1 q-arm is duplicated, occurring in 40% of newly diagnosed MM and increasing to 60–70% at relapse. Gain(1q) reduces survival and promotes therapy resistance, therefore an understanding of how gain(1q) impacts malignant plasma cell survival could improve survival outcomes. **Methods:** Patient bone marrow samples were obtained from newly diagnosed and relapsed patients, and CD138+ plasma cells were isolated and sent for Illumina RNA sequencing. Following validation by RT-qPCR and western blotting, stable and inducible knockdown cell lines were generated, and proliferation, viability and drug sensitivities were assessed using viability assays and flow cytometry. **Results:** RNA sequencing of gain(1q)-positive patients (n = 5) compared with patients without gain(1q) (n = 9) identified 262 differentially expressed genes ($p < 0.01$), of which there were 65 up- and 8 downregulated long non-coding RNAs. LncRNAs have prognostic implications in many diseases, but their impact in MM is still limited. One of the most significantly upregulated lncRNAs was SNHG25 with a 9-fold increase in gain(1q) patients ($p < 0.001$). Additional sequencing of seven myeloma cell lines with varying 1q21 copy numbers showed a positive trend between SNHG25 and 1q21 copy number. Two cell lines obtained from the same patient, KMS-12-BM and KMS-12-PE, have two and four 1q21 copies respectively, also show a 7-fold increase of SNHG25 ($p < 0.0001$). Knockdown of SNHG25 reduced proliferation in KMS-12-PE cells, and subsequent RNA sequencing of SNHG25 knockdown cells compared to scrambled control identified 3441 differentially expressed genes – 1650 up- and 1704 downregulated (FDR< 0.05). KEGG pathway analysis identified enrichment of NF-κB signalling within down-regulated genes; primarily affecting the canonical arm of the pathway, including downregulation of BTK, which inhibitors against have shown activity in other B-cell malignancies. Ongoing work is assessing the impact of SNHG25 overexpression and resulting drug

sensitivities to common myeloma drugs, as well as BTK inhibitors. **Conclusions:** SNHG25 is an upregulated lncRNA in gain(1q) patients and in myeloma cell lines with increasing 1q21 copy number. Knockdown of SNHG25 reduces proliferation and may impact the NF-κB pathway, known to be dysregulated in MM. We hypothesise that gain(1q) induces SNHG25 expression which in turn may promote canonical NF-κB signalling to support disease progression and resistance to therapy, highlighting the potential use of canonical NF-κB inhibitors to target poor prognosis MM.

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Imbalance of Glycine Metabolism Contributes to Osteolysis in Multiple Myeloma

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Introduction: Metabolic imbalance is a critical factor in the process of bone remodeling and regulation. Our previous work indicates that glycine is enriched in multiple myeloma (MM) and promotes the progression of MM[1]. However, it remains unclear whether enriched glycine regulates bone remodeling in myeloma. **Methods:** Bone marrow and serum samples of MM patients were collected in multiple clinical institutions. Differential metabolites were screened by targeted metabolomics and high performance liquid chromatography. Osteoclastogensis using Raw 264.7 cells in vitro, 5TGM1 MM mice fed with a high-level glycine diet in vivo were performed to explore the effect of glycine on osteolysis. Pull-down and chip screening methods were used to identify the interacting proteins with Biotin-Glycine in the process of osteoclastogensis. **Results:** The concentration of glycine increased significantly in MM patients with osteolysis To screen the differential metabolites between MM patients with and without osteolytic destruction, we analyzed the spectral intensities of metabolites using SIMCA-P 14.1 software and MetaboAnalyst 5.0. Targeted metabolomics Q300 sequencing analysis revealed the characteristic metabolites of osteolytic MM patients and identified multiple amino acid metabolic abnormalities. Especially, the concentration of glycine was significantly increased in MM patients with osteolysis. The clinical characteristic analysis showed that the glycine concentration in MM patients was positively correlated with bone dissolution. High-level glycine promotes osteolysis in MM To explore the underlying mechanisms of the effect of glycine on osteoclasts differentiation, we cultured PBMC/BMM/Raw 264.7 with different concentration of glycine media, TRAP staining shows high-level glycine can promote osteoclast differentiation. Osteolysis in MM mice was more severe after being fed with high-level glycine feed, with higher concentrations of CTX-1 and PINP, together with lower BV/TV, Tb.N, and Tb.Th of micro-CT analysis. The interaction of Aco2/IDH2 and glycine promotes the formation of MM osteoclasts To examine the molecular mechanism of glycine in osteolysis, Pull-down and chips assay were used to detect the proteins interacting with Biotin -Glycine in Raw 264.7 cells. Mass spectrometry detection revealed that most of the proteins interacting with glycine were involved in glucose metabolism and the tricarboxylic acid cycle,such as Aco2 and IDH2. Knockdown Aco2/IDH2 leads to a decrease in osteoclast differentiation. The level of Aco2 and IDH2 were significantly increased in MM patients with osteolytic destruction. The above results suggests that the interaction of Aco2/IDH2 and glycine promotes the osteoclasts differentiation. **Conclusions:** In summary, our current research results indicate that the elevated glycine is associated with the occurrence of osteolysis in patients with MM, and glycine promotes the occurrence of osteolysis by interacting with tricarboxylic acid cycle-related proteins Aco2 and IDH2.

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Immune Age Acceleration Predicts Early Progression in Transplant-Eligible Patients With Multiple Myeloma Independent of Frailty

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Introduction: Current risk stratification in multiple myeloma (MM) relies on chronological age, cytogenetics, and clinical frailty, but these do not capture molecular immune aging withing the bone marrow immune microenvironment (IME). We hypothesize that immune age acceleration constitutes an independent prognostic axis to identify vulnerable patients who may appear fit by conventional measures. **Methods:** We developed a deep learning (DL) based single-cell immune aging clock trained on 1,260 healthy samples from peripheral blood and bone marrow, generating both cell-type specific and global immune age predictions with strong performance (Pearson r = 0.942). We applied DL model to scRNA-seq profiles of 336 newly diagnosed MM patients from the MMRF immune atlas initiative to compute immune age acceleration (biological minus chronological age) across major immune populations. Immune age acceleration was integrated with reconstructed IMWG frailty scores and evaluated in multivariate models of early progression including ISS stage, ASCT and sex. **Results:** Predicted immune ages in MM cohort were consistently elevated relative to chronological age, indicating systemic premature IME aging. IMWG frailty retained modest prognostic value after ASCT adjustment (HR = 1.26, p = 0.003), driven mainly by patients ≥70 years (HR = 2.13, p = 0.001), but was not significant in patients < 70 (HR = 1.26, p = 0.072). In contrast, immune age

acceleration strongly predicted early progression in patients <70 years old (HR = 1.86, p = 0.02) and was independent from IMWG frailty (Chi-square p = 0.194). Cell-type decomposition revealed that that predictive power was concentrated in CD4 memory T cells (HR = 1.96, p = 0.007) and CD8 memory T cells (HR = 1.63, p = 0.057), with correlated contributions from B cells, NK cells, and Naïve T cells suggesting a broader immune co-aging program. Fast-aging CD4 memory T cells showed increased cytotoxicity and loss of memory maintenance with elevated GZMB and PRF1 and reduced IL7r and SELL. CD8 memory T cells displayed a parallel shift toward an effector/interferon responsive state marked by FGFBP2, GNLY, and IFNG. Together, these patterns suggest a shift from resting memory toward chronically activated, functionally exhausted T cells, consistent with immune aging. Immune age acceleration appears to have an upper limit, as patients with chronological age >70 no longer showed outcome differences based on immune age (HR = 1.26, p = 0.53). These results suggest immune age acceleration identifies a high-risk subset among fit younger patients missed by frailty scoring, motivating deeper understanding of molecular drivers of this age acceleration. **Conclusions:** Standard frailty metrics miss a molecularly defined high risk group: clinically fit patients under 70 with prematurely aged IMEs who progress early despite ASCT. This scRNA immune aging clock provides an independent and biologically grounded risk stratification tool and suggests that targeting immune senescence may improve outcomes in transplant-eligible MM.

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Immune Determinants of MRD Response in Ultra-High-Risk Multiple Myeloma: Analysis from the UK MRA RADAR Study

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Introduction: Clinical outcomes in transplant-eligible newly diagnosed multiple myeloma (NDMM) are much improved but patients with genetic high-risk (HR) disease continue to experience treatment failure and early progression. While genomic instability and cell proliferation drive biology, the contribution of baseline immune function to treatment response remains unknown. We explored baseline immune profiles in relation to treatment outcomes in HR patients treated on the UK RADAR study. **Methods:** UKMRA RADAR is a multi-centre, risk-adapted phase II/III trial for patients with NDMM eligible for ASCT. Patients enter a HR pathway based on the presence of ≥2 HRCA (t(4;14), t(14;16), t(14:20), del(17p), del1p and gain(1q)). In protocol v4, they received 4 cycles of isatuximab, bortezomib, lenalidomide, cyclophosphamide and dexamethasone (Isa-VRDc) followed by ASCT and a further 4 cycles of Isa-VRD then IsaR maintenance. MRD was assessed by NGF (10–5) post-induction and post-ASCT. A total of 125 participants were recruited to HRv4. Extended T- and NK-cell flow cytometry was performed in 66 patients, comprising the analysis cohort. **Results:** Median age was 61yrs (42–74), ISS stage was 28.8%/51.5%/18.2% for stage I/II/III respectively, and 9/66 had ≥3 HRCA. MRD negativity rates were 35% (16/45) at end of induction (EOI) and 74% (40/54) post-ASCT. We first examined immune profiles at baseline in relation to MRD response at end of induction (EOI). Few differences were observed between major immune subsets, except for higher dendritic cell (DC) frequencies in MRD-pos patients (p = 0.03). A trend toward increased NK-cell frequencies was also observed in MRD-neg patients. Within NK-cell subsets, MRD-pos patients had more bone marrow-resident NK cells and less CD56dim cytotoxic NK cells at baseline. Within T-cell populations, MRD-pos response at EOI, as well as post-ASCT, associated with more CD8 CD57+ terminal effectors at baseline (p = 0.01, p = 0.02), and proportionally lower CD4/CD8 central memory subsets, indicating skewing to a terminally differentiated phenotype at diagnosis. Further assessment of immune activation and receptor phenotypes at baseline identified distinct patterns according to treatment stage. At EOI, innate immune populations were most strongly associated with MRD status, including increased inhibitory receptor-expressing NKG2A+ NK cells in MRD-pos patients (p = 0.03), consistent with anti-CD38 mechanisms. In contrast, post-ASCT MRD status was associated predominantly with baseline T-cell phenotypes, with MRD-pos patients demonstrating reduced CD27+ early activated CD4 and CD8 effectors (p = 0.002, p = 0.06) and increased GzmB+ CD8 terminal effectors, suggestive of a terminally differentiated cytotoxic state. **Conclusions:** Distinct immune mechanisms may underpin response depth at different treatment stages, with early response to CD38 therapy linked to innate immunity, and later ASCT responses increasingly shaped by adaptive T-cell immunity.

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Immune Dysregulation of Non-Malignant B Cells Reveals Early Functional Derangement Across Plasma Cell Dyscrasias

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Introduction: Non-malignant B cells are an underexplored component of the tumor microenvironment (TME) in monoclonal gammopathy of unknown significance (MGUS), smoldering (SMM) and overt MM. Here, we sought to characterize signatures of early humoral immune dysfunction by integrating single-cell transcriptomics and paired B-cell receptor (BCR) profiling. **Methods:** Single-cell 5′ RNA-seq with paired scBCR-seq was performed on CD138neg bone-marrow fractions from 41 samples (7 MGUS, 13 SMM, 21 MM; 6 progression pairs). Data was processed using Seurat, ClusterProfiler, Multinichenet, and Immcantation workflows; cell-type annotation relied on the BoneMarrowMap reference. Analyses included unsupervised clustering, differential expression, pathway enrichment, interactome inference, and BCR somatic hypermutation (SHM) metrics. **Results:** We profiled a total of 106,595 CD138neg cells, identifying 9,606 B cells. In MM, compared to asymptomatic stages, we observed a significant depletion of early stages (pro- and pre-B cells; $p < 0.05$), indicating impaired B-cell ontogeny. Unsupervised clustering analysis resolved 11 distinct B-cell subpopulations. Among mature cells, an interferon (IFN)-driven subset was detected almost exclusively in MM. In addition, we identified a non-canonical activated NR4A+ population significantly expanded in overt MM ($p < 0.05$). Notably, non-progressive MGUS/SMM cases preserved physiological proliferation and maturation transcriptional programs, including STMN1, RAG2, TCL1A, and MYC/mTORC signaling. In contrast, MM samples underwent a marked inflammatory and stress-associated rewiring, characterized by activation of JUND, FOSB, EGR1, and IER5 genes. Strikingly, TNFα and IFNγ pathways were enriched across both mature and early-stage B-cell compartments in MM, pointing to early immune dysregulation. Interactome reconstruction revealed an impairment of the CD40LG-CD40 Th-B cell axis in symptomatic MM. Functionally, this alteration was associated with major changes in the BCR repertoire, including a markedly lower SHM rate in progressing MGUS/SMM cases and overt MM ($p < 0.0001$). Lastly, we validated the MM-specific B-cell subsets in the NDMM samples of the MMRF public dataset (823,261 total cells; 80,636 B cells). Notably, the progressive depletion of pro- and pre-B cells across ISS stages suggests a detrimental effect of disease burden on early B-cell survival, consistent with our previous observations during progression to symptomatic disease. Finally, we observed that IFN-driven B-cell subsets identified a favorable immune state associated with improved PFS (HR 0.52, $p < 0.0001$) and OS (HR 0.49, $p < 0.001$) in MM. **Conclusions:** Non-malignant B-cells undergo immune and functional rewiring toward symptomatic MM. Inflammatory programs, early-stage depletion, expansion of NR4A+/IFN-driven mature subsets, and a T-independent, low-SHM BCR repertoire define the dysfunctional humoral ecosystem of overt MM. These data suggest a loss of physiological B-cell immunity accompanying MM progression.

PA-238

Immune Recovery and Infectious Events with Ixazomib versus Anti-CD38 Maintenance in MRD-Negative Transplant-Ineligible NDMM

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Introduction: Maintenance therapy for transplant-ineligible newly diagnosed multiple myeloma (NDMM) aims to sustain disease control while preserving immune function, particularly in patients with sustained minimal residual disease (MRD) negativity. We compared immunoglobulin recovery, infectious events, and other adverse events during ixazomib (IXZ) maintenance with anti-CD38 antibody maintenance. **Methods:** This retrospective matched study included 15 transplant-ineligible NDMM patients who maintained MRD negativity during IXZ maintenance and 15 matched controls receiving anti-CD38 antibody maintenance. Patients were evaluated for 2 years from the start of maintenance therapy. Infectious events, serum IgG recovery, immunoglobulin replacement, lymphocyte counts, neutrophil counts, and other adverse events were assessed. IgG change was calculated as the value at each time point minus the maintenance baseline value. Longitudinal IgG recovery was analyzed using a mixed-effects model including group, time, and group-by-time interaction. Exploratory pairwise comparisons were performed using the Mann-Whitney U test with Holm correction. **Results:** The anti-CD38 antibody group comprised isatuximab ($n = 10$) and daratumumab ($n = 5$). MRD negativity was maintained during the observation period. The IXZ group experienced two episodes of bronchopneumonia of unknown etiology, whereas the anti-CD38 antibody group experienced 14 infection-related episodes, including bronchopneumonia, respiratory syncytial virus infection, and

COVID-19. Serum IgG recovery was greater with the IXZ group. At 24 months, the median IgG increase from baseline was 543 mg/dL in the IXZ group and 62 mg/dL in the anti-CD38 antibody group. Longitudinal IgG recovery differed significantly between groups (group-by-time interaction, p = 2.55 x-28). Pairwise differences emerged from 9 months (Holm-adjusted p = 0.0037) and remained significant through 24 months. Immunoglobulin replacement was numerically lower with the IXZ group, although not statistically significant (mean 7.1 vs 12.5 g per patient over 2 years; p = 0.915). No apparent lymphocyte or neutrophil changes were observed. Infections were the predominant adverse events in the anti-CD38 antibody group, whereas diarrhea, constipation, and arthralgia were the main adverse events in the IXZ group. **Conclusions:** In MRD-negative transplant-ineligible NDMM patients who maintained disease control during maintenance therapy, IXZ was associated with greater endogenous IgG recovery and fewer infection-related episodes than anti-CD38 antibody maintenance. These findings suggest recovery of host immune function after induction therapy during IXZ maintenance. IXZ may be a useful option for elderly or frail patients in whom infection prevention and immune preservation are important, and may offer clinical and potential health-economic advantages in the maintenance setting.

PA-239

Immunomodulatory Salvage Reverses Primary Refractoriness to Bispecific T-Cell Engagers in Multiple Myeloma

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Introduction: Bispecific T-cell engagers (TCEs) targeting BCMA or GPRC5D induce high response rates in relapsed/refractory multiple myeloma (RRMM), but about one-third of patients are primary refractory. The common clinical strategy after TCE failure is to switch the target antigen, assuming that resistance is structural, but resistance can instead be a reversible functional immune state. **Methods:** We report five patients (pts) with RRMM treated between 2023 and 2026 in three tertiary cancer centers who were primarily refractory or have shown progressive disease after at least one full cycle of teclistamab (n = 2) or talquetamab (n = 3). All 5 pts received immunomodulatory salvage with pomalidomide (POM) added to ongoing TCE therapy (POM mono, n = 2) or initiated shortly after TCE discontinuation (daratumumab (DARA)-POM-cyclophosphamide (CY)-dexamethasone (dex), n = 1; POM-CY-dex, n = 1; elotuzumab-POM-dex, n = 1). Teclistamab's half-life of 27 days (SD 8.2 days) and talquetamab's of 12 days suggest that relevant TCE concentrations were still present at salvage initiation (0–37 days after the last TCE dose). Peripheral CD4+ and CD8+ T-cell counts from routine flow cytometry were available in three patients. **Results:** All five pts responded rapidly. 4/5 pts reached at least VGPR (IMWG) within 11–24 days, including one MRD- sCR. Median PFS was not reached. 4/5 pts maintained response at last follow-up (3, 5, 12, and 15 months). 4/5 pts had been refractory to one or more components of the salvage regimens in prior lines, three to POM. The three pts with longitudinal immunophenotyping all showed CD8+ T-cell expansion paralleling response. One patient developed CRS grade 2 and CMV reactivation after the addition of the salvage regimen DARA-POM-CY-dex. **Conclusions:** Response depth and kinetics exceeded what is expected from used salvage regimens alone. Persistent TCE concentrations after discontinuation together with POM-based salvage led to a de facto combination therapy. This combination was able to reverse functional TCE resistance, even in pts refractory to the salvage drugs. CRS and CMV reactivation in patient 1 are consistent with renewed TCE-mediated T-cell engagement. IKZF1/IKZF3 degradation by immunomodulatory drugs, such as POM, can rescue anergic T-cells via IL-2, reverse T-cell exhaustion by repressing exhaustion genes such as TIGIT and restore cytokine production. CY depletes regulatory T-cells (Tregs), lowers tumor burden and soluble BCMA (BCMA sink effect), and DARA depletes CD38+ immunosuppressive Tregs, remodeling the tumor microenvironment. Therefore, immunological resensitization, rather than antigen retargeting, is a feasible strategy after early TCE monotherapy failure in RRMM.

PA-240

Impact of Clinical Whole Genome Sequencing in Immunotherapy-Exposed Patients

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Introduction: The new IMS/IMWG consensus genomic staging (CGS) system recommends the adoption of next-generation sequencing based assays for accurate risk stratification of patients at diagnosis and subsequent progression events. To support these requirements, we developed and put into practice a CAP/CLIA certified clinical whole genome sequencing (WGS) platform. This

clinical WGS test leverages CD138 enrichment of plasma cells, >118x PCR-free WGS, optimized analysis and reporting workflows to return a myeloma specific clinical report in under 72 hours. **Methods:** To establish the clinical utility of this test, we initiated a clinical trial that enrolls patients at relapse/progression treated with a CAR-T or T-cell engager (TCE) therapy in a prior line of therapy. The primary objective is to establish the incidence of target antigen loss in a prospective cohort after exposure to one of these treatment modalities. A secondary aim is to establish how often the clinical WGS report alters a patient's treatment plan. **Results:** Of the 17 currently evaluable patients in this study, 11 (64.7%) met at least one IMS/IMWG CGS high-risk criteria, highlighting the aggressive nature of this patient population. Compared to concurrent FISH testing, 4 additional patients were categorized as high-risk by the WGS test. The comprehensive nature of WGS identified other likely high-risk events such as CDKN2C loss by mutations, TP53 loss by translocation and a t(8;14)/IGH::MAFA case with 1q21 gain, which are not currently captured by the IMS/IMWG CGS criteria. All patients were previously treated with at least one anti-CD38 containing regimen, and surprisingly 2/17 (11.8%) patients had lost both copies of CD38. One of these cases highlighted the benefit of WGS over focused panel tests with the detection of a translocation disrupting a CD38 allele. Only 1/13 (7.7%) CAR-T treated patients had detectable loss of the therapeutic antigen, while 5/12 (41.7%) TCE treated patients had lost the therapeutic antigen(s). Within the entire cohort, the treatment plan was altered based on the WGS test in 2/17 (11.8%) patients. When only cases with previous treatment against the next line of therapy target antigen are considered, physicians changed their treatment plan in 2/4 (50%) cases due to the loss of the target antigen. **Conclusions:** Overall, the preliminary result in this study shows the benefit of transitioning to a clinical WGS test over historic approaches in accurately identifying high risk patients. The adoption of this approach in this patient population can identify patients who can benefit from a subsequent immunotherapy. Even in this small cohort, the savings from planned CAR-T and TCE therapies is greater than $410,000, which far exceeds the minimal additional cost of replacing FISH testing with WGS. Not only is it ensuring patients get the right therapy at the right time, the comprehensive nature of the test is also identifying new therapeutic options for these advanced patients with limited alternative options.

PA-242

Impact of Immunomodulatory (IMiD) Containing Holding Therapy (HT) Regimens on Outcomes in Relapsed/Refractory (RRMM) Patients Receiving Chimeric Antigen Receptor–T Cell (CAR-T) Therapy

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Introduction: CAR-T is an effective treatment strategy for relapsed/refractory multiple myeloma (RRMM). Many patients require HT prior to CAR-T collection to maintain disease control. IMiDs have been shown to modulate the T-cell phenotype and reduce regulatory T cells, potentially affecting CAR-T efficacy. However, the impact of IMiD-containing HT on CAR-T outcomes has not been well defined. This retrospective study aimed to assess the impact of IMiD-containing HT regimens on PFS, OS, response to CAR-T and CAR-T associated toxicities in patients with RRMM. **Methods:** We retrospectively analyzed data from seven centers participating in the U.S. Myeloma Innovations Research Collaborative (USMIRC). This study examined the records of 363 patients who received holding therapy prior to commercial CAR-T from 2021 to 2024. The primary outcome was PFS, and secondary outcomes included OS, the incidence of CRS/ICANS, ICAHT, IEC-HS and infectious complications. Statistical significance was set at $p < 0.05$. OS and PFS distributions were estimated using the Kaplan–Meier method. **Results:** Of the 363 patients, 164 patients received ide-cel therapy and 199 patients received cilta-cel therapy. Among ide-cel recipients, 45 patients (27%) received IMiD-containing HT and 119 (73%) did not. Patients were older in the IMiD group (median 69 vs 64 years; $p < 0.001$) but the two cohorts were otherwise balanced in prior lines of therapy ($p = 0.079$), proportion of high-risk cytogenetics patients (44% vs 42%, $p = 0.8$) and extramedullary disease burden ($p = 0.5$). Rates of CRS (78% vs 84%, $p = 0.3$) and ICANS (16% vs 24%, $p = 0.3$) were comparable between cohorts. For the ide-cel group, IMiD-containing HT was associated with a statistically significant improvement in OS on both univariate (HR = 0.55; 95% CI:0.31–0.98; $p = 0.043$) and multivariate analysis (HR = 0.52; 95% CI: 0.28–0.94; $p = 0.032$), after adjusting for high risk cytogenetics. No significant PFS benefit was observed (HR = 0.74, $p = 0.2$). Among cilta-cel recipients, 99 patients (50%) received IMiD-containing HT and 106 patients did not. Cohorts were well-matched by age (67 vs. 67 years; $p = 0.8$) and high-risk cytogenetics (55% vs 57%, $p = 0.8$) though IMiD recipients had fewer prior lines of therapy (median 4 vs. 5; $p = 0.04$). Rates of CRS were significantly higher in the non-IMiD cohort (80% vs 67%, $p = 0.038$), while ICANS rates were similar (20% vs 17%, $p = 0.6$). IMiD-containing HT was not associated with significant improvement in PFS (HR = 0.72; $p = 0.2$) or OS (HR 1.12; $p = 0.7$). **Conclusions:** IMiD-based HT regimens did not demonstrate a statistically significant improvement in PFS for either ide-cel or cilta-cel although they did significantly improve OS in ide-cel patients. Rates of CAR-T associated toxicities were relatively similar, demonstrating that IMiD based regimens are relatively safe.

However, IMiD based HT regimens do not improve CAR-T efficacy in the clinical environment despite demonstrating improvement in T-cell selection in vitro.

PA-243

Impact of Infusion Timing in Multiple Myeloma Patients Receiving Bispecific Antibody Therapy: A Single-Institution Retrospective Analysis

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Introduction: Bispecific antibodies (BsAbs) have transformed treatment of relapsed/refractory multiple myeloma (RRMM); however, cytokine release syndrome (CRS) remains a significant toxicity during step-up dosing. Cytokine production, T-cell function, and immune activation are subject to circadian regulation, with earlier CAR-T cell infusion having shown to be independently associated with improved PFS in large B-cell lymphoma. Yet, the impact of infusion timing of BsAbs in MM has not been explored. This study evaluates whether BsAb administration timing is associated with treatment response and CRS incidence and severity. **Methods:** We retrospectively analyzed 33 MM patients receiving BsAb therapy across 42 courses at a single institution. Agents included teclistamab (52.4%), talquetamab (23.8%), elranatamab (19.0%), and teclistamab/talquetamab (4.8%). Median age was 69 years; 48.5% female; 81.8% ECOG PS 0–1; 48.5% penta-refractory; 34.4% high-risk cytogenetics. Step-up dosing was inpatient in 97.6% of courses. Infusion timing data from cycle 1 up to cycle 3 (320 infusions) were analyzed. Courses were classified by predominant timing (AM vs PM, cutoff 12:00 noon). Fisher exact test was used for categorical comparisons; Mann-Whitney U for CRS grade. A sensitivity analysis was restricted to first BsAb course per patient. Analyses were performed using Python 3.9.19 (SciPy library). **Results:** Of 42 courses, 8 (19.0%) were predominantly AM and 34 (81.0%) PM. ORR (≥PR) did not differ significantly between AM and PM courses (62.5% vs 79.4%, OR 0.43, $p = 0.369$), nor did ≥VGPR rate (62.5% vs 76.5%, OR 0.51, $p = 0.412$). Median time to response was similar between AM and PM courses (34 vs 27 days, $p = 0.55$). AM courses were associated with significantly lower CRS incidence compared to PM courses (25.0% vs 70.6%, OR 0.14, $p = 0.038$), with a trend toward lower maximum CRS grade (median 0 vs 1, $p = 0.060$). ICANS occurred in 4.8% of courses ($n = 2$, grades 1 and 2). Sensitivity analysis restricted to first courses ($n = 33$) showed consistent results for both response (ORR 83.3% vs 81.5%, $p = 1.000$) and CRS incidence (33.3% vs 74.1%, OR 0.17, $p = 0.146$). **Conclusions:** In this single-institution retrospective analysis, morning BsAb administration was associated with significantly lower CRS incidence than afternoon dosing (25.0% vs 70.6%, OR 0.14, $p = 0.038$) without compromising response rates or time to response. Consistent odds ratios across the full and first-course analyses (OR 0.14 vs 0.17) suggest the loss of significance in the sensitivity analysis reflects reduced power rather than a diminished effect. These hypothesis-generating findings suggest infusion timing may represent a modifiable strategy to mitigate CRS risk, warranting further investigation.

PA-244

Impact of Lecture on Knowledge of IM Residents in Diagnosing and Managing CRS and ICANS

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Introduction: Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) will become more prevalent in the outpatient setting as immunomodulatory drugs like chimeric antigen receptor T-cell therapy (CAR-T) and Bi-specific antibody therapy become more ubiquitous. Because of this, there is a vast need for internal medicine (IM) physicians to be aware of this. **Methods:** Our project entailed educational lectures for IM physicians at multiple hospitals throughout the state of Michigan in a community and academic setting. Thirty-five participants completed paired pre- and post-intervention surveys after a 1-hour educational lecture. These responses were then analyzed using a paired T-test analysis. **Results:** Our survey demonstrated an increase from 83% to 97% in knowledge of diagnosing CRS/ICANS and a corresponding increase from 73% to 97% in knowledge about selecting the correct treatment for CRS/ICANS. A composite toxicity confidence score (average of CRS and ICANS ratings) increased from 1.67 pre-intervention to 3.50 post-intervention, corresponding to a mean improvement of 1.83 points. Improvement was observed in nearly all participants, demonstrating a large and highly consistent effect of the educational intervention. Individually, both CRS and ICANS domains showed highly statistically significant improvements (both $p < 10^{-9}$). **Conclusions:** Our project shows that lecture-based education on this topic in the era of emerging immune-based therapy shows robust improvement in recognition and treatment of CRS and ICANS. This can be modeled and upscaled for distribution to other disciplines, states, and institutions throughout the United States already utilizing CAR-T and bispecific antibodies.

PA-245

Impact of Prior Anti-BCMA Antibody-Drug Conjugate Exposure and High-Risk Cytogenetics on Outcomes With BCMA Bispecifics in Relapsed/Refractory Multiple Myeloma: A Single Centre Real-World Analysis

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Introduction: The impact of prior anti-BCMA antibody-drug conjugate (ADC) exposure on long-term outcomes with subsequent BCMA-targeting T-cell engaging bispecific antibody (TCEs) therapy in relapsed/refractory multiple myeloma (RRMM) remains unclear. In addition, the prognostic role of cumulative high-risk cytogenetic abnormalities (HRCA) in the TCE setting is poorly defined. Here, we evaluated long-term outcomes of RRMM patients treated with standard-of-care anti-BCMA TCEs in context of prior BCMA ADC therapy and cytogenetic abnormalities in a real-world cohort. **Methods:** We analysed RRMM patients treated with standard of care (SOC) teclistamab or elranatamab between July 2022 and December 2024 at The Royal Marsden Hospital, London. Responses were assessed according to IMWG criteria. HRCA included complete information on t(4;14), t(14;16), t(14;20), gain/amp(1q), del(1p), and del(17p). Patients were classified as having 0, 1, or ≥2 HRCAs. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier and Cox regression analyses. **Results:** Fifty-five patients were included; median age was 67 years and 87% were triple-refractory. About half of patients would not have not fulfilled standard clinical trial eligibility criteria. Median follow-up was19.7 months (IQR 17.2–30.76). Overall response rate was 73%, with ≥VGPR in 56% and ≥CR in 35%. Median PFS was 9.8 months, with no difference between teclistamab and elranatamab (HR 1.05, p = 0.87). Fourteen patients (25%) had prior belantamab mafodotin exposure and all were ADC-refractory before TCE treatment. The majority of patients received belanatamab immediately prior to and up until the start of TCE therapy. Prior belantamab exposure did not adversely affect PFS following TCE therapy (HR 1.29, 95%CI 0.61–2.69; p = 0.5); 12-month PFS was 48% versus 53% in belantamab-exposed versus non-exposed patients, respectively. Among 52 evaluable patients, 7 had 0 HRCA, 20 had 1 HRCA, and 25 had ≥2 HRCAs. Twelve-month PFS was 71%, 50%, and 36%, respectively. Extramedullary plasmacytomas were associated with significantly worse PFS (HR 3.25, 95%CI 1.33–7.91; p = 0.009), while paraskeletal disease showed a non-significant trend (HR 2.04, 95%CI 0.88–4.74; p = 0.09). **Conclusions:** In this real-world RRMM cohort with prolonged follow-up, prior anti-BCMA ADC exposure did not impair outcomes of subsequent BCMA-targeting TCE therapy. Conversely, extramedullary disease and cumulative HRCA burden remained associated with inferior outcomes, supporting their continued prognostic relevance in the bispecific antibody era.

PA-246

Impact of Prior Daratumumab or Isatuximab: An Analysis of Relapsed and Refractory Multiple Myeloma (RRMM) Patients Treated With Melflufen Plus Dexamethasone in the OP-106 HORIZON Study

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Introduction: Patients (pts) with heavily pretreated relapsed/refractory multiple myeloma (RRMM), and especially triple-class refractory (TCR) disease with exposure to prior immunomodulators, proteasome inhibitors, and anti-CD38 monoclonal antibodies (mAbs) have poor outcomes and limited therapeutic options. OP-106 HORIZON study was a multicenter, single-arm Phase II trial evaluating melphalan flufenamide (melflufen) plus dexamethasone (dex) in RRMM pts with ≥2 prior lines, refractory to pomalidomide and/or an anti-CD38 mAb, and where most pts had TCR disease (76%). Daratumumab (DARA) and isatuximab (ISA) both target CD38 but bind different epitopes. ISA has more direct cytotoxic effects and relies less on complement-dependent cytotoxic activity, which in turn may impact the effects of later-line treatments. A descriptive subgroup analysis was conducted comparing the presentation and outcome in RRMM pts with prior DARA vs prior ISA exposure in pts from HORIZON. **Methods:** HORIZON enrolled 157 RRMM pts; all received melflufen (40 mg IV Day 1) plus weekly dex (40 mg; 20 mg if ≥75 years) in 28-day cycles until progression or toxicity. The primary endpoint was overall response rate (ORR). Pts previously exposed to DARA (n = 117) or ISA (n = 10), were identified, their characteristics and key efficacy outcomes compared (ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). **Results:** The ISA group were older (median age 72 vs 64 years), had a higher frequency of high-risk cytogenetics (50% vs 34%) but a lower frequency of EMD (20% vs 42%) compared to the DARA group. Both groups had a median of 5 prior lines (ISA: 4–9, DARA: 2–12). Pts in the ISA group were able to receive twice as many cycles of melflufen as the DARA group (6 vs 3). ORR was 40% (4/10 pts) in the ISA group and 29% (34/117 pts) in the DARA group (95% CI 12.2–73.8 vs 21.0–38.2). Among

responders, median DOR was 7.5 mos with prior ISA vs 5.5 mos with prior DARA (95% CI 3.0-NA vs 3.9–10.4). Median PFS was 5.1 mos with prior ISA vs 3.8 mos with prior DARA (95% CI 2.4–9.4 vs 2.9–4.6), and median OS was 11.7 vs 9.7 mos, respectively (95% CI 4.0–16.5 vs 6.5–12.3). Outcomes overall were consistent with the total HORIZON population (ORR 29%, median PFS 4.2 mos, median OS 11.6 mos). The safety profile was similar between the two groups and was comparable to the total HORIZON population. **Conclusions:** Melflufen plus dex has shown clinically meaningful activity in heavily pretreated RRMM. This analysis suggests that type of prior anti-CD38 therapy may potentially impact the effect of later treatments and patterns of relapse. In the limited group of pts previously exposed to ISA, ORR, DOR, PFS and OS where numerically higher and may suggest better response to melflufen compared to pts with prior DARA exposure, despite having higher risk disease and older age. This difference seen between the two groups, including EMD-rates, is noteworthy, hypothesis-generating around therapeutic mechanism and warrants further study.

PA-247

Implications of Electromyography for Treatment-Related Peripheral Neuropathy in Patients with Multiple Myeloma

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Introduction: Treatment-related peripheral neuropathy (TRPN) is one of the major complications of multiple myeloma (MM) therapy based on proteasome inhibitors and/or immunomodulatory agents. Grade ≥2 adverse events can severely compromise treatment continuity and quality of life. Currently, studies on the predictive value of pre-treatment electromyography (EMG) for TRPN are lacking. **Methods:** This study retrospectively analyzed the clinical information of 96 newly diagnosed MM patients treated at our center. Patients were grouped according to the presence or absence of abnormalities on pre-treatment EMG, and the incidence and severity of TRPN during subsequent treatment were compared between the two groups. **Results:** The median age of the enrolled patients was 65 years, with a male-to-female ratio of 1.18:1. Fifty-one patients (53.1%) had abnormal pre-treatment EMG findings; in this group, 24 patients developed TRPN during treatment, including grade 1 in 3 patients, grade 2 in 13, and grade 3 in 7. In the group with normal pre-treatment EMG, 24 patients also developed TRPN, including grade 1 in 9, grade 2 in 12, and grade 3 in 3. Compared with patients who had normal pre-treatment EMG, the group with abnormal EMG showed a trend toward higher incidences of grade ≥2 and grade ≥3 TRPN (grade ≥2: 41.2% vs. 15.7%, p = 0.281; grade ≥3: 33.3% vs. 6.7%, p = 0.144). Univariate analysis revealed that MM patients who developed grade ≥2 TRPN had a higher detection rate of pre-treatment EMG abnormalities (58.3% vs. 25%, p = 0.047). Multivariate analysis incorporating five variables (height, weight, fasting blood glucose, EMG abnormality, and alkaline phosphatase) confirmed that EMG abnormality was an independent risk factor for grade ≥2 TRPN (OR: 11.19, 95%CI: 1.02–123.41, p = 0.049). The occurrence of TRPN, grade ≥2 TRPN, or grade ≥3 TRPN had no significant impact on the best response achieved (p = 0.095, p = 0.218, p = 0.440, respectively), and dose or frequency modifications of bortezomib also did not affect treatment efficacy (p = 0.137). **Conclusions:** This study suggests that pre-treatment EMG abnormalities may predict the occurrence of grade ≥2 TRPN during therapy in patients with multiple myeloma.

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Improving Quality of Life in Multiple Myeloma Patients Through Patient Navigation and Supportive Care: A WHOQOL-Based Study Within a Multiple Myeloma Care Programme

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Introduction: Multiple myeloma is a plasma cell malignancy that affects patient wellbeing. Patients in low-resource settings face challenges including limited access to clinical care, poor understanding of disease management, and psychosocial barriers, contributing to reduced quality of life. However, there is limited evidence on the impact of structured patient navigation and supportive care programmes on patient-reported quality of life in this population. The Multiple Myeloma Care Programme was implemented to address these challenges through patient navigation and supportive care. This study aimed to evaluate the impact of the programme on patient-reported quality of life using the WHOQOL survey. **Methods:** A prospective longitudinal observational study with a pre–post design was conducted among patients with multiple myeloma enrolled in a care programme. Participants were recruited from a haematology clinic and care facility. The programme included patient navigation (regular follow-up across the care pathway), nurse-led symptom management, and supportive care including counselling, education, and lifestyle guidance. Quality of life was measured using WHOQOL across physical, psychological, social, and environmental domains at baseline and at 1, 3, 6, and 9 months. Data was analysed using descriptive statistics and a Qualtrics dashboard. Follow-up scores were compared with baseline, and patients were classified as improved, stable, or deteriorated. Proportions were calculated at each timepoint, including comparisons with the most recent assessment. Data were anonymised, and informed consent was obtained. **Results:** Quality of life improved over the programme. At baseline, WHOQOL scores were low, reflecting a high symptom burden. Across follow-up, most patients demonstrated improvement.Compared with baseline, 60–70% of patients improved, 20–30% remained stable, and 10–15% deteriorated. Improvement was greatest at early follow-up (1–3

months), with ~60% improving, while 30–35% were stable and ~10% deteriorated. At later timepoints, changes were smaller, with reduced improvement and increased stability. Compared with the most recent assessment, improvement ranged from 14 to 41%, stability 41–64%, and deterioration 18–41%. Improvements were most pronounced in physical functioning, energy, mobility, sleep, and social support, while deterioration occurred more in pain, emotional, and environmental domains. **Conclusions:** The Multiple Myeloma Care Programme is associated with improved patient-reported quality of life. Patient navigation and supportive care contribute to improved symptom management and overall wellbeing in patients with multiple myeloma. As an ongoing programme, these findings represent interim outcomes, and the observed pattern of early improvement followed by stabilisation suggests that continued participation may support sustained or further gains in quality of life. Ongoing longitudinal follow-up is required to assess long-term outcomes and the durability of these effects.

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Improving Real-World Outcomes in the Frail and Elderly With Myeloma: Data From the UK Haematological Malignancy Research Network

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Introduction: Overall survival (OS) for patients with myeloma (MM) has improved dramatically with the introduction of novel therapies, but gains in the older and frailer have been far less impressive. **Methods:** The Haematological Malignancy Research Network tracks all patients diagnosed with a hematological malignancy in Yorkshire and the Humber since 2004, linking centralized diagnostic laboratory data with medical records, national death and cancer registration and Hospital Episode Statistics. We examined outcomes in 4545 patients diagnosed with MM (smouldering/symptomatic) 2005–2022. **Results:** Median age at diagnosis was 73y, with 25% aged ≥80. 62% were frail by the simplified IMWG frailty (s-IMWG) score, 3% high risk by the Hospital Frailty Risk (HFR) score and 16% severely frail by the SCARF deficit index. Median OS doubled from 2.4y in 2005 to 5y in 2022. There was a stepwise improvement in OS of patients aged <80 in the 2011–2013 period, corresponding with the introduction of bortezomib to UK practice and recruitment to the UKMRA Myeloma XI study. OS improvement in ≥80 s was not seen until 2017–2019, when 5-year OS rose from 7.9% to 18.9% in those receiving MM therapy. 5-year net survival (adjusted for non-MM deaths) in the ≥80 s rose from 15.3% to 37.1%. Shifting trends in treatment options for the ≥80 s can be seen, with oral melphalan and CTDa dominating in 2005–2010, transient use of RCD during the UKMRA Myeloma XI trial, bortezomib-based combinations gaining popularity from 2014, followed by IRD in the UKMRA FiTNEss study from 2020. Daratumumab-based combinations became available for transplant-ineligible patients in Oct 2023 and so follow-up is not yet mature. Despite improvements in treatment, 15.7% of ≥80 s received only palliative care, this figure was 6% in those aged 70–79. 84% of s-IMWG frail patients received first line chemotherapy, compared to 98% in the fit group, with an OS of 2.3y for frail patients cf. 8.2yin the fit. Similar patterns were seen for the SCARF and HFR scores. Of note 14% of ≥80 s did not undergo skeletal imaging, compared to 6% in younger age groups, highlighting age-related inequality in use of key diagnostic investigations. **Conclusions:** It is encouraging that real-world OS is now improving in those aged ≥80. This likely reflects not only access to novel agents, but a better understanding of how to employ them optimally to balance toxicity and efficacy in frailer patients (e.g once- vs twice-weekly bortezomib, pre-emptive IMiD dose reductions and rapid steroid tapering etc.). Further improvements are anticipated following daratumumab adoption. Nonetheless, OS remains starkly obtunded for the frailest. These data highlight that as a clinical community we can learn how to best use novel MM therapies in older and frailer patients, and that age alone should not hinder access to emerging highly effective MM treatments.

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Improving the Inclusion of Underserved Myeloma Patients in Clinical Trials: A Scoping Review of Inclusion Frameworks and Their Applicability to Myeloma Trials in Europe

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Introduction: Clinical trials should reflect the real-world population of patients to foster more equitable, effective and trusted advances in the treatment for all patients. There is no consensus on how to improve the inclusion of underserved populations in European myeloma clinical trials. This scoping review maps out the evidence on existing frameworks, toolkits, best practice guides (all hereafter referred to as 'frameworks') intended to support the recruitment of underserved populations into any clinical trials and evaluates their use within the European myeloma context. **Methods:** This scoping

review followed JBI methodology. MEDLINE (Ovid), Embase, PsycINFO, and ERIC databases, alongside targeted Google searches, were systematically searched (March 2026) to identify published and grey literature. Eligible studies reported in on frameworks aimed at improving the inclusion of underserved groups in clinical trials of any phase, any disease area, worldwide were included without any restrictions on study designs. Studies published in languages other than English, Spanish and Portuguese were excluded. Screening was done by two independent reviewers, with double screening of 10% of records until the >80% agreement was achieved. Data extraction was performed and checked for accuracy with differences resolved via comparison and consensus. **Results:** A total of 185 studies were included. Over one third 67 (36%) were not disease-specific, while 60 (32%) focused on oncology. Nearly half, 81 (43%), were developed for a single-country context, predominantly the United States, 76 (41%). Race and ethnicity were the most frequently targeted characteristics, addressed in 119 (64%) frameworks. The least targeted characteristics were mental health, addressed in only 5 (3%), impaired capacity for consent in 12 (6%) and immigrant status 16 (9%). Most frameworks 125 (68%) included an intersectional-lens considering multiple social or contextual factors together. Most frameworks were broadly applicable to myeloma in their entirety 128 (69%) or partially 32 (17%). A smaller number were explicitly designed with myeloma in mind or used myeloma data or clinical trials within their development 15 (8%). **Conclusions:** A substantial body of frameworks exists to support improved inclusion of underserved populations in clinical trials, many of which are applicable to myeloma. However, the strong US focus highlights the need for adaptation to European populations and contexts. There is a further gap in frameworks aiming to increase the inclusion of underserved populations outside of race and ethnicity. These findings will inform ongoing multistakeholder work to develop prioritised, actionable recommendations to enhance the inclusion of underserved groups in European myeloma clinical trials.

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IMS/IMWG CGS Risk Stratifies Terminal T Cell Accumulation, Loss of B Cell Immunity, and Proliferative Tumor Transcriptional Programs in Rapidly Progressing Myeloma

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Introduction: Multiple myeloma progression is associated with both tumor-intrinsic genomic features and the bone marrow immune microenvironment. Although updated IMS/IMWG consensus genomic staging (CGS) criteria have refined the definition of high-risk disease, it remains unknown whether rapid progression within standard- and high-risk groups reflects distinct immune or tumor-cell programs. **Methods:** We analyzed baseline single-cell RNA sequencing (scRNA-seq) profiles from our immune atlas initiative, stratifying rapid progressors (RP, PFS< 18 mo) and non-progressors (NP, PFS >4 yrs) by Standard (n = 208) or High (n = 78) CGS risk. CGS risk (n = 15) was defined by the presence of one or more high-risk features: TP53 mutation or del(17p13); high-risk IgH translocations co-occurring with gain(1q21) or del(1p32); gain(1q21) with del(1p32); biallelic del(1p32); or elevated β2-microglobulin with normal creatinine. Differential cell-state abundance and transcriptional programs were compared across immune and tumor compartments. **Results:** In standard-risk patients, RP was characterized predominantly by immune microenvironment remodeling: depletion of naïve $CD4^+$/$CD8^+$ T-cells, broad reductions across B-cell states, enrichment of cytotoxic and HLA-expressing $CD8^+$ T cells ($p < 0.05$). Notably, standard-risk RP lacked clear enrichment of tumor-cell proliferation or established high-risk myeloma transcriptional signatures, suggesting that immune dysfunction rather than intrinsic tumor aggressiveness drives early progression in this group. By contrast, CGS high-risk RP showed comparatively modest immune microenvironment differences from high-risk NP, but exhibited pronounced tumor-cell proliferation and enrichment of the UAMS70 high-risk transcriptional signature ($p < 0.01$). Further stratification within CGS high-risk disease revealed that patients meeting two or more CGS criteria (multi-hit) had substantially worse progression-free and overall survival than single-hit or standard-risk patients (PFS: HR = 3.73, p = 1.32e-5; OS: HR = 5.08, p = 1.27e-6). This multi-hit subgroup demonstrated the strongest enrichment of proliferative and high-risk transcriptional programs, suggesting it underlies much of the tumor-intrinsic signal observed among high-risk RP. Comparing the immune microenvironment from those with multi-hit high risk, we identified reductions in CD8+ Naïve T cells, and enrichment of T-regs and BM resident NK cells compared to both standard and single-hit high risk patients. **Conclusions:** These findings indicate that the biology of rapid progression differs by genomic risk context. In standard-risk myeloma, rapid progression appears driven by immune microenvironment remodeling, while in CGS high-risk disease it is more strongly linked to intrinsic tumor proliferation and high-risk transcriptional programs. Multi-hit CGS status identifies a particularly adverse subgroup with the most pronounced tumor-intrinsic features, highlighting its potential value as a refined prognostic and therapeutic stratification criterion.

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Incidence and Baseline Predictors of Venous Thromboembolism in Isa-VRd and VRd Arms of the Phase 3 IMROZ Trial in Patients With Transplant Ineligible Newly Diagnosed Multiple Myeloma (Ti NDMM)

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Introduction: Immunomodulatory drug (IMiD)-based regimens are associated with an increased risk of venous thromboembolism (VTE) in NDMM patients (pts), even despite the use of thromboprophylaxis during induction. Limited information exists on VTE incidence with novel lenalidomide-based regimens in NDMM. Isatuximab plus bortezomib, lenalidomide, and dexamethasone (Isa-VRd) showed improved efficacy and safety vs VRd in the Phase 3 IMROZ trial (NCT03319667; median follow-up: 60 months [mo]) and is approved for Ti NDMM pts. This post-hoc analysis evaluated VTE incidence and risk factors in the IMROZ trial. **Methods:** Pts (n = 444) were randomized 3:2 to Isa-VRd or VRd per protocol; those receiving ≥1 dose were included. VTE was defined as ≥1 event from treatment initiation through follow-up, determined from adverse events via a case-insensitive search of MedDRA 26.0 queries. Pts were classified as ≥1 VTE (n = 72) or no VTE (n = 372). Cumulative VTE incidence was assessed at mo 6, 12, 36, and 60. Rates and rate ratios were estimated using a negative binomial model based on all VTE and bleeding events. A Fine-Gray model estimated subdistribution hazard ratios (sHRs). Additional assessments included baseline VTE predictors, VTE rates, pre-VTE antithrombotic coverage, and bleeding event rates per patient-year (PY). **Results:** Isa-VRd showed consistently lower VTE cumulative incidence vs VRd at end of induction period (6 mo: sHR = 0.544; 95% confidence interval [CI] 0.269, 1.103; p = 0.092) and during maintenance (landmarks from treatment start): 12 mo (sHR = 0.661; 95% CI 0.387, 1.131; p = 0.131), 36 mo (sHR = 0.706; 95% CI 0.433, 1.152; p = 0.163), and 60 mo (sHR = 0.778; 95% CI 0.490, 1.235; p = 0.287). VTE rates were lower with Isa-VRd vs VRd during induction (16.7 vs 23.5 per 100 PY, rate ratio: 0.711, p = 0.287) and maintenance (3.0 vs 4.3 per 100 PY, rate ratio: 0.695, p = 0.243), while bleeding rates were comparable (0.06 vs 0.09 per 100 PY, rate ratio: 0.675, p = 0.463 and 0.01 vs 0.01 per 100 PY, rate ratio: 1.251, respectively). During follow-up, Isa-VRd vs VRd showed lower overall VTE rates (4.4 vs 6.9 per 100 PY, rate ratio: 0.675, p = 0.075), lower Grade ≥3 VTE rates (1.8 vs 2.8 per 100 PY, rate ratio: 0.653, p = 0.223), and reduced VTE incidence among pts with ≥1 VTE (14.8% vs 18.2%, difference: −3.4%). Pre-VTE antithrombotic coverage was 95.8% (69/72 pts receiving ≥1 dose). Antithrombotic analyses will be presented at the congress. In this trial, the baseline VTE predictors showed higher median body mass index (BMI) in pts with VTE vs no VTE (28.7 vs 26.0 kg/m^2; p < 0.001), with a greater proportion with BMI ≥25 kg/m2 (75.0% vs 60.2%; p = 0.023). **Conclusions:** These findings support VTE safety in using IMID-containing quadruplet therapy in NDMM pts, with Isa-VRd associated with lower VTE rates and cumulative incidence vs VRd from induction to 60 mo. Elevated BMI was identified as a potential baseline VTE predictor. These findings support Isa-VRd as a standard of care in Ti NDMM.

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Incidence and Timing of Cytokine Release Syndrome (CRS) Observed With Linvoseltamab (LINVO) in LINKER-MM1 in Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: LINVO, a B-cell maturation antigen × CD3 bispecific antibody, demonstrated high, durable response rates and a generally manageable safety profile for RRMM in the pivotal LINKER-MM1 study (NCT03761108), in which all-grade CRS events occurred in 46% of pts (Grade 1, 35.0%; Grade 2, 10.3%; Grade 3, 0.9%). Here we present a further analysis to assess onset, frequency, and severity of CRS. **Methods:** LINKER-MM1 is an open-label, Phase 1/2 study of LINVO in adults with active multiple myeloma (MM) by International Myeloma Working Group criteria. Eligible pts were aged ≥18 years, with Eastern Cooperative Oncology Group performance status of 0 or 1, and active MM, and had received ≥3 prior lines of therapy, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody; pts were double-refractory and exposed to an anti-CD38 antibody (Phase 1 only) or

triple-class refractory (Phase 2 only). In Weeks 1 and 2, an optimized dosing regimen included premedication (no tocilizumab prophylaxis) and step-up dosing to mitigate CRS risk, with 24-hour inpatient monitoring after each step-up dose. In this retrospective analysis using pt-level data (LINVO 200 mg, N = 117; data cut-off July 2024; median follow-up: 21.3 mos), we analyzed CRS symptom onset (fever, hypoxia, and hypotension, as per protocol) and severity during LINVO step-up dosing: after step-up dose 1 (5 mg on Day 1), step-up dose 2 (25 mg on Day 8), and full dose 1 (200 mg on Day 15). CRS events with missing start time were excluded. **Results:** After step-up dose 1, 31 pts (26.5%) had signs and symptoms of CRS. Grade 1 events (n = 24; 20.5%) occurred 4–25 hours after step-up dose 1. Grade 2 CRS (n = 6; 5.1%) occurred at 5–13 hours. One case of Grade 3 CRS (n = 1; 0.9%) occurred during the seventh hour post-dose. CRS frequency peaked 6–8 hours post-dose, after which three Grade 2 events and intermittent Grade 1 events were observed. After step-up dose 2, 15 pts (13.3% of 113 pts on this dose) had CRS. Events were mostly Grade 1 (n = 14). CRS occurred at 4–21 hours post-dose, with most events (n = 10) observed at 4–11 hours. One Grade 2 CRS event was observed (n = 1) during the eighth hour post-dose, and no Grade 3 CRS occurred (n = 0). After full dose 1, three pts (2.7% of 111 pts on this dose) had CRS. Events occurred during the fifth hour (Grade 1), seventh hour (Grade 1), and 10th hour (Grade 2) post-dose, with no Grade 3 CRS (n = 0). In LINKER-MM1 (N = 117), the treatments administered to pts with select CRS signs and symptoms included tocilizumab (n = 22; 18.8%), corticosteroids (n = 13; 11.1%), oxygen support (n = 9; 7.7%), vasopressors (n = 1; 0.9%), and intravenous fluid bolus (n = 11; 9.4%). **Conclusions:** CRS occurred early following LINVO administration, was primarily low grade, and decreased in frequency and severity across step-up dosing, with few higher-grade CRS events at later dosing levels. This detailed analysis enables optimization of administration and implementation of timely monitoring and interventions to improve pt safety.

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Individualized Holding and Bridging Therapy Achieves High Response Rates and Reduces Toxicity of BCMA-Directed CAR-T Cell Therapy in Multiple Myeloma

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Introduction: BCMA-directed chimeric antigen receptor T-cell (CAR-T) therapy has transformed the treatment of relapsed/refractory multiple myeloma (RRMM), but can be associated with substantial toxicity. Reduction of tumor burden prior by bridging therapy prior to CAR-T has emerged as key factor for reducing CAR-T toxicity, particularly severe CRS and neurotoxicity. No clear treatment standards exist for bridging therapy and many treatment options are available. **Methods:** In this single-center retrospective analysis, 88 consecutive RRMM patients received idecabtagene vicleucel (ide-cel; n = 22) or ciltacabtagene autoleucel (cilta-cel; n = 66). Holding therapy (before apheresis) and bridging therapy (after apheresis) were reviewed. Pre-infusion response was assessed by IMWG criteria. The primary endpoint was a composite of any ≥Grade 2 toxicity across six categories: cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), IEC-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), early and late immune effector cell-associated hemato-toxicity (ICAHT), and infection, evaluated using log-link regression to estimate risk ratios (RR). **Results:** Patients had a median of 4 prior lines of therapy (range 1–10); holding and bridging therapy were administered in 90.9% and 99%, respectively. Twenty-four different therapeutic regimens were used; the bridging regimen was changed in 40% after apheresis with the intent to maximize response. Polychemotherapy-based regimens (PACE; n = 17) achieved an ORR of 76.5% without manufacturing failures when used as holding therapy; the out-of-specification product rate was 5.6% across the entire cohort. Overall, 68.2% achieved ≥partial response to pre-infusion therapy. Patients achieving at least a very good partial response (VGPR) had a composite ≥Grade 2 toxicity rate of 22.9% versus 47.2% in those with less than VGPR (RR 0.48, 95% CI 0.25–0.95; p = 0.035), persisting after multivariable adjustment (adjusted RR 0.50, 95% CI 0.26–0.98; p = 0.042) and supported by an ordinal trend analysis (likelihood-ratio p = 0.008). The association was consistent across all toxicity categories. No movement and neuro-cognitive adverse events were observed. Non-relapse mortality was 2.3%. **Conclusions:** Adaptive, individualized holding and bridging therapy with a wide variety of treatment regimens achieved high pre-infusion response rates. Intensive chemotherapy as holding therapy did not compromise CAR-T product quality or manufacturing success. Deeper pre-infusion disease control was associated with significantly lower composite toxicity after BCMA-directed CAR-T therapy without severe neurotoxicity, positioning pre-infusion response as a potentially modifiable determinant of CAR-T-related toxicity. Prospective validation is warranted.

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Indole-Related Metabolites Suppress the Anti-Tumor Function of CD8+ T Cells in the Bone Marrow Microenvironment of Multiple Myeloma

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Introduction: MM remains incurable due to the complex BM microenvironment. Recent studies highlight metabolic

reprogramming's role in tumor progression and CD8+ T cell dysfunction,yet the metabolic landscape of MM BM is poorly understood. We show that MM CD8+ T cells,despite elevated immune checkpoint expression,avoid canonical exhaustion but are reversibly suppressed by microenvironmental changes. Metabolomic analysis reveals tryptophan pathway remodeling,with nitrogen-rich metabolites and indole derivatives impairing CD8+ T cell function. Indole-related metabolites emerge as key immunosuppressive regulators, promoting immune evasion. These findings unveil a novel immune suppression mechanism and suggest metabolic targets for immunomodulatory therapies in MM. **Methods:** Antibodies against IFNγ,TNFα,IL-2, perforin,GzmB were added and incubated. Cells were analyzed by flow cytometry. K562,U266,CAR-T or PBMC were mixed with tumor cells at indicated ratios in U-bottom 96-well plates and incubated for 24 h with or without different concentrations of bone marrow supernatant. Mix 100 µL bone marrow supernatant with 300 µL PBS, then add the mixture into a 3 kD ultrafiltration tube. The material in the outer sleeve is designated 3 kD-up, and that remaining in the ultrafiltration tube is 3 kD-down. Add 800 µL of methanol pre-chilled to −80°C to achieve a final concentration of 80% (v/v) methanol. Mix gently and incubate overnight at −80°C. Centrifuge and transfer the supernatant to a new tube. Lyophilize to dryness. **Results:** While a substantial CD8+ T cell population persists in the MM microenvironment, they do not exhibit the canonical exhausted phenotype typically seen in chronic viral infections or other malignancies. Unexpectedly, fresh BM CD8+ T cells display blunted cytokine responses, which are reversible after overnight culture but inhibited by autologous BM supernatant. This suppression is BM-specific. The < 3 kDa hydrophilic fraction of BM supernatant significantly impairs the cytotoxic capacity of BCMA CAR T cells. Untargeted metabolomic profiling reveals that multiple indole derivatives are upregulated in the tryptophan metabolic pathway. Significant upregulation of IAA, IPA, and kynurenine in inhibitory BM supernatant. Both IAA and IPA significantly upregulate AHR expression. Indole-related metabolites may impair antitumor T cell function through AHR-mediated signaling. **Conclusions:** Flow cytometric and transcriptional analyses revealed that CD8+T cells in the MM bone marrow microenvironment exhibit an activated phenotype rather than classical exhaustion markers,despite their functional impairment. Ultrafiltration and functional assays demonstrated that the < 3 kDa hydrophilic fraction of MM bone marrow supernatant significantly inhibits CD8+ T cell effector functions. IAA and IPA are significantly elevated in the bone marrow of a subset of MM patients, where they potently inhibit the anti-tumor function of CD8+ T cells, likely through activation of the AhR signaling pathway on T cell surfaces.

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Infection Spectrum, Etiology and Severity in Patients Treated With Teclistamab for Relapsed/Refractory Multiple Myeloma: A Real-World Cohort

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Introduction: Infections are a major cause of morbidity and mortality in patients treated with anti-BCMA bispecific antibodies. In MajesTEC-1, infections occurred in 76% of patients, including grade ≥3 infections in 45%. Real-world data remain limited, particularly in Latin America. We describe the incidence, characteristics, timing, and severity of clinically significant infections in patients receiving teclistamab outside a clinical trial. **Methods:** We conducted a single-center retrospective cohort study of 24 consecutive patients with relapsed/refractory multiple myeloma treated with teclistamab between January 2023 and March 2026. Infections were classified according to site, microbiological etiology, and severity, including hospitalization and intensive care unit (ICU) admission. Time-to-infection was calculated from the first teclistamab dose to symptom onset. All patients received antimicrobial prophylaxis and intravenous immunoglobulin replacement. Data cutoff was May 16, 2026. **Results:** Nineteen infectious episodes were identified in 19/24 patients (79%) during a median follow-up of 25 months. Median age was 75 years, and median prior line of therapy was fourth (range, 2–10). Median time from teclistamab initiation to infection was 42 days (range, 0–536), with 79% occurring within the first 100 days. Thirteen episodes (68%) required hospitalization, four (21%) ICU admission, and one infection-related death occurred. Three patients permanently discontinued teclistamab because of infections and remained in myeloma remission. Five patients had no documented clinically significant infection; two died within 30 days of treatment initiation and three achieved deep responses without infectious complications. Lower respiratory tract infection/pneumonia was the most common site (58%), followed by gastrointestinal or upper respiratory tract infections (26%). Urinary tract and central nervous system infections occurred in one episode each. Viral pathogens were identified in 15/19 episodes (79%) and bacterial pathogens in 9/19 (47%), including five viral-bacterial co-infections (26%). The most frequent viruses were rhinovirus (n = 6), cytomegalovirus (n = 3), SARS-CoV-2 (n = 2), and respiratory syncytial virus (n = 2). Other viral pathogens included parainfluenza virus, coronavirus NL63, norovirus, and JC virus. Bacterial pathogens included Escherichia coli (n = 4), Pseudomonas aeruginosa (n = 2), Klebsiella pneumoniae, Acinetobacter baumannii, Mycoplasma pneumoniae, and Enterobacter spp. teclistamab is administered weekly and may be transitioned to every-other-week dosing after 6 months of complete

response. **Conclusions:** Teclistamab was associated with a high burden of infectious complications, predominantly within the first 100 days of therapy. These findings support intensive infectious surveillance, preventive strategies, and the evaluation of earlier teclistamab dose-spacing approaches during treatment.

PA-257

In-Hospital Mortality in Multiple Myeloma and Plasma Cell Disorders at a North Indian Tertiary Center

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Introduction: Infections remain a major cause of mortality in multiple myeloma (MM). There is limited contemporary data from low- and middle-income countries (LMICs) examining the interplay between disease biology, treatment-related immunoparesis, multi-drug resistant (MDR) pathogens, and in-hospital mortality patterns. **Methods:** We retrospectively reviewed death summaries of all consecutive patients with MM and plasma cell disorders who died between January 2021 and December 2025 at our center. Demographic details, clinical parameters, and laboratory investigations, including FISH, CRAB features, prior lines of therapy, and microbiology were retrieved. Causes of death were categorized as septic/infectious, cardiogenic/cardiac amyloid, or non-septic respiratory failure. Associations with septic versus non-septic death, and with early (≤ 7 days) versus late (>7 days) death were explored using univariate Fisher's exact tests; odds ratios (OR) were calculated with 95% confidence intervals (Cornfield method). **Results:** Fifty in-hospital deaths were analyzed. Median age was 61 years (range 32–90 years); 66% were males. Fifteen patients (30.0%) had newly diagnosed MM (NDMM) and 23/50 (46.0%) had relapsed/refractory MM (RRMM); 9/50 (18.0%) had AL amyloidosis. IgG was the most common paraprotein (24/50, 48%); 32/45 (71.1%) patients had ISS stage III. Renal dysfunction at admission was present in 30/50 patients (60.0%); hypercalcemia in 24/50 patients (48.0%). Median duration of hospital stay was 9 days (range 2–130 days). Early deaths accounted for 21/50 patients (42.0%); 29/50 deaths (58.0%) occurred after 7 days. Septic/infectious causes accounted for 27/50 deaths (54.0%). MDR organisms were documented in 12/50 patients (24.0%); colistin was used pre-terminally in 6 patients (12.0%), 3 patients had pan-resistant MDR pathogens. High-risk FISH abnormalities were present in 19/39 patients (48.7%), and were more frequent in septic vs. non-septic deaths (50% vs 7%; OR 13.0, 95% CI 1.5–110.1, p = 0.019). Hypercalcemia was more frequent in NDMM vs RRMM (66.7% vs 30.4%; OR 4.57, 95% CI 1.13–18.4, p = 0.04). Nine patients (18.0%) were treatment-naive at the fatal admission. Three or more prior treatment lines were associated with septic death (OR 6.0, 95% CI 1.4–26.6). Terminal cardiac events were more frequent in AL amyloidosis vs. non-amyloid patients (88.9% vs 12.2%; OR 57.6, 95% CI 9.1–364, p < 0.01). Treatment-naive patients had significantly higher early mortality (OR 6.3, 95% CI 1.15–34.6, p = 0.035). Autopsy was performed in only 3 cases (6.0%). **Conclusions:** In this small real-world Indian cohort, infections due to MDR pathogens dominated the terminal events in MM patients. High-risk FISH and heavier treatment burden appear to be associated with death due to sepsis. Mortality in AL amyloidosis is predominantly driven by cardiac events. These findings highlight the need for prospective studies integrating cytogenetic risk, infection prevention strategies, and antimicrobial stewardship in LMICs.

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Inobrodib Sensitivity in Multiple Myeloma Patients and in Cell Lines Is Associated With H3-Modifier Dysregulation

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Introduction: Multiple myeloma shows epigenetic dysregulation; patient genomes often contain histone H3-modifier alterations that can drive survival and drug resistance. Inobrodib (Ino), a selective oral p300/CBP H3K27 acetyltransferase bromodomain inhibitor, disrupts its recruitment at enhancers and downregulates MYC and IRF4, causing cell-cycle delay and growth inhibition. We are exploring how clinical response results from its mechanisms of action in myeloma. We analysed baseline genomic/transcriptomic data from Ino-treated patients, correlation with clinical response and in vitro sensitivity of H3-modifier mutant cell lines. **Methods:** MGP panel assessed mutations in 24 H3-modifier genes in Ino-treated patient samples (Sudha et al, 2022, CCR). DepMap was queried for H3-modifier mutations in OPM2, JJN3, and H929 cells. Cells were treated with Ino (100 or 500 nM) or DMSO. RNA-seq was performed in duplicate at 0, 6 and 24 h for all lines, plus 96 h for H929 and JJN3. DESeq2 evaluated dose-, time- and cell line-specific effects. Viability was measured by CellTiter-Glo at 96 h. **Results:** Responder/non-responder analysis identified a positive trend between Ino response and higher mutant KMT2B/KMT2C (H3K4 methyltransferases) variant allele frequency (VAF) in patients (see details in Hasheminasab et al abstract). We hypothesised potential synthetic lethality between high-VAF mutations and p300/CBP inhibition. In vitro sensitivity was tested in 3 H3-modifier mutant lines: OPM2 (KMT2B/KMT2D), H929 (KDM5A; H3K4 demethylase), and JJN3 (EZH2; H3K27 methyltransferase). OPM2 was most sensitive, H929 - intermediate, and JJN3 least sensitive, with GI50 s of

31.24 ± 22.59, 47.75 ± 30.37 and 74.25 ± 4.40 nM, respectively. RNA-seq of treated cells vs controls showed MYC/E2F target gene suppression in all 3 lines. Cell line-specific effects on H3-modifiers were noted: in OPM2, KDM5A expression was induced, supporting H3K4 demethylation. Also, HDAC1 (H3K27 deacetylase) was induced, accompanying Ino-mediated inhibition of H3K27 acetylation, resulting in increased cytotoxicity. In contrast, KDM6A (H3K27 demethylase) was also induced. In H929, NSD2 (H3K36 methyltransferase) was induced and KDM2B (H3K36 demethylase) - reduced, suggesting altered H3K36 dimethylation. In JJN3, KMT2D was induced, potentially affecting H3K4 methylation, while KDM6A and EZH1 were also induced. **Conclusions:** Our results suggest Ino's p300/CBP-mediated effects may be linked to broader H3-modifier dysregulation, particularly H3K4 alterations. OPM2, with mutant H3K4 methyltransferases, was the most sensitive in the viability assay, while H929 (H3K4 demethylase mutant) and JJN3 showed more compensatory epigenetic responses and lower sensitivity. These findings suggest that H3K4 dysregulation may be linked to p300/CBP-driven epigenetic/transcriptional pathways and share some interdependency. Ongoing/future work includes KMT2 family knockdowns, mechanistic and more patient sample analyses.

PA-259

Inobrodib Treatment Synergises With IMiDs to Epigenetically Downregulate IRF4 Expression in Drug-Resistant Myeloma

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy driven by oncogenic transcription factors (TFs) including IRF4. Standard-of-care immunomodulatory drugs (IMiDs), e.g. pomalidomide (Pom), target the TFs IKZF1/3 to the E3 ubiquitin ligase CRBN for degradation, resulting in IRF4 downregulation. In relapsed/refractory MM (RRMM), IMiD resistance is driven either by CRBN inactivation, preventing loss of IKZF1/3 and IRF4 downregulation, or epigenetic rewiring to allow IRF4 expression independent of IKZF1/3. Thus, alternative approaches are needed to downregulate IRF4 in RRMM patients. The acetyltransferases P300/CBP promote the expression of key MM genes, including IRF4. The P300/CBP inhibitor Inobrodib (Ino), in combination with Pom and dexamethasone, is currently showing promise in phase IIa clinical trials for RRMM. Here, we sought to understand the mechanistic basis for synergy between Ino and IMiDs. **Methods:** We separately evolved MM cell lines with resistance to Pom or Ino and isolated clones for analysis. Drug sensitivity and synergy were assessed with CellTiter-Glo and Annexin V staining. RNA-seq and ChIP-seq were used to capture epigenetic differences between sensitive and drug-resistant cell lines. IRF4 overexpression was achieved with a retroviral expression system. **Results:** Despite only having been exposed to one drug, we identified cross-resistance between Ino and Pom. Ino-resistant cells displayed tolerance to both Pom and the CELMoD mezigdomide, and Pom-resistant cells were tolerant to Ino. Of note, Ino resistance was only observed in Pom-resistant cells with functional CRBN, i.e. in cells no longer dependent on IKZF1/3 activity. Across multiple resistant clones and cell lines, a common feature was the maintenance of IRF4 expression in the presence of either drug. ChIP-seq demonstrated the IRF4 enhancer retained activity in the presence of Ino, arguing for epigenetic rewiring at this locus driving resistance to both Ino and IMiDs. We also confirmed that the genome-wide disruption of IRF4 binding induced by Ino was stabilized in resistant cells. Importantly, in cells resistant to Pom and Ino individually, combined Ino/Pom treatment synergistically downregulated IRF4 and induced apoptosis. Exogenous expression of IRF4 abrogated this synergistic effect. Ino/Pom synergy was also observed in RRMM patient myeloma cells. **Conclusions:** Our findings implicate epigenetic rewiring of IRF4 expression as a common mechanism of resistance to Ino and IMiDs. However, combined treatment with Pom and Ino is able to downregulate IRF4 expression in resistant cells, depending on the presence of functional CRBN. Therapeutically, this indicates that addition of Ino to Pom treatment may help resensitise IMiD-resistant RRMM patients.

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Integrated Analysis of Myeloma Genome Project Panel (MGPP) and Immune Profiling Reveals Baseline Immunogenetic Correlates of Newly Diagnosed MM in the UK-MRA RADAR Trial

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Introduction: Genomic aberrations influencing tumour immunogenicity may alter immune cell composition and differentiation within the tumour niche. We employed targeted sequencing in newly diagnosed (ND) MM patients enrolled in the UK-MRA RADAR trial to explore associations between recurrent genetic abnormalities and immune cell function. **Methods:** The MGPP includes 228 genes, copy number (CNA) calling and Ig loci and MYC

translocations. The UK-MRA RADAR trial is a prospective, phase II/III trial in NDMM patients eligible for ASCT. DNA from 418 CD138+ diagnostic samples were run on the MGPP. Immune cell phenotype was assessed by flow cytometry on freshly isolated bone marrow cells. Associations between genetic lesions were assessed using Fisher's exact tests, and differences in immune subsets using t-tests. **Results:** A cohort of 418 patients was studied, median age 62 (35–75), 65% male. 396/418 (93.8%) samples run on the MGP panel had at least one non-silent mutation (median panel-derived tumour mutational burden (TMB) = 6). As expected, KRAS(30%), NRAS (24%), BRAF(13%), DIS3(11%) and TP53(11%) were the most frequently mutated genes. Key canonical Ig translocations were t(11;14)(18.6%), t(4;14)(14.9%), t(8;14)(5.4%), t(14;16)(4.5%), t(14;20)(1.9%) and t(6;14)(3% CCND3 and 0.5% IRF4), with good concordance with FISH. Mutual interactions were found between DIS3 and FGFR3 ($p = 0.02$), both enriched in t(4;14)($p = 0.038$, $p < 0.001$). Mutations affecting the NFκB pathway are prevalent in MM; non-canonical NFκB pathway mutations were found in 19% of patients, with a recurrent hotspot in TRAF3 (p.S84X). To investigate the association of genetic lesions with immune profiles, we first examined TMB and neoantigen load. As expected, HR lesions including t(14;16), del(17p) and TP53 mutations associated with a significantly greater tumour load ($p < 0.05$) and TMB ($p < 0.05$). In contrast, NFκB mutations associated with TMB but not with tumour load. We hypothesised that increased mutational load per se may shape the T-cell compartment. Aberrations in the NFkB noncanonical pathway associated with increased T-cell abundance ($p = 0.057$), primarily driven by expansion of the CD4+ compartment ($p = 0.096$). More strikingly, we also observed proportional reductions in naïve CD4 and CD8 cells ($p = 0.05$, $p = 0.031$), with increased CD4, CD8 effectors ($p = 0.003$, $p = 0.007$) and γδ T cells($p = 0.034$). We also noted a shift in NK-cell populations, with a proportional increase in immature CD56bright NK cells ($p = 0.025$). Finally, CD57+ expression was higher across all effector T-cell and cytotoxic NK cell subsets ($p < 0.05$), consistent with a more terminally differentiated phenotype. **Conclusions:** Our findings demonstrate the utility of the MGPP for comprehensive genomic profiling in NDMM, facilitating dissection of immunogenetic associations. We report a skewed T and NK cell composition in context of non-canonical NFkB pathway alterations, possibly related to chronic antigen exposure.

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Integrated Genomic and Transcriptomic Profiling Identifies Response-Associated Transcriptional Programs in Relapsed/Refractory Multiple Myeloma Treated With Inobrodib-Based Therapy

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Introduction: Inobrodib (ino) is a first-in-class oral selective p300/CBP inhibitor. Ino plus pomalidomide/dexamethasone (pom/dex) is under investigation in heavily pretreated relapsed/refractory multiple myeloma (RRMM), including patients refractory to proteasome inhibitors, anti-CD38 antibodies, IMiDs, and/or BCMA-targeted therapy (NCT07096778). We performed integrated genomic and transcriptomic analyses to identify molecular programs associated with disease biology and response. **Methods:** Targeted DNA sequencing was performed on pre-treatment CD138+ cells from an expanded RRMM cohort treated with ino-based therapy. Matched RNA-seq, targeted DNA-seq, and clinical annotation were analysed in a subset with high tumour purity and RNA quality. Differential gene expression (DGE), GSEA, and Multi-Omics Factor Analysis were performed using standard methods. Significance was defined as adjusted $P < 0.05$, with DGE additionally requiring $|\log2FC| \geq 1$. Response analyses classified patients achieving ≥PR as responders, while SD/progressive disease and MR cases were classified as non-responders. Validation studies were performed in MM cell lines. **Results:** Targeted DNA sequencing of 77 patient-derived samples identified recurrent alterations in KRAS (21%), ATM (17%), TP53 (16%), NRAS (14%), and KMT2C (12%), together with frequent high-risk features including 1q gain, del(1p), del(17p), and IGH translocations. High-risk disease was identified in 37/51 evaluable patients (72%). Among 19 patients with matched DNA/RNA sequencing, 15 were response evaluable (10 responders, 5 non-responders). Responder samples were enriched for proliferative transcriptional programs, including G2M checkpoint, E2F and MYC targets, epithelial-mesenchymal transition, hypoxia, coagulation, and inflammatory-response pathways. In contrast, non-responders showed enrichment of interferon, TNFα/NFκB, IL6/JAK/STAT3, and unfolded protein response pathways, consistent with stress-adaptive biology. Consistent with these findings, ino treatment of MM cell lines (H929, OPM2, JJN3) suppressed G2M, E2F, and MYC-associated transcriptional programs across models and timepoints. Responses were observed in both pom-naive and pom-treated patients. **Conclusions:** These findings identify activated MYC/G2M/E2F transcriptional states linked to response to ino-pom-dex therapy, with suppression following ino treatment in vitro. The data support further investigation of integrated genomic and transcriptional biomarkers associated with sensitivity and resistance to ino-based therapy, including in patients previously exposed/refractory to second-generation IMiD Pom and BCMA-targeted therapies. Larger multimodal and correlative analyses with clinical outcomes and laboratory validation are ongoing.

PA-262

Integrated Multi-Omic Profiling Reveals Compensatory Cytotoxic CD8 T-Cell Rewiring, NK-Cell Remodeling, and Systemic Immune Dysfunction During Progression From MGUS to Multiple Myeloma

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Introduction: Multiple myeloma (MM) evolves through precursor stages, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). To identify biological determinants of progression, we performed an integrated multi-omic characterization of immune and microbial alterations across the MGUS–SMM–MM continuum. **Methods:** Single-cell transcriptomic, CITE-seq, and TCR/BCR profiling was performed on 248,924 cells from paired bone marrow (BM) and peripheral blood (PB) samples obtained from healthy donors (HD, n = 9), MGUS (n = 12), SMM (n = 12), and MM (n = 17). Multiparametric flow cytometry was performed in 46 patients, cytokine profiling in 72 samples and 4 HDs, and gut microbiota profiling in 51 patients (MGUS n = 15, SMM n = 18, MM n = 18). **Results:** Single-cell analyses revealed progressive immune remodeling characterized by expansion of plasma cells and CD8 memory T cells together with marked alterations of NK-cell, myeloid, and progenitor compartments. Notably, an Immune Dysregulation Score showed progressively increasing inter-patient heterogeneity from HDs to MGUS, SMM, and MM in both BM and PB, indicating diversification of immune trajectories during disease evolution. Unexpectedly, CD8 T-cell analyses did not support a model of progressive exhaustion. Exhaustion-associated transcriptional programs and inhibitory receptors, including TIGIT and CD39, progressively declined from HD to MM (all FDR-adjusted $p < 0.001$). In contrast, cytotoxic programs displayed a stage-dependent pattern, with an early reduction in MGUS followed by progressive enrichment in SMM and MM (all FDR-adjusted $p < 0.001$ versus MGUS). Expanded TCR clones were enriched for cytotoxic, IFN-response, and effector-associated programs without enrichment of exhaustion signatures, supporting a non-canonical CD8 rewiring characterized by compensatory cytotoxic activation despite ineffective tumor control. NK-cell analyses revealed expansion of CD56dim populations and enrichment of IFN-response and cytotoxic programs. Flow cytometry confirmed depletion of transitional memory CD8 T cells and expansion of TEMRA populations. Cytokine profiling demonstrated broad suppression of immune mediators, indicating impaired immune-cell communication already detectable in precursor conditions. Microbiota profiling revealed preserved alpha- and beta-diversity across disease stages but selective species-level remodeling involving Enterocloster sp000431375 and short-chain fatty acid-associated taxa, including Ruminococcus bromii, suggesting subtle microbial changes rather than overt dysbiosis. **Conclusions:** Progression from MGUS to MM is characterized by increasing immune-state heterogeneity, compensatory cytotoxic CD8 rewiring, NK-cell remodeling, cytokine suppression, and selective microbiota changes rather than classical T-cell exhaustion. These findings provide a framework for biomarker-driven risk stratification and disease interception strategies.

PA-263

Integrated Single-Cell and Functional Profiling of Bone Marrow Immune Remodeling After IsaKRD Induction in Newly Diagnosed Multiple Myeloma

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Introduction: Isatuximab, a CD38-targeting monoclonal antibody, has demonstrated deep and durable responses when combined with carfilzomib, lenalidomide, and dexamethasone (IsaKRD) in newly diagnosed multiple myeloma (NDMM). However, the determinants of therapeutic resistance, particularly the contribution of the bone marrow immune microenvironment, remain poorly characterized. A better understanding of immune dynamics in response to IsaKRD could inform strategies to overcome resistance mechanisms. **Methods:** We performed single-cell RNA sequencing of $CD45^+$ bone marrow immune cells from 84 NDMM patients enrolled in the IFM "MIDAS" trial. Paired samples were collected at baseline (C0) and after six cycles of IsaKRD induction (C6), and immune remodeling was analyzed according to minimal residual disease (MRD) status. Findings were extended in a longitudinal C0/C6 cohort of 70 high-risk patients carrying del(17p) and/or TP53 alterations. Forty NDMM patients treated with Dara-VRD or VRD served as comparator cohorts to distinguish broad induction-associated effects from anti-CD38–containing regimen–specific changes. Confirmation of the main immune remodeling patterns was assessed at the proteomic level by flow cytometry. Functional validation was performed using C0/C6 cohort bone marrow samples. **Results:** IsaKRD induced global reductions in B, NK, and T-cell populations alongside expansion of myeloid subsets. Cytotoxic NK cells were markedly depleted, particularly in MRD-positive patients, who instead exhibited expansion of inflammatory, bone marrow–resident NK cells. $CD4^+$ and $CD8^+$ T cells shifted from naïve and cytotoxic states toward inflammatory and resident memory–like phenotypes. Conversely, MRD-negative patients preserved $CD8^+$ T-cell cytotoxicity and expanded effector memory $CD4^+$ T cells.

Myeloid remodeling featured increased inflammatory monocytes, with MRD-positive patients showing expansion of hypoxic/glycolytic subsets and loss of non-classical monocytes. These trajectories were also observed in high-risk patients, while comparators resolved induction-related versus anti-CD38–associated remodeling. Functional assays showed that lymphocytes collected after six cycles of IsaKRD had higher responsiveness to BCMA-directed bispecific antibody stimulation. Compared with baseline NDMM samples, post-C6 samples showed increased cytokine production, enhanced $CD4^+$ and $CD8^+$ T-cell proliferation, acquisition of activation and cytotoxic markers, and improved killing of myeloma target cells in vitro. **Conclusions:** IsaKRD drives coordinated bone marrow immune remodeling in NDMM. MRD-positive disease is associated with hypoxia- and inflammation-driven myeloid programs and impaired cytotoxic lymphoid compartments, whereas MRD-negative patients retain protective cytotoxic and innate immune features. Despite cytotoxic subset depletion, residual post-induction T cells remain functionally responsive, supporting sequencing with T-cell–redirecting immunotherapies and biomarker development.

PA-264

Integrated Single-Cell and Proteomic Profiling Reveal Immune Mechanisms of Response and Resistance to BCMA × CD3 Bispecific Antibodies in the RESISTEC Study

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Introduction: BCMA × CD3 bispecific antibodies (BsAbs) have transformed the treatment landscape of relapsed/refractory multiple myeloma (RRMM), achieving high response rates in heavily pretreated patients. However, approximately one-third of patients exhibit primary resistance, and the mechanisms underlying treatment failure remain poorly understood. While tumor burden and soluble BCMA have been implicated, the immune determinants of response to BsAbs remain incompletely characterized. **Methods:** We performed a longitudinal immunogenomic analysis of RRMM patients from the IFM RESISTEC study treated with BCMA × CD3 bispecific antibodies (teclistamab or elranatamab). Bone marrow (BM) and peripheral blood (PB) samples were collected longitudinally and analyzed using single-cell RNA sequencing with paired TCR profiling, spectral flow cytometry, and Olink plasma proteomics. Immune and proteomic remodeling, clonal dynamics, and trafficking were correlated with clinical response. **Results:** Baseline BM immune composition revealed enrichment of NK-cell populations in non-responders (NR), whereas responders (R) displayed higher frequencies of PB $CD4^+$ and $CD8^+$ T cells. Plasma proteomics identified baseline signatures strongly associated with resistance. Longitudinal PB analyses identified that responders developed marked expansion of terminally differentiated cytotoxic $CD8^+$ T cells, together with increased tissue-resident memory–like (TRM) $CD8^+$ T cells and contraction of $FOXP3^+$ regulatory T cells (Tregs). In contrast, non-responders failed to expand cytotoxic $CD8^+$ T cells and instead accumulated Tregs with activated phenotype. Longitudinal proteomic analyses showed that both responders and non-responders activated interferon-associated inflammatory pathways, but only responders developed robust cytotoxic immune signatures. TCR analyses revealed marked clonal remodeling during therapy. Responders showed increased T-cell clonality during the first treatment cycles, whereas non-responders did not. In responders, PB expanding clones frequently originated from BM-restricted clonotypes present at baseline, indicating mobilization and recirculation of BM-derived T cells during effective responses. Transcriptomic analyses further showed that expanding clonotypes initially belonged to interferon-responsive $CD8^+$ T-cell populations in the BM and progressively acquired cytotoxic programs during treatment. **Conclusions:** Response to BCMA × CD3 bispecific antibodies is associated with dynamic clonal remodeling characterized by expansion of BM-derived interferon-primed $CD8^+$ T-cell clones that differentiate into circulating cytotoxic effectors. In contrast, non-responders exhibit activation of suppressive Treg programs and proteomic signatures associated with tumor burden. These findings identify coordinated immune, clonal, and proteomic mechanisms underlying response and resistance to BsAbs and provide a rationale for predictive biomarkers and novel combinatorial therapeutic strategies in RRMM.

PA-265

Integrated Spatial and Single-Nucleus Analyses Identify Osteoblast Suppression as a Dominant Feature of Bone Disease in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is frequently associated with osteolytic bone disease, classically attributed to increased osteoclast (OC) activity and suppressed osteoblast (OB) function. However, the relative contribution of altered OC versus OB to MM bone disease remains unclear. Here, we investigated bone remodeling dynamics in patient samples, murine, and in vitro models to better define the cellular mechanisms underlying MM bone disease. **Methods:** Bone marrow biopsies from healthy controls (n = 9), MGUS (n = 10), and MM patients (n = 13) were analyzed by combined TRAP immunostaining and COL1A1 RNA fluorescence

in situ hybridization to identify OCs and OBs, respectively. Bone histomorphometry quantified osteoid (newly formed bone), COL1A1+ OB and TRAP+ OC surfaces. To model MM bone disease, Vk*MYC MM cells were intrafemorally transplanted into C57BL/6 mice, with disease confirmed by serum protein electrophoresis and bone lesions by µCT. Mechanistic studies employed an in vitro OC differentiation system from mouse bone marrow mononuclear cells, enabling characterization of osteoclast precursors (OCPs) and OCs. Single-nucleus RNA sequencing (snRNA-seq, 10X Genomics) characterized osteoclastogenic transcriptional programs. Cytokine profiling of mouse serum and OC culture supernatants was performed using multiplex assays, and the OCP population was further analyzed by flow cytometry. **Results:** Histomorphometric analyses across healthy controls, MGUS, and MM patient biopsies demonstrated reduced bone formation in MM, characterized by decreased osteoid surfaces compared with control, without a corresponding increase in OC abundance or surfaces. Similarly, despite osteolytic lesions detected by µCT, Vk*MYC mice showed no detectable increase in trabecular or cortical OC surfaces compared with PBS controls at mid- or late-stage disease. SnRNA-seq of in vitro differentiated OCPs and OCs derived from Vk*MYC and control mice demonstrated no evidence of enhanced osteoclastogenic transcriptional activation in MM derived cultures, further supported by RT-qPCR analysis of OC associated genes. Multiplex cytokine profiling identified elevated IL-10 levels in Vk*MYC serum and OCP/OC supernatants, suggesting a microenvironment permissive to suppression of osteoclastogenesis. In parallel, snRNA-seq identified depletion of a macrophage associated OCP subset in Vk*MYC, suggesting reduced generation of OC progenitors. This was further evaluated by flow cytometry, which confirmed reduced total macrophage population, including CD206+Arg1+ macrophages, in MM-derived OCP cultures. **Conclusions:** These findings suggest that MM bone disease is driven predominantly by impaired OB formation within the remodeling process rather than increased OC abundance or activity, potentially explaining the limited repair of osteolytic lesions observed clinically. While antiresorptive therapies remain effective, our data support investigating OB directed or bone anabolic strategies alongside current standards of care.

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Integrative Whole-Genome and Transcriptome Sequencing Reveals a Distinct Multiple Myeloma Subtype Characterized by Somatic Hypermutation Signatures

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Introduction: Multiple myeloma (MM) is a molecularly heterogeneous disease, yet the molecular mechanisms underlying specific subtypes and their clinical implications remain incompletely understood. **Methods:** We collected bone marrow samples from 37 patients with MM and isolated myeloma cells using CD138-based selection. Whole-genome sequencing (WGS) and whole-transcriptome sequencing (WTS) were performed to characterize the molecular landscape of MM, including somatic alterations and mutational signatures. In addition, we analyzed WGS and WTS data from CD138-positive bone marrow cells of 680 patients enrolled in the Multiple Myeloma Research Foundation (MMRF) CoMMpass study (NCT01454297). Drug sensitivity analysis was performed using pharmacogenomic data from cancer cell lines in the Genomics of Drug Sensitivity in Cancer (GDSC) database. **Results:** Mutational signature analysis revealed marked interpatient heterogeneity across MM samples. Single base substitution signature 9 (SBS9), a mutational signature associated with somatic hypermutation (SHM), defined a distinct SBS9-high subtype of MM, representing 5/37 patients (13.5%) in the SNUH cohort and 34/680 patients (5.0%) in the MMRF cohort. SBS9-high MM was associated with inferior clinical outcomes, including significantly shorter median overall survival in the MMRF cohort (45.3 vs. 97.4 months, $p = 0.037$). This subtype showed marked enrichment for IgD MM, comprising 4/5 patients (80.0%) versus 0/32 patients (0%) in the SNUH cohort ($p < 0.001$), and 3/34 patients (8.8%) versus 5/646 patients (0.7%) in the MMRF cohort ($p = 0.005$). Transcriptomic analyses revealed a distinct transcriptional profile of SBS9-high MM characterized by upregulation of DNA repair and SHM-related programs and downregulation of B-cell receptor signaling and immune-related pathways in both cohorts. These findings suggest that SHM-related MM may arise from an earlier stage of B-cell differentiation. Timing analysis of SBS9-attributed mutations further indicated that SBS9-associated mutagenesis emerged prior to malignant transformation. Deconvolution analysis using in-house MM single-cell RNA sequencing data revealed a higher proportion of immature B-cells in SBS9-high MM ($p < 0.05$). Therapeutic response prediction based on transcriptional profiles revealed enrichment of anti-apoptotic programs in SBS9-high MM. In particular, differential expression of BCL2 family genes suggested potential therapeutic vulnerability to BCL2 family inhibitors in this subtype. Consistently, MM cell lines with high SHM signature activity showed increased sensitivity to BCL2 family inhibitors in GDSC analyses. **Conclusions:** SHM-related MM represents a biologically distinct subtype associated with poor prognosis, unique molecular characteristics, and potential therapeutic vulnerabilities. Further investigation of this subtype may improve our understanding of MM pathogenesis and facilitate subtype-specific therapeutic strategies.

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Intermediate Dose of AraC As Safe and Effective Salvage Therapy for Multiple Myeloma Poor Mobilizers

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Introduction: Efficacy of therapies for multiple myeloma (MM) patients are improving so fast and so well that we are quite ready to define, in selected cases, a patient functionally "cured" (Engelhardt M, Haematologica, 2024). Today, despite all new drugs available, autologous stem cell transplantation (ASCT) remains the core of the therapy for transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM) patients (Sonneveld P et al, NEJM, 2024). However, the patient's ability to undergo ASCT depends upon adequate collection of hematopoietic stem cells (HSCs) and in up to 35% of cases, especially with novel agents used for induction, HSC harvest can be difficult or suboptimal (Bittrich M et al., Transfus Med Hemother, 2023; Chhabra S et al., Transplant Cell Ther, 2023). Patient not reaching the target of at least 2 × 106 CD34+ cells/kg body weight are commonly defined as "poor mobilizers" and, therefore, the International Myeloma Working Group (IMWG) recommend the minimum target of 4 × 106 CD34+ cells/kg progenitor for auto-SCT in MM patients (Hsu TL et al, Transfus Med Hemother, 2023). Granulocyte-colony stimulating factor (G-CSF) with or without cyclophosphamide (Cy) and on demand plerixafor is currently a standard regimen for HSCs mobilization in MM patients, but the HSC collection success rate is still less than 100% (Mina R et al, Haematologica, 2024). Given the effectiveness shown in some studies (Czerw T et al., Biol Blood Marrow Transplant, 2019) of intermediate doses of cytarabine (Ara-C) plus G-CSF and plerixafor in poor mobilizers, we used this strategy for patients who had failed at least two mobilizations, analyzing retrospectively its effectiveness and safety. **Methods:** We retrospectively analyzed the efficacy and safety of intermediate dose of cytarabine (Ara-C 400 mg/m2, every 12 h d1–2), plus G-CSF from day 5 and plerixafor if needed in six poor mobilizers MM patients. **Results:** Six MM patients who failed their first attempt to effectively mobilize HSCs after receiving Cy 2g/m2 + G-CSF + plerixafor and, in two cases, also a second attempt with G-CSF and plerixafor, were mobilized with intermediate dose Ara-C + G-CSF; four of these patients (66.6%) received also plerixafor. An adequate mobilization (≥2.0 × 106 CD34+ cells/kg) was reached in 100% of patients, with an optimal mobilization (≥5.0 × 106 CD34+ cells/kg) reached in 50% of the patients. We observed a peripheral blood CD34+ peak concentration of 62.5/μL and harvests with median number of 5.0 CD34+cells/kg. Furthermore, no hematological grade 3 or 4 toxicities or infections were observed for the patients after intermediate dose Ara-C mobilization and all patients received an adequate number of HCSs for engraftment after MEL200. **Conclusions:** We can therefore conclude that, even if in our limited number of poor mobilizers, mobilization with intermediate dose of Ara-C+G-CSF and plerixafor was adequate in all patients and it could be considered an effective and safe salvage mobilizing strategy.

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Investigating and Targeting Lipid-Induced Resistance to Venetoclax in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a largely incurable plasma cell malignancy in which therapeutic response is strongly influenced by the bone marrow (BM) microenvironment. While metabolic crosstalk within the BM niche is increasingly recognized, the contribution of BM-derived metabolites to therapy resistance remains poorly defined. Venetoclax (Ven), a BCL-2 antagonist, shows marked activity in t(11;14) MM; however, patients relapse to therapy refractory disease. We and others have shown that cellular metabolism regulates BCL-2 dependence, with reduced electron transport chain (ETC) activity and oxidative phosphorylation predicting Ven sensitivity. More recently, we demonstrated that uptake of extrinsic heme promotes Ven resistance by increasing ETC activity and de novo purine biosynthesis. The BM microenvironment is enriched in lipids that support MM progression, with oleic acid (OA) being the most abundant fatty acid. Aims To determine how BM-derived lipids reprogram anti-apoptotic dependencies and identify translatable strategies to overcome lipid-driven resistance. **Methods:** MM cell lines and primary patient samples were exposed to BM-derived lipids and assessed for drug sensitivity. Lipidomics, RNA sequencing, and kinome profiling were used to identify signaling changes associated with resistance. Pharmacologic inhibitors targeting fatty acid oxidation (FAO), ether lipid synthesis, and signaling pathways were evaluated. A high-throughput screen using the Emory Enriched Bioactive Library (EEBL), comprising 2,036 biologically annotated small molecules, including 1,018 FDA-approved compounds to overcome OA mediated drug resistance was implemented. **Results:** MM cell lines and primary patient samples were exposed to BM-derived lipids and assessed for drug sensitivity. Lipidomics, RNA sequencing, and kinome profiling were used to identify signaling changes associated with resistance. Pharmacologic inhibitors targeting fatty acid oxidation (FAO), ether lipid synthesis, and signaling pathways were evaluated. A high-throughput screen using the Emory Enriched Bioactive Library (EEBL), comprising 2,036 biologically annotated small molecules, including 1,018 FDA-approved

compounds to overcome OA mediated drug resistance was implemented. **Conclusions:** OA uptake alters the MM lipidome to support FAO and ether lipid remodeling, which, together with HDAC1 and c-JUN activation, promote resistance to BCL-2 antagonists. By illuminating a previously unrecognized mechanism of lipid-induced therapeutic escape, this work has the potential to extend the benefit of BCL-2–targeted therapies, overcome adiposity-related resistance and ultimately improve outcomes for patients with myeloma and related BCL-2 dependent hematologic malignancies.

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Investigating Vγ9Vδ2 T-Cell Cytotoxicity in Multiple Myeloma in Combination With BCMA Targeting

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Introduction: The therapeutic landscape of multiple myeloma (MM) is challenged by response heterogeneity and continuous immune evasion. Vγ9Vδ2T (γδ2 T) cells present promising, MHC-independent cytotoxic effectors, through the recognition of stress-induced ligands in malignant cells, driven by the tumour microenvironment. However, mechanisms regulating antibody-based therapies and γδ2 T cell-mediated cytotoxicity remain completely misunderstood. This study aims to investigate molecular mechanisms associated with the variable response to the combination treatment with the antibody-drug conjugate Belantamab-Mafodotin (Bel-Maf). **Methods:** Bioinformatic analyses from publicly available MM patient and cell lines databases were initially performed to characterize BCMA expression and immune-related signatures. Surface BCMA expression was subsequently quantified in MM cell lines by flow cytometry. In vitro-expanded γδ2 T cells were immunophenotypically characterized for cytotoxic and Fc receptor-associated markers, like CD16 and CD56. MM cell lines were cultured alone or co-cultured with Vγ9Vδ2 T cells in the presence or absence of Bel-Maf under four experimental conditions: MM alone, MM+Bel-Maf, MM +Vγ9Vδ2 T cells, and MM+Bel-Maf+Vγ9Vδ2 T cells. Treatment-induced cytotoxicity was evaluated at three different timepoints by Annexin V/propidium iodide-based flow cytometric analysis. In parallel, baseline surface expression of stress-induced ligands involved in immune recognition, including NKG2D and DNAM-1 ligands, was assessed by flow cytometry to investigate their potential association with differential susceptibility to Vγ9Vδ2T cell-mediated cytotoxicity. **Results:** BCMA expression was heterogeneous across MM cell lines and positively correlated with Bel-Maf-mediated cytotoxicity. Co-culture experiments demonstrated enhanced cytotoxic activity following combined Bel-Maf and Vγ9Vδ2 T-cell treatment compared with single-agent conditions in selected MM models, supporting a synergic interaction between BCMA-directed targeting and immune-mediated effector functions. Expanded Vγ9Vδ2 T cells exhibited a cytotoxic phenotype characterized by CD56 and CD16 expression. Moreover, MM cell lines displayed marked variability in their susceptibility to Vγ9Vδ2 T cell-mediated killing. Flow cytometric profiling identified differential expression of NKG2D and DNAM-1 ligands among MM models, implicating tumor-cell immunophenotypic heterogeneity as a potential determinant of Vγ9Vδ2 T cell response. **Conclusions:** These preliminary findings reveal heterogeneous responses to Bel-Maf and Vγ9Vδ2 T-cell-mediated cytotoxicity across MM models. Further studies are required to define the biological factors governing susceptibility to BCMA-targeted and immune-mediated antitumor responses.

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Isatuximab in Combination (Isa VRd) in Patients With Newly Diagnosed Multiple Myeloma Not Candidates for Transplant: Clinical Practice Experience in Hospitals in Spain

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Introduction: Newly diagnosed multiple myeloma (NDMM) in patients who are not candidates for transplant presents a significant therapeutic challenge due to its clinical heterogeneity and associated frailty, as established in the IMROZ study findings. This study highlights the importance of evaluating the efficacy and safety of innovative treatments in this vulnerable population. Therapy has advanced considerably with the incorporation of combinations of proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies, which have been shown to improve survival and quality of life. Geriatric assessment is crucial in these patients, as therapy tolerance, treatment intensity, and continuity may be

compromised by factors such as functional reserve, comorbidities, and treatment response. **Methods:** This work describes a cohort of older patients with multiple myeloma treated in the first line and not undergoing autologous transplant, treated in routine clinical practice across different hospitals in Spain. **Results:** A cohort of 84 evaluable patients with multiple myeloma in first-line therapy not undergoing autologous transplant was analyzed Patients had a mean and median age of 73.0 years, interquartile range of 70.8 to 77.0 years. The sex distribution was balanced, with 43/84 patients being women (51.2%) and 41/84 men (48.8%). The most frequent monoclonal subtype was IgG, present in 40/84 patients (47.6%), followed by IgA in 18/84 (21.4%) and light chain disease in 16/84 (19.0%). Light chain restriction was kappa in 58/84 patients (69.0%) and lambda in 26/84 (31.0%). Among the 83 patients with available glomerular filtration, 42/83 (50.6%) had a filtration > 60 ml/min, 25/83 (30.1%) 30–60 ml/min, 13/83 (15.7%) 15–29 ml/min, and 3/83 (3.6%) <15 ml/min. According to available ISS-R, the majority of patients were classified as ISS-R 2, with 44/79 cases (55.7%), followed by ISS-R 1 in 25/79 (31.65%) and ISS-R 3 in 10/79 (12.65%). Response was evaluable in 80/84 patients. The overall response rate, defined as partial response or better, was 75/80 (93.8%). The proportion of patients with very good partial response or better was 63/80 (78.8%), and the proportion with complete response or strict complete response was 29/80 (36.2%). By categories, 10/80 patients (12.5%) achieved strict complete response, 19/80 (23.8%) complete response, 34/80 (42.5%) very good partial response, 12/80 (15.0%) partial response, 2/80 (2.5%) no response, 2/80 (2.5%) were pending re-evaluation, and 1/80 (1.2%) was not evaluable. **Conclusions:** Therefore, in our real-life experience, the ISA-VRD scheme for non-candidates is an effective and safe option, with good management of patient frailty, and the data on PFS and, of course, quality of life, even in frailer patients, are expected to exceed the data we previously had with triplets.

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Isatuximab Plus Pomalidomide-Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma: Subgroup Analysis by Prior Anti-CD38 Exposure From the Phase 3 IRAKLIA Trial

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Introduction: With the growing use of anti-CD38 therapies in early multiple myeloma (MM) management, there is a need for data in patients previously exposed to anti-CD38 therapy to guide decision-making. In the Phase 3 IRAKLIA trial (NCT05405166), patients with relapsed/refractory MM (RRMM) received the anti-CD38 monoclonal antibody isatuximab (Isa) subcutaneously (SC) delivered via an innovative on-body injector (OBI) or intravenously (IV), with pomalidomide and dexamethasone (Pd). In this post hoc analysis, we examined outcomes in IRAKLIA patients with vs without prior anti-CD38 exposure. **Methods:** Patients with RRMM ≥18 years with ≥1 prior line of therapy including lenalidomide and a proteasome inhibitor were randomized to receive Isa SC OBI (n = 263) or Isa IV (n = 268) weekly in Cycle 1, then every 2 weeks, with Pd. Patients with prior anti-CD38 exposure < 9 months (mos) before randomization or intolerance to anti-CD38 were excluded. Refractory patients were defined as those who failed to achieve minimal response on treatment or had progression within 60 days after the last dose. Patients receiving Isa SC OBI or Isa IV were pooled. **Results:** Overall, 67 patients (12.6%) had prior anti-CD38 exposure with a median washout period of 20.2 mos, of which 26 (38.8%) were anti-CD38 refractory. Baseline characteristics were largely consistent between patients with or without prior anti-CD38 exposure; the median follow-up for the overall population was 12 mos. Patients with prior anti-CD38 exposure had an overall response rate (ORR) of 52.2%, 12-mo progression-free survival (PFS) rate of 40.6%, and median PFS of 8.5 mos. In patients without prior exposure, an ORR of 73.5%, 12-mo PFS of 68.8%, and non-estimable (NE) median PFS were reported. Anti-CD38 non-refractory vs refractory patients had an ORR of 48.8% vs 57.7%, 12-mo PFS of 38.9% vs 42.2%, and median PFS of 9.0 vs 7.5 mos. Patients with a longer washout period (> median of 20.2 mos) had an ORR of 63.6%, 12-mo PFS of 61.8%, and NE median PFS, whereas patients whose prior anti-CD38 therapy ended more recently (≤median of 20.2 mos) had an ORR of 41.2%, 12-mo PFS of 19.2%, and median PFS of 6.7 mos. The safety profile of Isa + Pd was similar in patients with vs without prior anti-CD38 exposure. **Conclusions:** Isa + Pd demonstrated clinical benefit across anti-CD38–naïve, anti-CD38–exposed, and anti-CD38–refractory patients. A washout period > median of 20.2 mos resulted in outcomes comparable to those in anti-CD38–naïve patients, and outcomes were consistent between anti-CD38–exposed and anti-CD38–refractory patients after a > 9-mo washout period. Efficacy of Isa + Pd in patients with prior anti-CD38 exposure from the IRAKLIA trial presents an opportunity to address an unmet need in a difficult-to-treat patient population.

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Ixazomib, Lenalidomide, Dexamethasone Treatment With Cytogenetic Risk-Based Maintenance in Transplant-Eligible Multiple Myeloma Patients: The Expanded Results of a Phase 2 Study

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Introduction: High-risk myeloma patients have poor outcome. There is insufficient data about proteasome inhibitor (PI) based maintenance. Ixazomib is an oral PI but not approved in frontline. We present updated results from the ixazomib + lenalidomide + dexamethasone (IRD) study after a median follow-up of 40 months (0–92) including progression-free survival (PFS) and measurable residual disease (MRD) results with next generation sequencing (NGS) in addition to next generation flow (NGF) and preliminary blood mass spectrometry (MS) findings. **Methods:** This prospective phase 2 study enrolled 120 transplant-eligible newly diagnosed (NDMM) patients. The treatment consisted of four cycles of IRD induction followed by autologous stem cell transplantation, IRD consolidation and cytogenetic risk-based maintenance therapy with lenalidomide + ixazomib for high-risk (HR) patients and lenalidomide alone for non high-risk (NHR) patients. In MRD studies we used clonotypic mass spectrometry for MS and NGF1 10–5 for flow cytometry. For NGS, the LymphoTrack IGH FR1 or IGH FR3 assay (Invivoscribe) was used to determine the patient clone and to assess the presence of the diagnostic clone in the follow-up samples at a 10–5 sensitivity. The sequencing was performed on a MiSeq instrument (Illumina). **Results:** Initial results showed no difference in PFS between HR and NHR patients and 95% of the patients with sustained (two negative samples every 12 months) NGF-MRD negativity were progression-free at 2 years on maintenance. In this updated analysis, the benefit of double maintenance for HR patients appears sustained, with a median PFS of 56 months (95% CI 46–65) in HR patients and 58 months (95% CI 50–67) in NHR patients ($p = 0.464$). Patients with sustained MRD negativity at a sensitivity of at least 10^{-5} by NGF and NGS had excellent outcomes, only one progression. In contrast, patients who were NGF-MRD negative but MRD-positive by NGS had a median PFS of 52 months (95% CI 32–72). Patients who lost NGF-MRD negativity during treatment showed outcomes comparable to those who remained MRD-positive (median PFS 44 vs 50 months). Patients with triple negativity showed best outcome. **Conclusions:** After a longer follow-up HR patients have still equal PFS with NHR patients when getting double maintenance. Mass spectrometry analyses are ongoing; however, preliminary data indicate that patients achieving triple negativity demonstrate the most favorable outcomes, with no observed progression.

Reference

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PA-273

Kinase-Independent PIM2-MYC Signaling Controls MYC-Driven Transcriptional Programs in Multiple Myeloma

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Introduction: Multiple Myeloma (MM) remains an incurable plasma cell malignancy driven by therapeutic resistance and adaptive transcriptional programs. PIM2, an oncogenic serine/threonine kinase overexpressed in MM, promotes tumor survival through canonical kinase-dependent signaling. We previously identified a distinct kinase-independent (Ki) function of PIM2 in sustaining its own expression via a MYC/SP1-driven autoregulatory loop. However, the extent to which Ki PIM2 regulates broader MYC-dependent transcriptional programs remains unclear. **Methods:** Kinase-independent and kinase-dependent PIM2 functions were pharmacologically dissociated using selective inhibitors (CpdA and CpdB respectively). MM1.S and KMS11 cells were treated with Ki-selective inhibitors (JP11646, CpdA) or kinase-dependent inhibitors (AZD1208, CpdB), followed by RT-qPCR and RNA-seq. MYC chromatin occupancy was assessed by ChIP-seq and validated by ChIP-qPCR. Luciferase reporter assays using PIM2 promoter and MYC promoter constructs were used to evaluate transcriptional regulation. **Results:** Ki-selective inhibition (JP11646, CpdA) suppressed MYC transcriptional signatures whereas kinase-dependent inhibition had minimal effect. MYC ChIP-seq demonstrated a global reduction in MYC chromatin occupancy following Ki inhibition and PIM2 knockdown. Luciferase assays showed that both Ki inhibition and PIM2 knockdown significantly decreased PIM2 and MYC promoter activity, while kinase-dependent inhibitors had no effect.

ChIP-seq with FLAG-tagged wild-type and kinase-dead PIM2 confirmed kinase-independent co-occupancy with MYC at the PIM2 promoter. **Conclusions:** PIM2 functions as a bifunctional regulator in MM, integrating both kinase-dependent survival signaling and kinase-independent control of MYC-driven transcription. Disruption of the kinase-independent PIM2-MYC axis selectively impairs oncogenic transcriptional programs and is a therapeutically actionable vulnerability in multiple myeloma.

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Kinetics of Multi-Modality Minimal Residual Disease (MRD) Testing During Isatuximab and Lenalidomide (IsaR) Maintenance

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Introduction: Several lines of evidence suggest multimodality MRD negativity (MRD-), defined as concomitant MRD- in bone marrow (BM), peripheral blood (PB), and novel imaging (NI), is associated with superior outcomes compared with MRD- in a single compartment. There is a lack of robust data on the concordance between these and whether serial PB MRD- predicts BM MRD- in patients treated with IsaR maintenance. Here, we evaluate concordances between BM, NI, and PB MRD and kinetics of PB MRD in the context of a single-center, investigator-initiated, phase II clinical trial investigating the role of IsaR maintenance. **Methods:** Elimination of MRD disease after ASCT is a single-center, investigator-initiated, phase II clinical trial investigating the role of IsaR maintenance in patients with persistent BM MRD following ASCT (NCT05690984). Key eligibility criteria include BM MRD+ as measured by ClonoSEQ next-generation sequencing (NGS) following ASCT. The primary endpoint was the proportion of patients achieving BM MRD- at a 10–6 sensitivity, by NGS at the end of 12 cycles of IsaR. All patients had pre-enrolment and end-of-treatment (EOT) NI. PB MRD was measured by MALDI-TOF mass spectrometry using MASS FIX and was considered positive, except when described as monoclonal antibody presence. Serial PB MRD was assessed pre-enrollment, during treatment, and at EOT. Stringent MRD negativity was defined as BM MRD- at 10–6 sensitivity, along with no detectable protein by mass spectrometry, and negative functional imaging. **Results:** 30 patients were enrolled, with a median age of 64 years (range 57–68). 43% (n = 13) were female, and 17% (n = 5) were Black. 21 patients have completed study treatment. 246 multimodality MRD assays were performed in 30 patients at any point. At study enrollment, all patients were BM MRD+ at 10–6, with 70% (n = 21) MRD+ at 10–5. NI MRD+ was noted in 17% of patients (n = 5) and PB MRD+ in 42% (n = 8). During the study, 72 serial PB MRD tests were performed, of which 31% (n = 22) were MRD+. 21 patients have completed study treatment, with 11% BM MRD- at 10–6 and 47% BM MRD- at 10–5. NI MRD- was achieved in 71% of patients. Stringent MRD- was attained in 5% (n = 1) of patients. PB MRD had 45.3% overall concordance with BM MRD by NGS, with 54.7% of samples discordant. The majority of discordant cases were due to BM MRD+, at 10–6. Overall concordance rates were higher for BM MRD at 10–5 (64.2%) than at 10–6 (45.3%). PB MRD showed concordance with a combined BM (10–6) and NI MRD of 30.6%, primarily due to failure to detect disease in 71% of patients who were positive by either modality. Serial PB MRD+ was more frequent and of greater magnitude in patients who were BM MRD+ at 10–5 than at 10–6. Patients who were BM MRD- at 10–6 remained PB MRD- in serial tests preceding. **Conclusions:** Serial PB MRD testing may serve as a complementary surveillance tool even in low-disease settings, but it shows modest concordance with BM MRD, particularly at a sensitivity of 10–6.

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Knowledge, Awareness, and Practice Patterns of Nephrologists in the Diagnosis and Management of Multiple Myeloma: The MIND-MM Study

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Introduction: A Cross-Sectional, Web-Based, CHERRIES-Compliant Survey with Position Statement from the Indian Myeloma Academic Groupe (IMAGe) and Indian Society of Nephrology (ISN) Background Multiple myeloma (MM) frequently presents with renal manifestations, yet the preparedness of nephrologists to recognize and manage myeloma-related kidney disease remains poorly characterized. No large-scale survey has previously evaluated the knowledge, awareness, and practice (KAP) patterns of nephrologists in this domain. Objective To assess nephrologists' knowledge, awareness, diagnostic approach, management practices, confidence, and educational needs regarding MM and related entities, including monoclonal gammopathy of renal significance (MGRS), kidney transplantation, and autologous stem cell transplantation (ASCT), in the context of renal failure. **Methods:** A cross-sectional, web-based, anonymous e-survey was conducted among practicing nephrologists across India from April 6–14, 2026. The survey instrument (52 items, 12 sections) was developed in accordance with the CHERRIES guidelines and content-validated by an expert panel. Data were collected via SurveyMonkey and analyzed descriptively.

Response metrics are reported per CHERRIES recommendations. **Results:** Of 100 respondents who accessed the survey, 97 (97.0%) consented, and 93 completed the demographics. The completion rate across all sections ranged from 67% to 77%. Nearly half (46.2%) had < 5 years' experience; 41.9% saw >200 CKD patients/month. Knowledge of myeloma presentations was high (hypercalcemia: 94.2%; bone pain: 88.4%), but recognition of recurrent infections was low (50.0%). Most identified cast nephropathy as the most common renal pathology (74.4%) and the combination of SPEP + sFLC + IFE as the optimal screening (95.4%). Regarding management, 71.4% correctly identified hydration with urgent hematology referral as the initial step in cast nephropathy, and 92.1% recognized the importance of early anti-myeloma therapy. MGRS awareness was excellent (100% correct definition). However, 36% had received no formal training, and 96.1% expressed interest in structured education. The commonest practice challenge was the cost of investigations (68.4%). For newer therapies, awareness of bispecific antibodies (27.4%) and antibody–drug conjugates (15.1%) was notably low. A position statement comprising 20 consensus recommendations was formulated based on survey findings. **Conclusions:** Indian nephrologists demonstrate strong foundational knowledge of myeloma kidney disease and MGRS, but have significant gaps in awareness of newer therapies and limited formal training. Cost of investigations and referral delays are the dominant practice barriers. These findings provide the evidence base for the joint IMAGe-ISN position statement on plasma cell disorders in nephrology.

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Latent Effector T Cells Mediate Immunotherapy Responses in the Bone Marrow Microenvironment

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Introduction: T cells are increasingly recognized as central effectors across multiple myeloma (MM) therapies, including bispecific T cell engagers (BTCEs), CAR-T cells, and immunomodulatory agents. Despite distinct mechanisms of action, these therapies converge on the requirement for a competent T cell compartment. Dissecting the immunological synapse between T cells and myeloma cells holds promise for identifying biomarkers of response and resistance. **Methods:** Bone marrow samples from patients with newly diagnosed MM (NDMM, n = 20) were analyzed using paired single-cell RNA and TCR sequencing (scRNA/VDJ-seq), antigen-agnostic microfluidic functional screening, and HLA class I immunopeptidomics on primary CD138+ myeloma cells. We developed TFiT (Tumor-reactive Features in T cells), a 15-gene scRNA-seq-based classifier, prospectively validated in an independent NDMM cohort (n = 9). TFiT was applied to NDMM patients receiving quadruplet induction (Dara-VRd, n = 19) and to relapsed/refractory MM (RRMM) patients treated with BCMA-targeting BTCEs (n = 16). **Results:** Myeloma-reactive T cells were rare (~1.29% of marrow T cells) but transcriptionally distinct, upregulating effector molecules and cytotoxicity-associated genes while lacking markers of terminal exhaustion. TFiT distinguished tumor-reactive from bystander and virus-specific T cells and outperformed existing solid-tumor-derived models (AUC = 0.895, prospectively validated). In NDMM patients treated with Dara-VRd, higher baseline TFiT-positive T cell frequencies predicted complete response (p = 0.021). In RRMM patients receiving BTCEs, TFiT-positive cells were enriched in responders at baseline, expanded during therapy, and tracked therapeutic engagement longitudinally. **Conclusions:** Transcriptionally defined tumor-reactive T cells are key determinants of immunotherapy response in MM. TFiT provides a scalable, biologically grounded biomarker to monitor anti-tumor immunity across multiple lines of MM therapy, with potential to guide treatment selection, monitor response, and inform sequencing strategies.

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Left Behind — National Geographic Disparities and Structural Inequities in CAR-T Cell Therapy Clinical Trial Access Across the United States

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Introduction: CAR-T cell therapy has transformed outcomes in relapsed and refractory hematologic malignancies, yet equitable access to investigational CAR-T trials remains uncertain. Cellular therapy delivery requires specialized infrastructure — including leukapheresis, manufacturing coordination, and post-infusion toxicity monitoring — concentrated within a limited number of academic centers. Comprehensive national evaluations of CAR-T trial infrastructure and geographic access disparities across all demographic subgroups remain limited. **Methods:** We performed a cross-sectional geospatial analysis of 307 interventional phase I–III CAR-T clinical trials registered on ClinicalTrials.gov (January 2015–May 2026). Trial sites (n = 1,561; 272 institutions) were geocoded and linked to ZIP Code Tabulation Area–level data from the 2020 US Census and American

Community Survey. Geographic access was quantified at 30-mile and 60-mile proximity thresholds across rurality, household income quartile, and race/ethnicity subgroups. Institutional concentration and longitudinal access trends were assessed using joinpoint regression and population-weighted estimates calculated annually from 2015 to 2025. **Results:** Annual CAR-T trial registrations increased from 3 in 2015 to 52 in 2023 (AAPC 34.1%; P < 0.001), followed by plateau-phase growth through 2025. Despite a >30-fold expansion in cumulative trial sites, 39.3% of the US population (130.1 million) lacked access within 30 miles and 22.9% (76.0 million) within 60 miles. Disparities were greatest among rural residents (89.6% lacking access at 30 miles; 57.5% at 60 miles) and the lowest income quartile (59.9% at 30 miles; 42.3% at 60 miles). Access gaps persisted among Hispanic (33.1%) and Black (30.1%) populations at 30 miles. Trial infrastructure was highly concentrated: 95.8% of US counties lacked active CAR-T trial sites, and the top 10% of institutions accounted for 45% of all sites nationally. Population-level access plateaued after 2023 despite continued site growth, indicating persistent clustering within established metropolitan hubs. Three deprivation phenotypes were identified: structural (>60 miles from any site), proximity (near hubs but outside practical thresholds), and socioeconomic (geographically covered but with high vulnerability). **Conclusions:** Rapid expansion of CAR-T clinical trials has not produced proportional improvement in geographic access. Infrastructure remains concentrated within metropolitan academic centers, creating persistent access gaps among rural, lower-income, and minority populations. Achieving equitable diffusion will require decentralized strategies — including hub-and-spoke models, satellite leukapheresis programs, and community oncology network integration — each tailored to distinct patterns of structural, proximity, and socioeconomic trial access deprivation.

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Lesion-Based Antigen Remapping Reveals Dynamic Target States for Sequential CAR-T Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: Antigen-directed CAR-T cell therapy is increasingly utilized in relapsed/refractory multiple myeloma (RRMM); however, the optimal sequencing of targeted therapies following immune-mediated selection pressure remains poorly defined. We hypothesized that repeated, lesion-specific antigen reassessment could identify actionable target states that are frequently overlooked by traditional diagnosis-based sequencing strategies. **Methods:** We integrated pathology and flow cytometry reports from 8 selected RRMM patients who had documented immunotherapy target selection or treatment switching. Seven patients underwent interpretable tissue antigen profiling, while one had peripheral blood flow cytometry assessed prior to GPRC5D-directed treatment. Extracted analytical variables included the specific infusion target, biopsy site, morphology, immunohistochemical antigen expression levels, and multiplex immune profiling when available. **Results:** Tissue evaluations revealed highly dynamic and lesion-specific target states. BCMA expression remained detectable in multiple lesions (65%–90% positivity in available reports); however, expression was notably heterogeneous or diminished in others, including one marrow specimen exhibiting only 10% weak positivity and an extramedullary lesion with complete BCMA loss. GPRC5D expression was similarly variable, ranging from absent to strongly positive. Notably, one post-treatment lesion retained BCMA expression (90% weak positivity) but remained GPRC5D-negative, whereas paired extramedullary lesions in a different patient co-expressed BCMA (70%–90%) and GPRC5D (80%–90%). Serial reassessment also identified robust CD70 expression (70%–90%) in available lesion reports, highlighting its potential as a salvage target. Spatial discordance was observed in an extramedullary plasmablastic lesion exhibiting regional CD19 expression (70% localized positivity) despite the absence of BCMA and minimal GPRC5D. Furthermore, multiplex immunohistochemistry of a marrow specimen revealed an immune-depleted microenvironment (0.92% CD3+ T cells; 0.09% CD8+ T cells) alongside weak BCMA/GPRC5D expression. In another patient, peripheral blood flow cytometry detected 0.17% aberrant plasma cells prior to GPRC5D-directed therapy, offering a valuable circulating anchor for disease monitoring. **Conclusions:** Target evolution following immunotherapy in RRMM does not follow a simple linear conversion between antigens. Instead, it reflects complex, dynamic, and lesion-specific antigen states characterized by BCMA retention, heterogeneity or loss, variable GPRC5D expression, the emergence of CD70, and regional CD19 discordance. These insights strongly support the implementation of systematic, lesion-based antigen remapping prior to sequencing CAR-T therapies, particularly in cases of aggressive extramedullary or plasmablastic relapse. Future prospective validation should incorporate standardized assessments of clinical response, MRD/ctDNA, toxicity, and survival endpoints.

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Lesion-Level PET/CT Analysis Identifies Anatomic and Biologic Predictors of Progression After BCMA CAR T-Cell Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: Despite deep responses with BCMA-directed CAR T-cell therapy for relapsed/refractory multiple myeloma (RRMM), most patients ultimately progress. Patterns of progression of disease (POD) at the lesion and anatomic compartment level (extramedullary [EM], paramedullary [PM], bone) remain poorly defined. We hypothesized that POD post-CAR T occurs in compartment-specific spatial patterns, and identification/characterization of high-risk sites may inform post-infusion monitoring or treatment escalation strategies. **Methods:** We analyzed 102 consecutive RRMM patients treated with ciltacabtagene autoleucel between 2018–2024 who underwent serial FDG PET/CT. Four PET/CT timepoints were analyzed: pre-apheresis (80 scans, 307 lesions), pre-lymphodepleting chemotherapy (LDC) (98, 336) to account for bridging therapy, day 30 post-CAR T (102, 134), and first POD (102, 178). Individual lesions were longitudinally followed to assess metabolic response and POD using SUVs per Lugano criteria given no accepted metabolic response standards for MM. Multivariable Cox regression (MVA) evaluated associations with progression-free (PFS) and overall survival (OS). **Results:** With a median follow-up of 19 months (95% CI 18–22), 24-month PFS and OS were 48% (37–61) and 74% (64–85), respectively. Among patients with POD, relapse was most often both biochemical and radiologic (63%), followed by radiologic only (28%), and biochemical only (10%). Radiologic POD involved both pre-existing and new disease sites (42%), pre-existing sites only (36%), or new sites only (22%). Prior to CAR T (pre-apheresis and/or pre-LDC), EM and PM disease (EMD, PMD) were present in 26% and 12% of patients, respectively. At POD, disease distribution shifted significantly toward non-bone sites, with EMD increasing to 47% and PMD to 25%, while bone-only disease declined from 62% to 28%. Pre-CAR T EMD/PMD was present in 72% patients with radiographic progression only, compared to 56% with combined biochemical/pathologic and radiographic progression and 24% with biochemical progression only/no progression. On MVA, pre-LDC PMD (Hazard Ratio (HR) 20.4) and EMD (HR 7.1) were independently associated with inferior PFS, and PMD (HR 5.4) and EMD (HR 3.9) with inferior OS. At the lesion level, progression rates differed by anatomic site, with 41% of EM, 31% of PM, and 11% of bone lesions progressing ($p < 0.001$). Importantly, persistent metabolic activity at day 30 associated with subsequent lesion progression (complete response: 2%, partial response: 27%, stable disease 40%; $p = 0.006$) and worse PFS ($p = 0.002$), with EM/PM lesions showing the highest progression rates across all response categories. **Conclusions:** We identified lesion-level characteristics associated with dominant resistance niches, including EM/PM sites, pre-existing lesions, and incompletely responding sites of disease. These findings suggest that lesion-directed or systemic escalation strategies for select patients may improve CAR T outcomes.

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Leveraging a High-Fiber Diet to Intercept Smoldering Multiple Myeloma Progression and Enhance Early Immunotherapy Efficacy

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Introduction: Smoldering multiple myeloma (SMM) is a mostly untreated, asymptomatic disease with an overall risk of evolution to incurable multiple myeloma (MM) at 10% per year, underscoring an urgent need for preventive therapies. We previously established a direct link between the intestinal microbiota, gut-born Th17 cells and MM aggressiveness in transgenic Vk*MYC mice, which develop de novo mSMM and invariably progress to mMM. Exposure to a high-fiber (HiFi) diet significantly delayed progression from mSMM to mMM. The inhibitory immune checkpoint T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is highly expressed on BM immune cells already at the stage of SMM, and treatment with an anti-TIGIT antibodies resulted in durable clinical response in patients affected by MM. Given that a greater abundance of fiber-fermenting microbes is associated with improved responses to immunotherapy, we evaluated a HiFi diet with TIGIT blockade in SMM Vk*MYC mice. **Methods:** C57BL/6J mice challenged with Vk*MYC-derived MM cells (t-Vk*MYC) and transgenic Vk*MYC mice affected by mSMM were treated with either an isocaloric control or a HiFi diet in combination with isotype control IgG or anti-TIGIT monoclonal antibodies. Mice were monitored for progression to MM and sacrificed for immunological analyses. Fecal 16S rRNA sequencing and metabolomics were performed to assess the impact of gut modulating strategies on microbiota composition. **Results:** Administration of a HiFi diet restrained MM aggressiveness in t-Vk*MYC mice and delayed SMM-to-MM evolution in Vk*MYC mice by limiting the expansion of Th17 cells while unleashing an anti-tumor immune response. Mechanistically, dietary fibers favored the expansion of SCFA-producing bacteria and increased fecal SCFA concentrations, which exerted both local and systemic anti-inflammatory activities. Although long-term disease progression data from ongoing experiments are still pending, preliminary results reveal that combining a HiFi diet and TIGIT blockade increased the frequency of CD226+ effector T and NK cells in both the BM and spleen, while simultaneously restricting immunosuppressive myeloid subsets. **Conclusions:** Modulation of the gut microbiota through dietary fibers impacts the trajectory of SMM-to-MM evolution in mice and establishes a favorable immune microenvironment that may enhance the efficacy of early immunotherapeutic strategies.

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Lipid droplets in multiple myeloma: association with disease progression and therapeutic resistance

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Introduction: Lipid droplets (LDs) are dynamic cytoplasmic organelles mainly involved in lipid storage and metabolic regulation. Their accumulation has been associated with a more aggressive phenotype and reduced therapeutic sensitivity in several oncological models. However, their functional role in Multiple Myeloma (MM) has not been fully defined. **Methods:** LD levels were determined by flow cytometry and confocal microscopy, using BODIPY 493/503 staining. LDs were analyzed in bone marrow samples from MM patients at different clinical stages (MGUS, n = 4; sMM, n = 3; NDMM, n = 16; RRMM, n = 6). LD levels were determined in MM cell lines, including MM1S and RPMI8226 sensitive and resistant to Belantamab mafodotin (BLMF), OPM2 and KMS11 sensitive and resistant to Bortezomib, and U266 sensitive and resistant to Melphalan. Expression of genes involved in LD biogenesis was evaluated by qPCR. The effect of the microenvironment was studied using co-culture systems between MM1S and mesenchymal stromal cells (MSCs) differentiated from bone marrow aspirates of MM patients. **Results:** Patients' plasma cells showed higher LD content than other cell populations (mean intensity: PCs: 184,609; lymphocytes: 37,930; granulocytes: 64,617; MSCs: 4,294). An increase in LDs was observed, with higher levels in NDMM patients compared with premalignant stages; however, LD levels decreased again in the CPs of treated patients (mean intensity: MGUS: 140,286; sMM: 96,425; NDMM: 312,392; RRMM: 189,333). Cell lines resistant to different treatments exhibited higher LD levels compared to their sensitive counterparts (MM1S: 277,465 vs 159,092; OPM2: 771,135 vs 321,525; KMS11: 544,772 vs 371,425; U266: 174,818 vs 129,036) ($p < 0.05$ in all cases). This finding was supported by increased transcription of lipid biogenesis-related genes such as PLIN2 (involved in the formation and stabilization of LDs), DGAT1 (responsible for triglyceride synthesis) or BSCL2 (a component of the LD membrane), as analyzed by qPCR. The influence of the microenvironment on lipid metabolism was assessed using co-cultures of MM cells with MSCs. LD levels were significantly increased in MM1S cells after 72 hours of coculture (mean intensity in MM1S: 104,436 vs 264,530; $p < 0.05$). **Conclusions:** LD accumulation is a distinctive feature of PCs in MM, suggesting the existence of metabolic reprogramming through disease progression, the microenvironment and therapeutic resistance. These results position lipid metabolism, and particularly LDs, as a potential therapeutic target in MM.

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Longitudinal Analysis of Minimal Residual Disease in the Phase 2 ISASOCUT Study of Subcutaneous Isatuximab-VRd in Newly Diagnosed Transplant-Ineligible Multiple Myeloma

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Introduction: Isa-VRd has emerged as a new standard of care (SOC) for newly diagnosed transplant-ineligible multiple myeloma (NDMM TI) based on the BENEFIT and IMROZ studies. A subcutaneous (SC) formulation of isatuximab has been developed. We report updated efficacy and safety results from the phase 2 ISASOCUT study. **Methods:** ISASOCUT is a prospective, multicenter, phase 2 study in NDMM TI patients (≥ 65 years). Bortezomib 1.3 mg/m2 SC, biweekly for cycle 1 then weekly for 11 months. Starting doses cycle 13 onward, isatuximab fixed 1400 mg SC once monthly and lenalidomide 25 mg daily oral route. The primary objective is to evaluate the ≥VGPR at 8 months post cycle 1 day 1. Secondary objectives included MRD and PK/ADA analysis. Data are presented in ITT. 74 patients were recruited across 23 IFM centers, median age was 73 years [IQR. 66;83], 25 (34%) were >75 years, 16 (22%) had HRMM IMS new score (Bobin et al. in press 2026). **Results:** At the data cutoff (December 5, 2025), median treatment exposure was 22.7 months. The ≥VGPR rate was 90.5% (95% CI, 81.5–96.1), with a CR or better rate of 52.7% (95% CI, 40.7–64.4). Responses were consistent across weight and cytogenetic-risk subgroups. MRD negativity at 10^-5 by NGS was achieved in 58.1% of evaluable patients (95% CI, 46.1–69.5), while sustained MRD negativity at 12 months was observed in 27.0% (95% CI, 17.4–38.6). Median PFS and OS were not reached. Nine PFS events (12.2%) and five deaths (6.8%) were reported. The estimated 18-month PFS rate was 91.6% (95% CI, 82.3–96.1). The compliance to treatment was high with relative dose intensity ≥90%. All patients

experienced at least one treatment-emergent adverse event (TEAE), and 93.2% had a grade ≥3 TEAE. The most frequent grade ≥3 events were lymphopenia (66.2%), neutropenia (62.2%) and thrombocytopenia (28.4%). TEAEs led to permanent discontinuation of at least one treatment component in a limited proportion of patients. Four patients (5.4%) experienced systemic isatuximab-related reactions, all grade ≤2. Injection-site reactions were reported in 33.8% of patients, with no grade ≥3 events. Three patients (4.1%) died from TEAEs considered unrelated to study treatment. Eleven patients developed treatment-induced anti-drug antibodies; all responded to treatment and no persistent ADA response was observed. **Conclusions:** Updated results from ISASOCUT demonstrate deep and durable responses with Isa SC-VRd in NDMM TI patients, including high MRD-negativity rates and encouraging progression-free survival. Safety was manageable and consistent with the known profile of Isa-VRd. These findings support SC isatuximab as an effective and convenient alternative to intravenous administration and further reinforce Isa-VRd as a standard-of-care option in NDMM TI.

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Longitudinal Analysis of TCR Repertoire in Smouldering Multiple Myeloma Reveals Relative Expansion of Shared-Sequence TCR Clusters Compared to Healthy Donors

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Introduction: While tumour-reactive T cells have been described in multiple myeloma (MM), their role in maintaining disease quiescence in smouldering multiple myeloma (SMM) and progression to MM remains unclear. We sought to perform longitudinal comparisons of TCR dynamics in SMM relative to normal temporal fluctuation in healthy donor (HD) TCR repertoire to help define T-cell contribution to disease control. **Methods:** Longitudinal samples from SMM patients enrolled in the COSMOS study (baseline through progression; progressors (P) n = 8, non-progressors (NP) n = 7) underwent TCR sequencing. HD repertoires were obtained from COVIDsortium participants (n = 13, 12-month interval). No significant differences in TCR count or clonality (Simpson's index) were observed between first and last timepoints across HDs, NP, and P. Thus, TCRs were filtered by edit distance ≤2 and clustered using TCRdist to group sequences with similar CDR3 regions (likely to target the same antigen). Per cluster abundance, defined as the summed abundance of constituent TCRs at each timepoint, was compared between baseline and final timepoints and sequentially filtered based on deviations from null expectations. Significantly expanding and contracting clusters (log2 odds ratio >0 and < 0, respectively) were identified by a ClusterScore (−log10FDR derived from Fisher's exact test < 0.05). **Results:** In paired samples with sufficient TCR reads (HD = 13, NP = 4, P = 4), the proportion of dynamic clusters retained after filtering was comparable between all groups. However, ratio of expanding to contracting clusters revealed a distinct skew at point of progression toward expanding clusters, not observed in HDs or NP. Linear modelling of median ClusterScore incorporating repertoire size confirmed progression status as a significant predictor of contracting cluster number, with progressors exhibiting markedly fewer contracting clusters, resulting in a relative expansion-dominant repertoire shift. Viral annotation using Tcrictionary (viral database) showed minimal enrichment among expanding clusters (1 viral cluster in each of 2 progressors). Single-cell analysis of matched samples showed clusters were predominantly CD8+ at baseline, enriched for cytotoxic and effector memory phenotypes. At progression, expanding clusters were characterised by increased early terminal effector memory (TEM) cells and reduced cytotoxic TEM representation, a shift not seen in contracting clusters. This indicates preferential expansion of T cells with a suboptimal cytotoxic phenotype, which may impair effective tumour control and facilitate disease progression. **Conclusions:** Together, comparison with HD dynamics identifies a progression-associated shift toward expanding TCR clusters, likely reflecting tumour-driven clonal expansion. The accompanying enrichment of less cytotoxic CD8+ TEM cells suggests impaired functional capacity, providing a potential mechanism for loss of immune control and transition from SMM to MM.

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Longitudinal Clonal Tracking of Ciltacabtagene Autoleucel in Relapsed/Refractory Multiple Myeloma

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Introduction: Ciltacabtagene autoleucel (cilta-cel) is highly effective against relapsed/refractory multiple myeloma (MM); however, emerging data highlight the significance of severe immune-related adverse events (irAE). Consequently, understanding long-term CAR-T cell kinetics remains a pivotal question. **Methods:** Peripheral blood immune-phenotyping data were analyzed for 87 MM patients following cilta-cel infusion. Evaluation time points comprised days 0 (D0), 4, 7, 14, 30, 100, and 180, with extended follow-up for patients with persisting CAR-T cells. Twenty-two patients experienced early death or loss-to-immune-follow-up. Single-cell RNA/TCR-seq of CAR-T cells were available at D30/100 (n = 8) and ≥D180 (n = 16). For 5 patients, whole exome sequencing (WES) of CAR-T cells was performed. Spatial transcriptomics (Visium HD, 10X Technologies) included custom cilta-cel probes. **Results:** In the global cohort (n = 87), maximum CAR-T expansion (Cmax) was detected after a median of 14 (range, 0–60) days with a median Cmax of 416 (0–27,173) CAR-T/μL. CAR-T cells persisted for a median of 91 days (0–729). Amongst the 65 patients with long-term immune monitoring, 15 (23%) were defined as long-term persisters (LTP) with CAR-T detection ≥D180 and 50 (77%) as short-term-persisters (STP) with earlier CAR-T cell clearance. Univariable time-dependent Cox regression revealed a trend linking CAR-T persistence to decreased OS (HR = 4.1, p = 0.09), but no correlation with PFS (HR = 0.9, p = 0.8). Time to B-cell recovery (>0 B-cells/μL; median: not reached vs. 3 months, p < 0.001) and endogenous T-helper cell recovery (>200 CD4/μL; median: 15 vs. 7 months, p = 0.04) were significantly prolonged in LTP vs STP. Crucially, late-onset (≥3 months) irAEs occurred in 7/15 LTP and 6/50 STP (p < 0.01). Spatial transcriptomic analyses were performed on month 12 intestinal biopsies from two LTPs. In a patient with severe IEC-EC, CAR-T cells comprised 1.6% of all cells. Conversely, a patient who experienced failure to thrive without IEC-like symptoms showed sparse CAR-T infiltration (0.1%). Single-cell CAR-T cell tracking in 6 LTP revealed divergent T-cell receptor (TCRab) dynamics: two patients exhibited monoclonal CAR-T cells, two showed oligoclonal persistence (≥2 clones comprising ≥1% of CAR-T), and two maintained polyclonal repertoires. While frequencies of oligoclonal CAR-T cells remained stable over time, the patients with monoclonal CAR-T cells showed secondary expansions, and both developed IEC-EC. In one individual, whole-exome sequencing (WES) of the expanded clone identified 2 TP53 mutations and 1 NF1 mutation. **Conclusions:** Our study demonstrates that prolonged cilta-cel persistence is associated with a distinct trend toward increased mortality, likely mediated by delayed immune reconstitution and severe, late-onset irAEs. These findings emphasize that post-infusion surveillance should expand beyond routine kinetic tracking to incorporate comprehensive immuno-genetic analysis to intercept cilta-cel-related complications.

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Longitudinal ctDNA Profiling Enables Early Detection of Relapse and Clonal Dynamics in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a genetically heterogeneous plasma-cell malignancy characterized by frequent relapse despite therapeutic advances, underscoring the need for sensitive, minimally invasive monitoring strategies. Bone marrow (BM)–based minimal residual disease (MRD) assays are prognostically informative but limited by invasiveness and spatial heterogeneity. Circulating cell-free DNA (cfDNA), which contains tumor-derived fragments (ctDNA), represents a systemic and real-time alternative for disease monitoring. We evaluated the analytical performance and clinical relevance of cfDNA profiling for MRD assessment and relapse prediction in MM. **Methods:** Forty-three newly diagnosed MM patients were prospectively followed for ≥24 months. Serial samples underwent BM immunoglobulin gene sequencing (clonoSEQ®), plasma cfDNA extraction followed by ultra-low-pass whole-genome sequencing (ULP-WGS) for copy-number alteration (CNA) profiling and tumor fraction (TF) estimation (ichorCNA), and ^18F-FDG PET/CT imaging. Forty-eight healthy donors served as controls. cfDNA quality, MRD status, and clinical variables were assessed longitudinally. **Results:** Overall, 755 DNA samples were analyzed. Median cfDNA yield was 13.3 ng/mL plasma and improved significantly with an optimized extraction protocol (p = 0.004). ULP-WGS enabled reliable CNA and TF inference in 92% of samples. Baseline TF correlated with disease stage and declined significantly with treatment (9.6% at diagnosis to ~1% during maintenance; p < 0.0001). Among relapsing patients, 82% exhibited TF ≥3% at least once prior to progression. Progressors demonstrated increased clonal complexity, genomic instability, and enrichment of chromosome 1p deletion. ctDNA positivity preceded relapse even in cases with negative BM MRD. **Conclusions:** ULP-WGS–based cfDNA profiling is a reliable, minimally invasive, and cost-effective strategy for dynamic MM monitoring, complementing BM MRD assays and improving risk stratification and personalized management.

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Longitudinal Single-Cell Profiling Reveals Reproducible Clonal Expansion of Cytotoxic CD8+ TEMRA Cells Following Daratumumab-Based Therapy

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Introduction: Daratumumab, an anti-CD38 monoclonal antibody, is approved as a single agent and in combination for newly diagnosed and relapsed/refractory multiple myeloma. Despite the efficacy of daratumumab-based quadruplets, 30–50% of patients do not achieve deep or durable remissions. We evaluated the immunomodulatory effects of daratumumab-based therapy in functional high-risk relapsed/refractory multiple myeloma. **Methods:** Bone marrow aspirates from patients in the MyDRUG umbrella trial (NCT03732703; n = 16) and the Molecular Profiling of Patients with Multiple Myeloma and Related Plasma Cell Malignancies (MPP) study (n = 62) were used to generate single-cell RNA-seq and paired TCR-seq. MyDRUG patients received daratumumab, ixazomib, pomalidomide, and dexamethasone (D-IPd), with samples collected after 2 cycles, 4 cycles, and at end of treatment or progression. MPP served as a validation cohort, including untreated controls and daratumumab-treated patients. **Results:** Single-cell RNA-seq of ~90,000 cells from 41 samples across 16 subjects identified major bone marrow immune populations, including NK cells, T cells, monocytes, B cells, and dendritic cells. Annotated subsets of CD8 T cells include effector memory (TEM), TEMRA, MAIT, precursor and terminally exhausted cells. Cell-cell communication analysis showed increased post-treatment interactions between TEMRA cells and multiple immune populations, consistent with enhanced cytotoxic engagement. Increased MHC class II expression on CD8 T cells supported chronic activation, while the TEM subset showed higher proliferation (unpaired Wilcoxon $p = 0.03$) and cytotoxic gene expression ($p = 0.024$). Immune-focused CyTOF on paired samples from seven patients confirmed these transcriptional changes at the protein level. CD38 decreased across NK cells, B cells, and monocytes, consistent with daratumumab target engagement. NK cells also showed reduced GZMB and CD57, while transitional and classical monocytes showed increased CD11c, consistent with myeloid activation and enhanced antigen presentation. TCR analysis showed variable changes in clonotype diversity and richness across patients. Despite this heterogeneity, TEMRA cells expanded significantly ($p = 6.6 \times 10–13$), and expanded CD8 clones upregulated cytotoxic genes including NKG7, GZMH, GNLY, and GZMB. The MPP cohort showed a similar increase in CD8 clonotype expansion, including significant expansion of TEMRA cells after daratumumab treatment ($p = 0.024$). **Conclusions:** These data provide a longitudinal, high-resolution view of the immune microenvironment in functional high-risk myeloma during D-IPd therapy and identify early treatment-associated remodeling of immune compartments. Across cohorts, daratumumab-based therapy was associated with expansion of clonally proliferative, cytotoxic TEMRA cells, supporting enhanced antigen-driven CD8 T-cell responses in the myeloma microenvironment. These findings support rational combinations of targeted and immune therapies to improve efficacy.

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Long-Read RNA Sequencing Enables Integrated Genomic Risk Stratification and Reveals Isoform-Level Drivers of High-Risk Multiple Myeloma in the UK MRA RADAR Study

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Introduction: Current IMWG risk stratification in multiple myeloma (MM) relies on genetic events detected by FISH and/or DNA sequencing but fails to identify all poor risk cases. Gene expression profiling (GEP) improves prognostication yet requires additional assays and does not resolve isoform diversity. Long-read RNA sequencing (LR-RNAseq) offers simultaneous detection of structural variants, gene expression, and alternative splicing. We evaluated whether LR-RNAseq could provide integrated genomic and transcriptomic risk assessment. **Methods:** Newly diagnosed MM patients from the UKMRA RADAR trial and Oxford HaemBiobank (n = 103) underwent Nanopore-based LR-RNAseq with UMI-based quantification, DNA profiling (Myeloma Genome Panel) and FISH defined IMWG-2025 risk classification. RNA-based detection of copy number alterations (CNA) and translocations was benchmarked against DNA, focusing on risk-defining structural variants. Published, validated GEP risk signatures were extracted from RNASeq as previously described. Isoform discovery and differential splicing analyses were performed. **Results:** LR-RNAseq accurately detected key CNAs (sensitivity 0.67, PPV 0.93) and translocations (sensitivity

0.89, PPV 1.0). Overall agreement with DNA-based IMWG-2025 risk classification was 83%. Discordant cases were largely due to TP53 mutations and deletions detectable only by DNA-based assays due to low TP53 gene expression. In 61 patients with day 100 post-autograft MRD assessment, LR-RNAseq-derived IMWG risk profiling demonstrated comparable predictive performance to FISH/MGP, with similar sensitivity (0.29 vs 0.32) and modestly higher PPV (0.50 vs 0.42). The 2 MRD+ve patients classed high-risk by DNA but not RNA both had TP53 mutations. Notably, a combined LR-RNAseq-based model integrating IMWG and established GEP-based risk assignment improved prediction of MRD positivity (sensitivity 0.77, PPV 0.57), indicating complementary prognostic information captured by transcriptomic and genetic risk features. LR-RNAseq uniquely identified novel splice isoforms in key myeloma drivers, including TP53 and KRAS, which were significantly enriched in high-risk disease across independent classification systems (e.g., TP53: OR 5.2 in ISS III; KRAS: OR 4.49 in GEP-HR). Differential isoform usage was observed in biologically important genes including BCL2, a key mediator of venetoclax sensitivity in MM. **Conclusions:** LR-RNAseq captures established genomic risk features while enabling GEP application and revealing potentially relevant isoform-level biology. In our cohort, integrated RNA-based risk models outperformed established DNA- and RNA-based approaches in predicting residual disease. This unified, cost-effective, single-assay approach has potential to streamline current molecular diagnostics while uncovering novel drivers of high-risk MM. Ongoing follow-up and cohort enlargement will determine the prognostic and therapeutic relevance of isoform-based stratification.

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Long-Term (≥5-Year) Remission and Survival With Ciltacabtagene Autoleucel (Cilta-Cel) in Relapsed/Refractory Multiple Myeloma (RRMM) With 1–3 Prior Lines of Therapy: CARTITUDE-2 Cohort A

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Introduction: CARTITUDE-1 demonstrated that a single cilta-cel infusion can achieve deep and durable responses in heavily pretreated RRMM, with 33% of patients (pt) alive and progression-free at 5 years, suggesting curative potential. The median overall survival (OS) was 60.7 months. We report 5-year efficacy, safety, and correlates of long-term disease control in CARTITUDE-2 cohort A in earlier-line pts with RRMM receiving cilta-cel. **Methods:** CARTITUDE-2 (NCT04133636) is a phase 2 multicohort study evaluating cilta-cel in different MM disease settings. Cohort A (initial subgroup) includes pts with 1–3 prior lines of therapy exposed to proteasome inhibitor who were lenalidomide-refractory, similar to pts in the registrational CARTITUDE-4 trial. Pts received a single cilta-cel infusion without maintenance. Pts were rolled over to an ongoing 15-year follow-up study, CARTinue (NCT05201781), and followed for long-term progression-free survival (PFS), OS, and safety, with pt evaluations per local standard of care (reported annually at a minimum). **Results:** Twenty pts in cohort A had been treated with cilta-cel; the median follow-up was 60.7 months (May 2026). At 5 years after infusion, 10/20 (50.0%) pts remained alive and progression-free. Median (95% CI) PFS was 60.5 months (12.9-not evaluable) and median OS was not reached. The 5-year OS rate was 69.2%. Minimal residual disease (MRD) at 5 years (not required per protocol) was assessed by bone marrow in 3 pts; all were MRD-negative at 10−6. Pts who remained alive and progression-free at 5 years (n = 10) versus those with progressive disease (PD)/death due to PD within 5 years (n = 7) had a trend towards lower baseline tumor burden shown by lower median soluble B-cell maturation antigen (14.1 vs 68.2 µg/L) and higher rates of lower (≤30%) bone marrow plasma cells (90.0 vs 42.9%), higher levels of CD4+-naive T-cells at apheresis, and higher CAR+ CD4+ central memory T-cell levels at peak expansion, similar to long-term responders in CARTITUDE-1 (Jagannath et al. JCO 2025; PMID: 40459151). Five of 10 pts who were disease-free at 5 years had ≥1 high-risk cytogenetic feature (4/5 pts had ≥2 high-risk cytogenetic features). There were 2 deaths reported since the last median follow-up of 29.9 months (1 PD at 4.6 years; 1 breast cancer after 5 years) and 7 total deaths on study—3 due to adverse events (COVID-19 pneumonia at Day 100, sepsis at Day 394, and breast cancer at Day 1840) and 4 due to PD. One pt developed a new hematologic malignancy (acute myeloid leukemia). There was no new CAR T-cell–related neurotoxicity. **Conclusions:** Half (10/20 [50.0%]) of the pts treated with a single cilta-cel infusion in earlier-line RRMM (CARTITUDE-2 cohort A; 1–3 prior lines of therapy and lenalidomide-refractory) had sustained remissions of ≥5 years. These results build on the long-term outcomes from CARTITUDE-1 and suggest that earlier use of cilta-cel may be associated with a higher likelihood of achieving 5-year remissions.

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Long-Term Follow-Up of Busulfan Plus Cyclophosphamide and Etoposide Versus High-Dose Melphalan as Conditioning in Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma

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Introduction: High-dose melphalan (HDMEL) represents the standard conditioning regimen before autologous stem cell transplant (ASCT) in multiple myeloma, but recent updates have suggested combination of busulfan with melphalan is also associated with favorable outcomes. In patients with hematologic malignancies, previous reports of etoposide, busulfan, and cyclophosphamide as a conditioning regimen have shown high efficacy with a wide maximal tolerated dose range. This retrospective study was performed to determine if the busulfan based conditioning without melphalan would be a tolerable and effective conditioning regimen. We conducted a follow-up analysis of the data we reported three years ago. **Methods:** A total of 35 patients with multiple myeloma, enrolled between March 2016 and September 2021, patients aged 47–67 (median 57 years) with multiple myeloma were enrolled to receive bortezomib, thalidomide and dexamethasone (VTD) induction followed by ASCT. All patients received HDMEL or BuCyE as conditioning regimen. BuCyE conditioning regimen consisted of busulfan 3.2 mg/kg from days −7 to days −5, etoposide 200 mg/m2 from days −5 to days −4, cyclophosphamide 50 mg/m2 from days −3 to days −2. HDMEL conditioning regimen consisted of melphalan 200 mg/m2. **Results:** The median age of patients was 58 years old (range, 47–67 years old) in HD-MEL group and 57 years old (range, 48–63 years old) in BuCyE group, respectively. Revised international staging system (R-ISS) was showed as follows; stage I with 0 in BuCyE vs. 27.2% in HD-MEL, stage II with 84.6% in BuCyE vs. 68.1% in HD-MEL, and 15.4% in BuCyE vs. 4.5%, respectively. The overall response rate before ASCT was 100% in both groups, including 76.9% in BuCyE and 63.6% in HDMEL with more than vary good partial response, and 30.8% in BuCyE versus 40.9% in HDMEL with complete response, respectively. Median follow-up for the group was 68 months. The 3-year progression-free survival (PFS) was 40.7% for the HDMEL conditioning group versus 38.5% for the BuCyE conditioning group and median PFS was 42.8 months in HDMEL (range, 28.3 to 57.3 months) and 44.8 months in BuCyE (range, 27.0 to 62.6 months) (P = 0.705). Five-year overall survival rate was 76.4% in HDMEL versus 90.9% in BuCyE (P = 0.222). The average time from ASCT to leukocyte recovery (≥ 1000/mm3 of absolute neutrophil count) and platelet recovery (≥50000/mm3 of platelet count) is as follows: 11 days in HDMEL versus 12 days in BuCyE (P = 0.101) and 39 days in HDMEL versus 34 days in BuCyE (P = 0.840), respectively. Among the patients who did not achieve complete remission (CR) before ASCT, the proportion of patients who achieved CR after ASCT was 46% (6/13) in HDMEL versus 50% (4/8) in BuCyE. **Conclusions:** Our study showed that BuCyE is an effective and well-tolerated alternative to HDMEL conditioning, with good PFS.

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Low CRS and ICANS Rates During Step-Up Dose Reinitiation After Prolonged Dose Delay of Bispecific Antibodies in Multiple Myeloma

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Introduction: Bispecific antibodies are associated with unique side effects including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). To reduce CRS and ICANS risks, step-up dosing (SUD) is required during treatment initiation, either as an inpatient or within proximity to a hospital. CRS occurs in ~60–70% of patients, with ICANS rate of < 10%. SUD is also required for therapy reinitiation after dose delay. Many UK district hospitals do not have facilities for SUD, which can cause delays in delivering or restarting treatment. We evaluated the CRS and ICANS rates of patients following SUD reinitiation (reSUD) after dose delay (>7 days). **Methods:** This was a single-centre, retrospective study. We included patients who received teclistamab, elranatamab or talquetamab. Clinical details were obtained via hospital's electronic health record. Disease response was assessed using IMWG criteria. CRS and ICANS were graded according to the ASCTC grading system. **Results:** Between Jan 2020 and May 2026, 221 patients received teclistamab, elranatamab or talquetamab. There were 22 dose delays that required reSUD in 18 patients. 12 (67%) were male, median age was 60 (54–79) and the median no. of prior treatment lines was 4 (1–12). The median number of doses received before delay was 12 (1–43). 15 (68%) of the 22 dose delays occurred at ≤4 cycles. The median dose delay interval was 87 days (9–455). 14 (64%) were due to infections, most were respiratory related including COVID-19. 4 (18%) were due to planned procedures. Other reasons included acute kidney injury, unexplained neurological symptoms and cytopenia. At reSUD, 15 (68%) patients were in VGPR or CR, 1 (5%) was in PR and 6 (27%) had stable disease. 19 (86%) reSUD were given as inpatient, the rest were given as outpatient. The median length of inpatient stay was 6.5 days (3–26). All but 3 reSUD were given as per Summary of Product Characteristics (SPC). Of the 3 cases that were delivered outside of SPC, 2 were teclistamab reinitiated at SUD level 1 (0.06 mg/kg) instead of level 2 (0.3 mg/kg), and 1 was elranatamab reinitiated at SUD level 2 (32 mg) instead of level 1 (12 mg). None of these

resulted in CRS or ICANS. There were 2 (9%) grade 1 CRS and 2 (9%) grade 2 CRS during reSUD. These included 3 patients receiving talquetamab and 1 receiving teclistamab. All of these occurred early (< 4 cycles) and in patients in less than VGPR at reSUD. Dexamethasone was given as premedication and all CRS events were treated successfully with 1 dose of tocilizumab. No ICANS were reported. **Conclusions:** CRS and ICANS rates were low during reSUD following prolonged dose delay of bispecific antibodies, particularly among patients in VGPR or CR who were well established in treatment. For these patients, reSUD may be safely administered in outpatient settings, avoiding costly inpatient stays. More studies are needed to ascertain the optimal SUD levels after dose delays and ways to mitigate CRS and ICANS risks in these situations.

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Lysosome-Mediated Selective Removal of eccDNA Drives Proteasome Inhibitor Resistance of Multiple Myeloma by Ubiquitination and Piezo1-Dependent ESCRT

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Introduction: Proteasome inhibitor (PI) is an effective class of drugs for treating multiple myeloma (MM), yet MM remains incurable in most cases due to PI resistance. Our previous study has revealed that specific extrachromosomal circular DNAs (eccDNAs) facilitate PI resistance of multiple myeloma (MM). However, the mechanism regulating specific eccDNAs enrichment in MM has not been investigated. **Methods:** In the present study, eccDNA chromatin immunoprecipitation (ChIP) was performed to identify proteins bind with eccDNA. Artificial eccDNAs were synthesized to mechanistical identification. Proteolysis targeting chimera (PROTAC) was utilized to targeted ubiquitination of hub proteins involved in specific eccDNAs enrichment. Results indicate that eccDNAs enriched in PI-resistant MM cells were selectively removed by lysosomes in PI-sensitive MM cells while eccDNAs enriched in PI-sensitive MM cells were selectively removed by lysosomes in PI-resistant MM cells. **Results:** Mechanistically, zinc finger protein 1 (ZFP1) binds and transfers eccDNAs enriched in PI-resistant MM cells to lysosome in PI-sensitive MM cells, and zinc finger CW-type and PWWP domain containing 1 (ZCWPW1) binds and transfers eccDNAs enriched in PI-sensitive MM cells to lysosome in PI-resistant MM cells. Moreover, ubiquitination enhances the recruitment of ZFP1 and ZCWPW1 to lysosomes by the endosomal sorting complex required for transport (ESCRT)-0. Furthermore, ubiquitination strengthens interactions of ZFP1 and ZCWPW1 with specific eccDNAs. Additionally, piezo-type mechanosensitive ion channel component 1 (Piezo1) activated by high MM cell density promotes ESCRT-0-dependent recruitment of ZFP1 and ZCWPW1 to lysosomes. **Conclusions:** In summary, the current study indicates that lysosome-mediated selective removal of eccDNA drives PI resistance of MM by ubiquitination and Piezo1-dependent ESCRT, and these findings provide novel targets and strategies for treating PI-resistant MM.

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Macrophage Reprogramming, Not CD8 T Cell Dynamics, Characterizes Durable Disease Control Following PD-1 Blockade in Smoldering Myeloma

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Introduction: Immune checkpoint inhibitors (ICI) have produced durable responses in a subset of multiple myeloma patients. However, recent work suggests the myeloma microenvironment lacks canonical CD8+T-cell exhaustion as seen in solid tumors. Whether the PD-1/PD-L1 axis drives ICI responsiveness in MM, as it does in solid tumors, and whether it correlates with depth of response remains unknown. Here, we asked if and how myeloma patients respond to ICI using samples from a phase II trial of nivolumab (anti-PD-1) with lenalidomide and low-dose dexamethasone (NivoRd) in untreated high-risk smoldering multiple myeloma (HR-SMM) (NCT02903381). **Methods:** Patients were stratified by complete or very good partial response (CR/VGPR, N = 4) or partial response or stable disease (PR/SD; N = 4) per IMWG criteria. Paired pre- and post-treatment bone marrow aspirates and biopsies were profiled via scRNA-seq (10X, Seurat) and imaging mass cytometry (IMC, Steinbock pipeline). Regions of spatially co-occurring cells in IMC were statistically quantified as cellular neighborhoods (CN). **Results:** Post-treatment plasma cell (PC) abundance was lower in CR/VGPR (IMC, median 5.4%) versus PR/SD (13.9%; P = 0.06), with CR/VGPR patients showing marked reduction of a PC–dominant CN (77% PC) demonstrating a response-associated disruption of clustered tumor growth. PD-L1 protein expression was highest on PC and macrophages, but PD-L1 abundance did not differentiate depth of response (P >0.34 for all timepoints). Notably, CD8+T-cell abundance in IMC was similar between CR/VGPR and PR/SD post-treatment (P = 0.62) with no change longitudinally with depth of response (P = 0.71). By scRNA-seq CD8+T-cell possessed minimal transcriptional changes post-treatment (7 genes FDR< 0.05), indicating no major rewiring of CD8+T-cells following deep NivoRd response. In contrast, macrophages were enriched in CR/VGPR post-treatment (median 10.5%, P = 0.12) with increased abundance of a macrophage-dominant CN (74.1% macrophages, P = 0.08) suggesting enhanced macrophage spatial organization. GSEA identified TNFα/NF-κB and inflammatory pathway

enrichment in CR/VGPR macrophages post-treatment (adjusted P < 0.002) but not pre-treatment (adjusted P >0.1), indicating a treatment-induced macrophage reprogramming following deep response. Additionally, we found the CD4+/CD8+ ratio was not only higher in CR/VGPR (P = 0.07) but correlated positively with macrophage-dominant CN (R = 0.52, P < 0.05) and negatively with plasma cell–dominant CN (R = –0.57, P = 0.03), connecting CD4+T-cells and macrophage differentiation. **Conclusions:** We find that depth of ICI response in HR-SMM is accompanied by treatment-associated macrophage inflammatory reprogramming coupled with a CD4+ T cell–macrophage signaling axis, rather than a canonical PD-L1 expression-dependent enhancement of CD8+ T-cell activity. This myeloid-centric mechanism provides a mechanistic framework for ICI efficacy in multiple myeloma and identifies potential biomarkers of response.

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Marrow Immune Features Are Most Informative of Sustained MRD Negative Response in Newly Diagnosed Standard Risk TE Patients: Findings From the UK MRA RADAR Study

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Introduction: Achieving sustained MRD negative(MRD-neg) response is a major determinant of survival outcomes, and is influenced by the intersection of disease, host and regimen related factors. We investigate the role of bone marrow (BM) immune profiles in MRD responses in standard risk(SR) patients on RADAR, utilising a modelling approach to integrate disease and clinical features. **Methods:** RADAR is a multi-centre, risk-adapted phase II/III trial for NDMM eligible for ASCT. Standard risk(SR) is defined as < 2 of t(4;14), t(14;16), del(17p), 1q+, 1p-. SR patients received 4 cycles of bortezomib, lenalidomide, cyclophosphamide and dexamethasone (VRDc) followed by ASCT and MRD test (flow, 10–5) at D100 and 15 m post ASCT. MRD-neg patients at D100 receive isatuximab alone, while MRD-pos receive multi-drug consolidation and maintenance. The MRD-pos cohort comprise those who were MRD-pos at D100 post ASCT, plus MRD-neg pts who relapsed or were MRD-pos at 15 m. MRD-neg cohort was MRD-neg at both D100 and15 m. Immune and CD138+ cells were analysed in fresh BM by flow, and 36 marker CyTOF lymphoid panel on thawed samples. We analysed baseline clinical, disease and immune features associated with sustained MRD-neg. We used an Elastic Net penalised regression model with a 20/80 test/train split to model MRD prediction. The test set was tuned using 5-fold cross-validation repeated 20 times. Missing values were imputed, and numeric variables normalised within the tuning process. In practice tuning tended to collapse to a Ridge Regression as the best model. **Results:** We studied 377 patients (median 61 y, male 60%, white 86%;), MRD-pos = 66%. Using a penalised logistic regression model we predicted MRD outcome on holdout test data with ~70% accuracy. We found that clinical parameters such as B2M and paraprotein had little prognostic value for sustained MRD-neg but Albumin had some predictive value (OR 1.23, binomial p-value 0.07). Among the immune biomarkers a higher fraction of myeloid cells (OR 0.7, p = 0.002) and CD4 cells (OR 0.77, p = 0.02) were associated with MRD-neg, while a higher CD8 (OR 1.29, p = 0.03) as well as double-negative (DN, CD4-CD8-) T-cells (OR 1.23, p = 0.1) were associated with MRD-pos response. CyTOF analysis on 18 patients (MRD-pos = 8, neg = 10) resolved T cell states from naïve (CCR7+CD27+) to terminally differentiated (GzmB+CD57+) CD4+ and CD8+ cells. Consistent with our predictive model, CD4+ T-cells were enriched in MRD-neg patients, mainly driven by naïve (CD27+CD45RO-CCR7+) cells, while differentiated effectors (CD28+GzmB+) were enriched in MRD-pos (p = 0.0031). MRD-pos was associated with terminally differentiated CD8 cells (GzmB+CD57+KLRG1+) and DN T cell clusters that are CD57+GzmB+, indicative of terminal differentiation. **Conclusions:** At baseline and pre-treatment, variables indicative of the state of the patient's own immune system are the most informative of sustained MRD-neg response in SR patients receiving induction and ASCT.

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Mass Spectrometry Identifies Actionable Myeloma Relapse Eight Months Before Electrophoretic Detection

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Introduction: A 78-year-old female was diagnosed in July 2024 with IgA lambda multiple myeloma with lambda light chain excess, following investigation for right lower limb bone pain. Initial workup demonstrated a paraprotein of 9.6 g/L, markedly elevated serum free lambda (1346 mg/L; ratio 0.01; dFLC 1336.5 mg/L), and bone marrow plasma cell infiltration of 20–39%. Congo red staining was positive, with amyloid deposition in the bone, and the patient was

managed as myeloma patient. She had ISS stage 3 disease with associated anaemia (Hb 106 g/L), AKI stage 2 (creatinine 189 µmol/L), and β2-microglobulin of 5.9 mg/L. PET-CT showed no lytic bone disease. First-line therapy commenced with daratumumab, bortezomib, cyclophosphamide, and dexamethasone (Dara-VCD) in July 2024, achieving a complete serological remission, and subsequently continued on daratumumab maintenance. **Methods:** Retrospective peripheral blood mass spectrometry analysis using the EXENT™ Immunoglobulin Isotypes (GAM) assay identified measurable peripheral residual disease despite serological complete remission. **Results:** In May 2025, an IgA lambda monoclonal protein of 0.0183 g/L at m/z 11,323.7 was detected, alongside therapeutic daratumumab (IgG kappa) of 0.915 g/L on the EXENT™ analyser. At this time, conventional electrophoretic methods detected only an IgG kappa of 0.5 g/L, and serum free light chains concentrations were kappa 7.2 mg/L, lambda 8.3 mg/L, with a FLC ratio of 0.87. By January 2026, the IgA lambda paraprotein at m/z 11,323.1 had risen to 0.225 g/L, with daratumumab measured at 0.659 g/L on EXENT™. The IgA lambda became detectable by immunofixation but remained too small to quantify. Serum free light chains concentrations were kappa 6.9 mg/L, lambda 14.7 mg/L, with a FLC ratio of 0.47, confirming biochemical relapse, though not clinically significant. Thus, mass spectrometry not only identified relapse approximately 8 months earlier than standard electrophoretic techniques, but also confirmed its progression by January 2026. **Conclusions:** Had this early relapse been recognised in real time, treatment escalation to a multi-class regimen such as belantamab mafodotin, bortezomib, and dexamethasone (Bela-Vd), or consideration of bispecific or CAR-T therapy (requiring disease control and potentially avoiding bridging therapy), could have been pursued earlier, with the aim of achieving a deeper response before the development of end-organ damage. This case demonstrates that mass spectrometry can detect relapse significantly earlier than conventional electrophoretic methods, providing a clinically meaningful window for earlier intervention at low disease burden. Prospective integration of assays such as EXENT™ GAM into routine monitoring pathways may enable more sensitive disease tracking, inform timely treatment escalation and deescalation, and ultimately improve outcomes in patients with plasma cell disorders.

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Matching-Adjusted Indirect Comparison (MAIC) of Belantamab Mafodotin, Bortezomib, Dexamethasone (BVd) vs Carfilzomib, Lenalidomide, Dexamethasone (KRd) in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: BVd is approved for RRMM based on superior efficacy vs daratumumab plus bortezomib/dexamethasone in the phase 3 DREAMM-7 trial (NCT04246047). MAIC was performed to estimate relative clinical efficacy of BVd vs KRd in second-line or later (2L+) RRMM using eligibility criteria from the phase 3 ASPIRE trial (NCT01080391), representing the diminishing patient (pt) population suitable for lenalidomide (len) at 2L. **Methods:** A systematic literature review identified KRd efficacy/safety data from the ASPIRE trial in 2L+ RRMM. The feasibility of indirectly comparing BVd vs KRd using data from DREAMM-7 (datacut Oct 7, 2024; median follow-up 39.4 months) and ASPIRE was assessed. BVd and KRd were indirectly compared in terms of progression-free survival (PFS), overall survival (OS), and response endpoints. As DREAMM-7 and ASPIRE lack a common comparator, an unanchored approach was required. Individual pt data (IPD) were available for BVd (n = 243) from DREAMM-7, while only aggregate data were available for KRd (n = 396) from ASPIRE. BVd-treated pts from DREAMM-7 were weighted using IPD to match KRd-treated pts from ASPIRE in terms of clinically important factors: prior lines of therapy (LOT), refractoriness to len/immunomodulatory drugs (IMD), cytogenetic risk, creatinine clearance (CrCl), age, and Eastern Cooperative Oncology Group performance status (ECOG PS). Revised International Staging System stage was not adjusted for in the base case analysis due to missing data in ASPIRE (31% missing). Outcomes for weighted BVd-treated pts were compared to those for KRd-treated pts. Cox regression was performed to compare survival outcomes and logistic regression was used to compare response endpoints. **Results:** After matching, equal proportions in both arms had 2/3 prior LOTs (53%), were refractory to IMDs (21% [len 7%]), had high cytogenetic risk (25%), ECOG PS 0/1 (90%), and CrCl < 50 mL/min (6%). Mean age was 63.3 years in both arms. Effective sample size of weighted BVd-treated pts was 126. PFS and OS were significantly longer with BVd than KRd (median PFS: 40 months BVd vs 26 months KRd, hazard ratio [HR] 0.66 [95% confidence interval {CI} 0.50–0.88]; median OS: not reached BVd vs 48 months KRd, HR 0.60 [95% CI 0.41–0.88]). There was no significant difference in overall response rate (84% BVd vs 87% KRd, odds ratio 0.79 [95% CI 0.47–1.33]), or rates of complete response or better (37% BVd vs 32% KRd, odds ratio 1.27 [95% CI 0.86–1.86]). **Conclusions:** BVd had significantly longer PFS/OS vs KRd when adjusting for differences in key baseline pt characteristics. Response outcomes were similar, though the inherent limitations of MAICs (e.g., population size, trial differences) may have affected these analyses. Prolonged survival benefits may be achieved with BVd over KRd, demonstrating its utility for treatment of pts with 2L+ RRMM. **Funding:** GSK (221835).

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Matching-Adjusted Indirect Comparisons (MAICs) of Anitocabtagene Autoleucel (Anito-Cel) Versus Teclistamab and Talquetamab for the Treatment of 4L+ Relapsed and/or Refractory Multiple Myeloma (RRMM)

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Introduction: T-cell-redirecting therapies, including chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies (BsAbs), have improved clinical outcomes for patients with RRMM after ≥3 prior lines of therapy (4L+). Early iMMagine-1 results suggest anito-cel is effective and well-tolerated, however, its relative efficacy and safety versus BsAbs have not been explored. MAICs were conducted to compare anito-cel with teclistamab (TEC; MajesTEC-1) and talquetamab (TAL; MonumenTAL-1) because they are the earliest approved and most widely used BCMA- and GPRC5D-targeting agents, respectively. **Methods:** Unanchored MAICs used individual patient-level data from iMMagine-1 (efficacy evaluable population; N = 117; median follow-up [mFU] = 15.9 m) and aggregate data from MajesTEC-1 (N = 165; mFU = 14.1 m) and MonumenTAL-1 (N = 143 for TAL 0.4 mg with mFU = 18.8 m; N = 145 for TAL 0.8 mg with mFU = 12.7 m). Adjustments were made for key prognostic factors identified through literature reviews and expert physician consultation including extramedullary disease, cytogenetic risk, refractory status, R-ISS, and % bone marrow plasma cells (BMPC) for efficacy; and ECOG, % BMPC, age, and sex for safety. Sensitivity analyses used the iMMagine-1 enrolled population (N = 129) and additional less impactful prognostic variables. **Results:** Between-trial population overlap was adequate, with well-balanced weights and effective sample sizes (range: 66–111). After adjustments, all response outcomes were significantly better for anito-cel, with higher odds of overall response rate (ORR) versus TEC, TAL 0.4 mg, and TAL 0.8 mg with odds ratios (95% confidence interval [CI]) of 8.74 (2.88–26.56), 4.14 (1.22–14.06), and 4.49 (1.33–15.14), respectively, and similar higher odds for more stringent response outcomes, and overall minimal residual disease negativity (10–5). Findings were consistent across sensitivity analyses. While there were no statistically significant differences between anito-cel and TEC or TAL for key toxicities, including grade ≥3 CRS, other safety outcomes indicated improved safety for anito-cel. While grade ≥3 ICANS was not significantly different between trials, anito-cel had significantly lower odds relative to TAL 0.4 mg (odds ratio [OR]: 0.15; 95% CI: 0.07–0.34) and 0.8 mg (OR: 0.24; 95% CI: 0.11–0.53). Anito-cel was associated with significantly lower odds of grade 3–4 infections versus TEC (OR: 0.11; 95% CI: 0.05–0.22), TAL 0.4 mg (OR: 0.32; 95% CI: 0.14–0.72), of grade ≥3 infections versus TAL 0.8 mg (OR: 0.46; 95% CI: 0.215–0.996), and of non-relapse mortality (NRM) versus TEC (OR: 0.18; 95% CI: 0.06–0.56) and TAL 0.4 mg (OR: 0.25; 95% CI: 0.08–0.81). **Conclusions:** Anito-cel showed superior response, and a differentiated safety profile versus TEC and TAL, highlighted by lower odds of any-grade ICANS versus TAL, and high-grade infections/NRM across all comparators, supporting a clinically meaningful benefit–risk advantage compared to BCMA and GPRC5D targeting BsAbs in 4L+ RRMM.

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Matching-Adjusted Indirect Comparisons (MAICs) of Efficacy and Safety Outcomes for Anitocabtagene Autoleucel Versus Ciltacabtagene Autoleucel in 4L+ Relapsed and/or Refractory Multiple Myeloma (RRMM)

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Introduction: BCMA-directed CAR T-cell therapies have improved outcomes for patients with relapsed and/or refractory multiple myeloma (RRMM) after ≥3 prior lines of therapy (pLOT; 4L+). iMMagine-1 and CARTITUDE-1 assessed anito-cel and cilta-cel, respectively, in patients with 4L+ RRMM. We conducted MAICs to compare their efficacy and safety. **Methods:** Unanchored MAICs used iMMagine-1 individual patient-level data (efficacy evaluable population; (N = 117; median follow-up [mFU] = 15.9 months) and CARTITUDE-1 published or previously presented aggregate data (N = 97; mFU = 18 months). In the analysis, baseline differences between trials were adjusted using high priority prognostic factors identified via systematic literature review and expert physician consultation. These were extramedullary disease, cytogenetic risk, refractory status, R-ISS (revised international staging system), and % bone marrow plasma cells (BMPC) for efficacy; and ECOG status, % BMPC, age, and sex for safety. Sensitivity analyses adjusted for additional factors. Relative treatment effects were estimated using odds ratios (OR), with risk differences used for endpoints with zero events. **Results:** Effective sample sizes for efficacy and safety analyses were 103 (88%) and 106 (91%), respectively, indicating substantial overlap between the two trials. After adjusting for baseline differences, the analyses found no statistically significant differences in efficacy of anito-cel versus cilta-cel for overall response rate (ORR, 96% vs 98%; OR: 0.34; 95% CI: 0.06–1.89) and ≥CR rate (74% vs 80%; OR:

0.66; 95% CI: 0.34–1.30). For safety, anito-cel demonstrated significantly lower risk of any-grade cytokine release syndrome (CRS, 85% vs 95%; OR: 0.33; 95% CI: 0.11–0.94) and any-grade immune effector cell-associated neurotoxicity syndrome (ICANS, 8% vs 23%; OR: 0.28; 95% CI: 0.12–0.67), grade 3–4 infections (9% vs 23%; OR: 0.28; 95% CI: 0.12–0.66), and non-relapse mortality (NRM, 3% vs 11%; OR: 0.20; 95% CI: 0.06–0.68). No non-ICANS neurotoxicity events were observed in iMMagine-1, compared to 12 in CARTITUDE-1. Anito-cel was associated with significantly lower risk of any-grade Parkinsonism (0 vs 5 in CARTITUDE-1). Other safety endpoints analyzed were comparable, including grade ≥3 CRS and ICANS (only 1 event for each outcome in iMMagine-1 vs 5 and 3, respectively in CARTITUDE-1), as well as any grade infections. Efficacy and safety outcomes were consistent across sensitivity analyses. **Conclusions:** After adjusting for clinically relevant prognostic factors, anito-cel demonstrated no statistically significant differences in ORR or ≥CR rate compared with cilta-cel but demonstrated a superior safety profile in patients with RRMM treated in the 4L+ setting.

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Matching-Adjusted Indirect Comparisons (MAICs) of Iberdomide, Daratumumab (DARA), and Dexamethasone (IberDd) Versus Regimens Containing DARA and IMiDs in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Minimal residual disease-negative complete response (MRDneg CR) is an accepted early endpoint for accelerated approvals in RRMM. Iberdomide (Iber), an oral CELMoD, induces greater Ikaros/Aiolos degradation leading to enhanced MM cell killing and immune stimulation vs IMiDs. In the ongoing phase 3 randomized controlled trial EXCALIBER-RRMM, IberDd demonstrated significantly higher MRDneg CR in comparison with DARA + bortezomib + dexamethasone (DEX) (DVd) in RRMM; however, head-to-head comparative evidence versus other DARA-based standard regimens is unavailable. Two unanchored MAICs were therefore conducted to estimate the comparative efficacy of IberDd versus DARA + lenalidomide + DEX (DRd) and DARA + pomalidomide + DEX (DPd). **Methods:** Key eligibility was first aligned across trials to define comparable analysis populations for each MAIC, after which individual patient data from EXCALIBER-RRMM (IberDd; July 3, 2025; median follow-up: 15.9 mo) were independently matched to aggregate data from POLLUX (DRd) and APOLLO (DPd) on prespecified prognostic factors and potential treatment-effect modifiers. Base-case models for each MAIC included 11 covariates: number of prior lines, prior exposure, refractoriness, cytogenetic risk, International Staging System disease stage, age, ECOG performance status, renal function, time since diagnosis, immunoglobulin, and biological sex. Sensitivity analyses evaluated alternative covariate combinations and race. The primary endpoint was MRDneg CR at any time (10^{-5} sensitivity) and treatment effects were estimated as odds ratios (ORs) with 95% CIs. Progression-free survival data are not yet available for EXALIBER-RRMM at the time of analysis. The main analysis used the closest available follow-up time to align with EXCALIBER-RRMM (POLLUX: 25.4 mo; APOLLO: 16.9 mo), with an additional scenario using the longest available POLLUX follow-up (79.7 mo). **Results:** Following trial eligibility alignment, 108 EXCALIBER-RRMM IberDd patients were MAIC-weighted to match to the 286 DRd intent-to-treat (ITT) population from POLLUX and 101 EXCALIBER-RRMM IberDd patients were MAIC-weighted to match the 151 DPd ITT population from APOLLO. Baseline covariates were well balanced after weighting, with effective sample sizes of 57.3 (POLLUX comparison) and 36.9 (APOLLO comparison) in base-case models. IberDd demonstrated significantly [REDACTED] odds of achieving MRDneg CR at any time versus DRd (MAIC-adjusted OR [REDACTED]; 95% CI, [REDACTED]) and versus DPd (MAIC-adjusted OR [REDACTED]; 95% CI, [REDACTED]). Findings remained consistent across sensitivity analyses and conservative scenarios using extended POLLUX follow-up. **Conclusions:** Across 2 independent unanchored MAICs, IberDd was associated with significantly [REDACTED] MRDneg CR rates versus commonly used DARA-based regimens in patients with RRMM after ≥1 prior line. Findings were robust across sensitivity analyses and support the clinical efficacy of IberDd, with potential implications for RRMM treatment paradigms.

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Matching-Adjusted Indirect Treatment Comparison of Teclistamab Monotherapy (Tec) vs Belantamab With Pomalidomide and Dexamethasone (BPd) for Early-Line Relapsed or Refractory Multiple Myeloma (RRMM)

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Introduction: In the phase 3 MajesTEC-9 study (NCT05572515), Tec monotherapy, a steroid-sparing BCMA × CD3 BsAb, significantly improved PFS and OS vs investigator's choice of PVd/Kd in patients (pts) with RRMM and 1–3 prior lines of therapy (pLOTs), across practice settings. Notably, 85% of MajesTEC-9 pts were refractory to an anti-CD38 mAb, a characteristic historically associated with poor outcomes and commonly underrepresented in RRMM trials. In DREAMM-8 (NCT04484623), belantamab mafodotin, a BCMA-directed ADC, plus Pd (BPd) also improved PFS vs PVd in early-line RRMM; 24% were anti-CD38 refractory. In the absence of direct head-to-head trials, matching-adjusted indirect treatment comparisons (MAICs) can help contextualize comparative treatment efficacy by adjusting for cross-trial differences. An anchored MAIC was conducted to compare relative treatment effects of Tec vs BPd in early-line RRMM. **Methods:** An anchored MAIC was performed using individual pt-level data (IPD) from the MajesTEC-9 Tec cohort (median follow-up, 17.3 mo) and aggregated data from the DREAMM-8 BPd cohort (median follow-up, 28 mo). Although DREAMM-8 used PVd as control, the primary anchored MAIC used pooled physician's choice (PVd or Kd) to improve precision, given the small number of pts who received PVd in MajesTEC-9; this was supported by consistent within-trial treatment effects (Tec vs PVd and Tec vs Kd). A PVd-anchored MAIC was also conducted as a sensitivity analysis to assess robustness to the choice of anchor. Pt baseline imbalances between trials, such as anti-CD38 refractory status, were adjusted by applying propensity score weights to MajesTEC-9 IPD to match DREAMM-8 characteristics. In the base-case adjustment set, validated covariates were included: IMiD-, PI-, and anti-CD38-refractory status, cytogenetic risk, ISS stage, extramedullary disease, ECOG PS, and age group. Estimated comparative efficacy for PFS, ORR, ≥VGPR, and ≥CR are presented. HRs and risk ratios (RRs) with 95% CIs are shown. **Results:** IPD and aggregated data were available for 593 MajesTEC-9 and 302 DREAMM-8 pts. After adjustment, effective sample size of the MajesTEC-9 Tec cohort was 129. Following adjustment, Tec-treated pts had significantly improved PFS vs BPd (HR, 0.44 [95% CI, 0.23–0.81]). In addition, Tec-treated pts also had significantly greater ORR (RR, 1.62 [95% CI, 1.18–2.22]) and ≥CR (RR, 2.03 [1.01–4.07]) vs BPd; ≥VGPR favored Tec over BPd (RR, 1.37 [0.89–2.11]). Additional sensitivity analyses will be presented. **Conclusions:** Tec monotherapy showed superior PFS benefit and doubled the likelihood of achieving ≥CR, an important indicator of durable responses, vs BPd in pts with early-line RRMM per anchored MAIC. Although MajesTEC-9 included a heavily anti-CD38 refractory population, Tec's comparative benefit persisted after MAIC adjustment, supporting Tec as a highly effective standard-of-care therapy as early as first relapse, regardless of anti-CD38 exposure/refractory status.

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Matching-Adjusted Indirect Treatment Comparison of Teclistamab With Daratumumab (Tec-Dara) vs Belantamab With Bortezomib and Dexamethasone (BVd) for Early-Line Relapsed/Refractory Multiple Myeloma

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Introduction: In the phase 3 MajesTEC-3 study (NCT05083169), Tec-Dara significantly improved PFS/OS vs Dara-based standard-of-care (SoC) in patients (pts) with RRMM and 1–3 prior lines of therapy (pLOTs). BVd, a BCMA-directed regimen, is approved for early-line RRMM based on the phase 3 DREAMM-7 study (NCT04246047). In the absence of head-to-head trials, matching-adjusted indirect treatment comparisons (MAICs) can be used to indirectly compare treatments, helping to contextualize efficacy given varying pt populations. Here we report an MAIC comparing Tec-Dara vs BVd in early-line RRMM. **Methods:** An unanchored MAIC was conducted using individual pt-level data (IPD) for Tec-Dara (MajesTEC-3) and published data for BVd (DREAMM-7). Baseline characteristic imbalances were adjusted by applying propensity score weights to MajesTEC-3 IPD to match baseline DREAMM-7 characteristics. In the base case, the most important prognostic covariates were adjusted for: PI-refractory status, cytogenetic risk, revised ISS, extramedullary disease, ECOG PS, and age group. No. of pLOTs, time since diagnosis, prior transplant, race, sex, and MM type were also adjusted for in a fully adjusted model. Estimated comparative efficacy for PFS, OS, overall response rate (ORR), and complete response or better (≥CR) are presented. HRs and risk ratios (RRs) with 95% CIs are reported. **Results:** In total, 291 Tec-Dara and 243 BVd pts were included; Tec-Dara effective sample size was 157 with base-case and 74 with full-model adjustment. After base-case adjustment, pts treated with Tec-Dara had significantly improved PFS (HR, 0.22 [95% CI, 0.13–0.37]) and OS (HR, 0.48 [0.30–0.79]) vs BVd. In addition, Tec-Dara had significantly greater ORR (91.1% vs 83.1%; RR, 1.10 [1.02–1.18]) and ≥CR (84.3% vs

35.8%; RR, 2.35 [1.96–2.83]) vs BVd. Following full-model adjustment, consistent Tec-Dara benefits were observed for PFS (HR, 0.26 [0.13–0.50]) and OS (HR, 0.55 [0.29–1.05]). Results continued to favor Tec-Dara for ORR (93.9% vs 83.1%; RR, 1.13 [1.05–1.21]) and ≥CR (85.3% vs 35.8%; RR, 2.38 [1.97–2.89]). Benefits with Tec-Dara were consistent in sensitivity analyses and in subgroup analyses of pts with 1 pLOT who were lenalidomide refractory. The consistency of comparative estimates in favor of Tec-Dara across base-case, full-model, and sensitivity analyses, illustrates the robustness of results. **Conclusions:** Tec-Dara showed clinical and statistically significant PFS/OS improvement, with a 78%/52% risk reduction, respectively, compared with BVd in the base-case MAIC. Moreover, Tec-Dara more than doubled the rate of ≥CR. Notably, MajesTEC-3 had a highly lenalidomide-refractory population (84% vs 34% in DREAMM-7); however, Tec-Dara's comparative benefit persisted after robust, conservative MAIC adjustment, highlighting Tec-Dara's ability to elicit deep and durable responses, supporting its use as a highly effective, fully immunotherapy-based, steroid-sparing SoC regimen in RRMM as early as first relapse.

PA-302

Measuring What Matters: Patient Behavioral Outcomes Across MMRF Education Programs

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Introduction: Multiple myeloma (MM) is a rare and complex blood cancer in which treatment options continue to evolve rapidly. Patients, particularly those in community settings without direct access to a myeloma specialist, risk falling behind on emerging therapies and care options. Ensuring patients receive timely, relevant education is critical to bridging this gap. The Multiple Myeloma Research Foundation (The MMRF) addresses this need by offering complimentary education programs designed to keep patients up to date and equipped with the skills to become effective advocates in managing their MM. **Methods:** Each year, the MMRF education team assesses feedback across all education programs to build program rationale, learning objectives, and behavioral and knowledge milestones. These elements are incorporated into programming and pre- and post-program surveys, which serve as a cornerstone of patient education data. In 2025, the MMRF delivered 25+ education programs. Prior to each event, patients completed a pre-event survey rating their agreement with key statements, followed by a post-event evaluation survey. To further measure impact and evaluate program resonance, a quarterly follow-up survey is distributed, presenting participants with a list of positive steps they self-report having taken as a result of attending an MMRF program. **Results:** In 2025 15,000+ patients and caregivers registered for MMRF's educational programs, 5,000+ attended or viewed a program on demand. The follow up survey was distributed to patients and caregivers every 3 months following their attendance. 5,246 surveys were delivered, yielding an 8% response rate (n = 398) including 347 patients, 39 caregivers, and 12 identifying as "other." Among survey respondents, 85% reported making at least one positive behavioral change related to their myeloma care. Results included: Lab Diagnosis and Interpretation: 93% reported interpreting their lab results and discussing them with their doctor Active Communication: 68% reported communicating to their doctor about their needs and goals for treatments Support & Community: 59% reported communicating with family members or caregivers about their myeloma and ways they could provide support. Identifying High-Risk:48% reported discussing next steps with their care team regarding their high-risk disease status. **Conclusions:** The 2025 results demonstrate that MMRF education programs are driving meaningful behavioral change among MM patients. However, survey findings also revealed key barriers patients face in navigating their myeloma, including clinical trial ineligibility, limited access to a medical center and/or myeloma specialist, and financial challenges. In 2026, efforts will focus on deeper analysis of engagement patterns across respondents, identifying correlations between disease stage and reported barriers, and improving response rates to support a more comprehensive assessment of the impact of MMRF patient education programs.

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Mechanistic Study on CD83+ Inflammatory Myeloid Cells Inducing T Cell Senescence Leading to BCMA CAR-T Treatment Failure in Multiple Myeloma

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Introduction: Although chimeric antigen receptor T (CAR-T) cell therapy has demonstrated remarkable efficacy in the treatment of multiple myeloma (MM), it still faces challenges of poor persistence and disease recurrence. The role of inflammatory microenvironment in CAR-T therapy efficacy remain unclear. **Methods:** Public single-cell RNA sequencing (scRNA-seq) data were collected and integrated, including five datasets (GSE143317, GSE164551, GSE210079, GSE234261, GSE246342) from patients with relapsed/refractory multiple myeloma (RRMM) who received BCMA CAR-T therapy. The Seurat analysis toolkit was used for data integration and unsupervised clustering. Pseudotime analysis was performed via the Monocle2 tool to resolve the differentiation trajectory of myeloid cell subsets. Patients who achieved a best response of partial response (PR) or better were defined as responders, while those who failed to reach PR were designated as non-responders. **Results:** Cellular profiling identified a total of 449,227 single cells across all samples, including immune (T/NK cells, myeloid cells, B cells), myeloma cell populations. A distinct subset of inflammatory myeloid cells was subsequently identified, which specifically highly expressed multiple

key proinflammatory cytokines including CCL3, IL1B and TNF, indicating the cellular source of systemic inflammation post CAR-T infusion. Immunophenotyping and pseudotime analysis revealed that this inflammatory myeloid subset expressed CD14 and CD83, and might be differentiated from granulocyte-monocyte progenitors (GMPs). Investigation into the functional differences of T cells post CAR-T infusion revealed that in non-responding patients to BCMA CAR-T therapy, the proportions of Naïve-CD4+ and Naïve-CD8+ T cells were markedly reduced, with downregulated expression of costimulatory molecules (CD27, CD28) and the stem-like gene TCF7 (encoding Tcf-1 protein). In contrast, the proportion of GZMK+ CD8+ effector memory T (Tem) cells was increased, and T cells exhibited upregulated activity of senescence-associated signaling pathways, including cell cycle arrest, DNA damage response, oxidative stress/integrated stress response, and MAPK cascade. The senescence score of T cell subsets was significantly elevated in non-responding patients. More importantly, T cell senescence was significantly positively correlated with the level of systemic inflammation and the proportion of the inflammatory myeloid subset. **Conclusions:** Systemic inflammation after CAR-T cell infusion is derived from the CD83+ inflammatory myeloid cell subset differentiated from GMPs, which characteristically highly expresses various proinflammatory cytokines. This subset is significantly enriched in RRMM patients with non-response to BCMA CAR-T therapy. Preliminary findings suggest that this CD83+ inflammatory myeloid subset induces CAR-T cell senescence via the secretion of proinflammatory cytokines, thereby leading to the failure of CAR-T therapy for MM.

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Mezigdomide (CC-92480) Following Idecabtagene Vicleucel (Ide-Cel) in Relapsed/Refractory Multiple Myeloma Is Safe and Leads to Deepening of Responses

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Introduction: Idecabtagene vicleucel (ide-cel), a BCMA-directed CAR T-cell therapy, achieves high response rates in relapsed/refractory multiple myeloma (RRMM), yet most patients relapse. Immune reconstitution post-infusion represents a window to deepen or sustain responses. Mezigdomide (CC-92480) is an oral CELMoD with potent anti-myeloma activity that can stimulate anti-tumor immunity and synergize with residual CAR T-cells. Translational work from this study reported separately shows that mezigdomide use after ide-cel is associated with early immune remodeling, with a trend toward decrease in the suppressive subset population, T cell shifts to an activated phenotype, and expansion of the highly activated HLA-DR$^+$/CD38$^+$ CAR T-cell subset. We hypothesized that sequential mezigdomide post ide-cel would augment depth and durability of response. **Methods:** This ongoing, single-center, open-label Phase 1 study (BOIN design) evaluates mezigdomide initiated 30–120 days post ide-cel, in the absence of progressive disease and ≥Grade 2 CAR-T toxicity. Eligible patients had RRMM with prior PI, IMiD, and anti-CD38 exposure. Dose levels: DL1 (0.3 mg) and DL2 (0.6 mg), days 1–21/28, up to 12 cycles. Primary endpoint: DLT per CTCAE v5.0. Secondary endpoints: ORR, DOR, PFS per IMWG. **Results:** Seven patients were enrolled: DL1 n = 3, DL2 n = 4. Median age was 81 years (range 39–86); median prior LOT was 5 (range 4–7). Median time from ide-cel to mezigdomide C1D1 was 108 days (range 48–112). No DLTs were observed at either dose level. The most common Grade ≥3 treatment emergent adverse event (TEAE) was neutropenia (DL1: n = 3 Grade 3; DL2: n = 2 Grade 3, n = 1 Grade 4). Prophylactic growth factors (filgastrim or pegfilgastrim) were used. No recurrent CRS, ICANS, or persistent cytopenias were observed from mezigdomide. The ORR was 85.7% (6/7): 5 patients (71.4%) had stringent complete response (sCR) and 1 (14.3%) had very good partial response (VGPR). DL2 ORR was 100% (4/4 sCR). Notably, mezigdomide deepened the ide-cel response in 5 of 6 responding patients (83.3%): 3 patients improved from partial response (PR) to sCR, 1 from VGPR to sCR, and 1 from PR to VGPR. One patient had sCR with ide-cel, which was maintained with mezigdomide. Median time to best response from ide-cel was 6.5 months (range 3.4–10.2). At a median follow-up of 17.9 months from ide-cel infusion (range 7.6–20.7), the 6-month PFS rate was 100%, 12-month PFS was 85.7% (95% CI: 33.4–97.9%), and the median PFS was 16.5 months, which is an improvement over the 8.5-month PFS from real-world experience of ide-cel alone in a comparable population (PMID: 36623248). **Conclusions:** This study is the first demonstrating that sequential mezigdomide following ide-cel is feasible. Mezigdomide is safe in the post CAR-T setting and shows preliminary efficacy in patients who have residual myeloma, supporting the hypothesis that mezigdomide augments CAR-T cell response via enhanced residual CAR-T efficacy and/or direct CELMoD anti-myeloma activity.

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Mezigdomide, Carfilzomib, and Dexamethasone (MeziKd) vs Carfilzomib and Dexamethasone (Kd) in Relapsed/Refractory Multiple Myeloma (RRMM): Results From the Phase 3 SUCCESSOR-2 Trial

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Introduction: Patients (pts) entering second-line treatment (tx) are increasingly anti-CD38 mAb- and lenalidomide (LEN)-exposed, limiting tx options. Mezigdomide (Mezi), a potent oral CELMoD, induces maximal, rapid Ikaros/Aiolos degradation leading to enhanced MM cell death and immune stimulation vs IMiDs. We report initial results from SUCCESSOR-2 (NCT05552976), the first randomized phase 3 study of Mezi in RRMM, evaluating MeziKd vs Kd. **Methods:** In this phase 3, 2-stage, inferentially seamless trial, eligible adult pts had ≥1 prior line of therapy (LOT) including an anti-CD38 mAb and LEN. Pts were randomized 3:3:3:2 (Mezi 0.3, 0.6, 1.0 mg + Kd, or Kd) to identify the optimal Mezi dose in stage 1, and 3:2 to compare efficacy and safety of MeziKd vs Kd in stage 2. MeziKd was given in 28-day (D) cycles of Mezi (D1–21), 56 mg/m^2 carfilzomib (CFZ) weekly (QW), and 40 mg dexamethasone (DEX) QW. The Kd arm received CFZ 56 mg/m^2 twice weekly or 70 mg/m^2 QW + DEX. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, selected Mezi dose (stage 1), overall response rate (ORR), and safety. **Results:** The Mezi dose selected for stage 2 was 1.0 mg. 479 pts (288 MeziKd at 1.0 mg Mezi; 191 Kd) were included in the analysis. Median (range) age was 68 (30–85) y with 25.1% of pts ≥75 y; median (range) number of prior LOTs was 2 (1–9); 92.1% of pts were triple-class-exposed, with 85.8% refractory to an anti-CD38 mAb and 75.8% to LEN; 37.2% were exposed to pomalidomide and 7.3% to anti-BCMA tx. At data cutoff, median follow-up was 10.6 mo with 52.4% (MeziKd) and 31.4% (Kd) of pts still on tx. Median tx duration was 8.9 (up to 32.1) mo for MeziKd vs 6.2 (up to 25.0) for Kd. MeziKd significantly improved PFS vs Kd (median [95% CI], 18.0 [14.5–22.1] vs 8.3 [5.6–10.7] mo; HR, 0.48 [95% CI, 0.36–0.63]; P < 0.0001), which was consistent across subgroups, including pts with >2 prior LOTs, prior tx exposure/refractoriness, high-risk cytogenetics, extramedullary disease, and age ≥75 y. Higher ORR (80.2% vs 53.4%) and complete response or better (26.7% vs 8.9%) were seen with MeziKd. Deaths were reported in 21.5% (MeziKd) vs 26.7% (Kd) of pts, mostly from progressive disease. Grade (Gr) 3–4 treatment-emergent adverse events were seen in 83.7% vs 56.5% of pts, neutropenia in 61.1% vs 9.1%, and infections in 34.0% vs 15.6% with MeziKd vs Kd; Gr 5 infections in this high-risk population were few (2.4% vs 1.1%). **Conclusions:** MeziKd showed a clinically meaningful PFS benefit as early as first relapse in predominantly triple-class-exposed, anti-CD38 mAb- and LEN-refractory pts, a population with significant unmet need. These data support Mezi, a potent oral tx with a predictable and manageable safety profile, as a readily accessible potential new standard of care for RRMM across multiple settings. © 2026 American Society of Clinical Oncology, Inc. Reused with permission. Previously presented at 2026 ASCO Annual Meeting. All rights reserved.

PA-306

MGUS With Advanced Chronic Kidney Disease: Clinical Profile, FLC Ratio Interpretation, and Progression to Multiple Myeloma in a Tertiary Hematology Center

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) and chronic kidney disease (CKD) frequently coexist, raising the challenge of differentiating monoclonal gammopathy of renal significance (MGRS) from coincidental findings. The differentiation between MGRS and coincidental renal disease remains a clinical challenge. This study aimed to characterize the clinical profile and risk of progression to multiple myeloma in patients with MGUS and advanced CKD. **Methods:** Single-center, observational, retrospective study of patients referred to a hematology outpatient clinic with monoclonal gammopathy and CKD (eGFR < 45 mL/min/1.73 m^2). Patients with smoldering or active multiple myeloma (MM) criteria at referral, M-spike >3 g/dL, or signs of lymphoproliferative disease were excluded. Variables were analyzed descriptively. Cumulative incidence of progression to MM was estimated using the Kaplan-Meier method with competing risk analysis (death as a competing event). **Results:** Of 131 patients referred with monoclonal gammopathy and renal dysfunction, 23% met criteria for smoldering or active MM and were excluded; 77% (N = 101) had MGUS without MM criteria. The overall cohort was 60% male, median age 65 years (IQR 54–72), with median eGFR 25 mL/min/1.73 m^2

(IQR 6–44), reflecting markedly advanced CKD. Among the MGUS subgroup (N = 101), demographics and renal function were comparable (59% male, median age 65 years, median eGFR 25 mL/min/1.73 m^2); 18% had a prior solid organ transplant. All patients underwent serum protein electrophoresis; 62% had a detectable serum M-spike (median 0.70 g/dL, IQR 0.4–0.9), with IgG as the predominant isotype (73%), followed by non-IgG (15%), light chain only (9%), and biclonal (3%). Urinary monoclonal component was assessable in 65% of patients, of whom 27% tested positive. Serum FLC measurement was available in 73% of patients; renal adjustment doubled the proportion classified as low risk (9.6% to 19.2%) and reduced high-intermediate risk (35.6% to 32.9%), indicating risk overestimation when standard unadjusted thresholds are used. Twenty patients underwent renal biopsy; of these, 2 (10%) had histopathologically confirmed MGRS. Median follow-up was 4.5 years (IQR 2.3–6). **Conclusions:** Approximately 80% of patients referred for monoclonal gammopathy and renal dysfunction did not meet MM criteria. In this advanced CKD population, standard FLC ratio thresholds are unreliable. Risk stratification must account for renal function when interpreting FLC ratios to avoid misclassification. The non-protocolized rate of renal biopsy observed in this cohort suggests that histological investigation may remain underutilized in clinical practice. Expanding this investigation to larger, multicenter cohorts may provide the evidence needed to guide standardized clinical pathways and improve the care of patients with MGUS and advanced CKD globally.

PA-307

Monoclonal Gammopathy of Renal Significance: Experience at a Single Center and Implementation of a Multidisciplinary Committee

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Introduction: Monoclonal gammopathy (MG) of renal significance (MGRS) comprises kidney disorders caused by monoclonal immunoglobulins (MIg) regardless of tumor burden. It is an evolving entity that requires a multidisciplinary approach. Not all forms of MGRS warrant immediate treatment, and there is ongoing controversy regarding its appropriate intensity. In conditions such as fibrillary glomerulonephritis (fGN) or proliferative GN with MIg deposits (PGNMID), the pathogenic clone cannot be identified in a substantial proportion of cases, and their definition and management strategies are under review. **Methods:** In 2024, a MG Committee was established at our institution, comprising specialists from the Departments of Nephrology, Pathology, and Hematology, with the aim of optimizing joint decision-making regarding indication for renal biopsy; hematologic and renal treatment strategies; eligibility for kidney transplantation; and streamlining the diagnostic and therapeutic pathway for patients with MG and kidney involvement. We present the results of the evaluation of patients (pts) discussed by this committee from January 2024 to March 2026. We analyze the clinical and biological characteristics of the pts reviewed, their final diagnoses, as well as treatment and outcomes, with particular emphasis on MGRS cases. **Results:** 41 pts were evaluated: 17 for kidney biopsy indication, 22 for treatment decision after kidney biopsy, 1 for kidney transplantation assessment, and 1 for biopsy review. Kidney biopsy was performed in 32 pts (65%), revealing MG-related renal lesions in 21 (66%). 16 pts were diagnosed with MGRS after excluding 1 cast nephropathy and 4 AL amyloidosis cases. Among MGRS pts, median age was 66 years (42–86). The most frequent diagnosis was PGNMID (6, 38%), followed by light-chain (LC) proximal tubulopathy (LCPT) (4, 25%), immunotactoid GN (2, 12.5%), C3/C4 GN (2, 12.5%), fGN (1, 6.2%), and LC deposition disease (1, 6.2%). 7 (43%) had no detectable pathogenic clone despite serum+urine electrophoresis+immunofixation and bone marrow evaluation (6 PGNMID and 1 fGN). Median glomerular filtration rate at diagnosis was 46 mL/min/1.73 m^2 (13–90) and median 24 h proteinuria was 2.4 g (0.1–18) 14/16 pts (87.5%) received clone-directed therapy, most commonly daratumumab-based regimens (72%). 4 (28%) received autologous stem cell transplantation The 2 untreated pts had mild, stable LCPT. All evaluable treated pts achieved at least hematologic very good partial response. Renal response (≥30% reduction in proteinuria or proteinuria < 0.5 g/24 h) was achieved in 9/12 evaluable pts (75%). Responses were durable; only one pt with PGNMID relapsed, progressed to end-stage kidney disease requiring hemodialysis, and received 2nd-line therapy. **Conclusions:** A multidisciplinary MGRS committee facilitates diagnostic workup, interpretation of kidney biopsy findings, and treatment selection. In our series, clone-directed therapy achieved high response rates, even in pts with PGNMID without an identifiable clone.

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Monocytic Myeloid-Derived Suppressor Cells in Multiple Myeloma: Roles of Soluble Factors, Tumor-Derived Exosomes, and Modulation by IMiDs and CELMoDs

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Introduction: Multiple myeloma (MM) evolves within a specialized bone marrow microenvironment where malignant plasma cells interact with immune and stromal cells. Among its immunosuppressive elements, monocytic myeloid-derived suppressor cells (M-MDSCs) are important mediators of impaired anti-myeloma immunity. By suppressing cytotoxic T cells and natural killer cells and promoting regulatory T-cell expansion, M-MDSCs may contribute

to immune escape, treatment resistance, and insufficient responses to immune-based therapies. **Methods:** We here investigated how myeloma cells induce M-MDSCs from peripheral blood mononuclear cells (PBMCs) and whether this process can be modulated, using in vitro transwell co-culture systems. **Results:** When co-cultured, selected human myeloma cell lines (HMCLs) induced CD14-positive, HLA-DR-negative/low M-MDSC-like cells from normal PBMCs. These cells were phenotypically consistent with M-MDSCs and functionally immunosuppressive, exhibiting IDO1 upregulation, inhibiting T cell proliferation, and enhancing regulatory T cell induction. We found that myeloma-derived CCL5 and macrophage migration inhibitory factor (MIF) were essential soluble mediators, and tumor-derived exosomes provided an additional pathway. Among exosomal microRNAs, miR-106a-5p and miR-146a-5p played central roles. Their transfer to PBMCs induced immunosuppressive and inflammatory programs, including increased expression of IDO1, CD38, PD-L1, CCL5, and MYD88, along with activation of the interferon response, TNF-α signaling, and IL-6/JAK/STAT3 pathways. These microRNAs cooperated with CCL5 and MIF, forming a self-amplifying network of immune suppression. Co-culture eventually revealed reciprocal transcriptional reprogramming. Myeloma cells exposed to PBMCs acquired inflammatory TNF-α/NF-κB signatures, whereas CD33-positive myeloid cells, including M-MDSCs, showed attenuated interferon-related immune activation. This process was inhibited by immunomodulatory drugs. lenalidomide and pomalidomide reduced CCL5 and MIF in myeloma cells, downregulated CCR5 in PBMCs, and induced IRF-8. Next-generation cereblon E3 ligase modulators, especially iberdomide and mezigdomide, were more potent, suppressing M-MDSC induction at nanomolar concentrations, reducing CCL5 expression, enhancing ISG15 and other interferon-related signatures in CD33-positive myeloid cells, and modulating gene expression patterns and decreasing IL-10 and MIF in myeloma cells. decreasing IL-10 and MIF. Collectively, these findings support a model in which myeloma cells induce M-MDSCs through soluble factors, exosomal microRNAs, and reciprocal transcriptional remodeling. **Conclusions:** This reframes MM immune escape as an active, targetable process. Targeting CCL5, MIF, IL-10, exosomal miR-106a-5p/miR-146a-5p, or downstream pathways may restore anti-myeloma immunity.

PA-309

Moving Ahead on the Interpretation of t(14;16) Driver Alteration Role in the Era of Novel Agent Therapy in Multiple Myeloma

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Introduction: The prognostic role of t(14;16) in multiple myeloma has remained controversial across previous risk stratification models. Recent IMWG/IMS criteria classify t(14;16) as a high-risk cytogenetic abnormality (HRCA) only if associated with additional alterations meanwhile only 18 patients in the reference cohort harboured isolated t(14;16). Notably t(14;16) is a primary driver alteration that frequently ended up associated with secondary HRCA suggesting a non-random association pattern. t(14;16) even when isolated may not significantly affect PFS but could negatively impact OS through progressive evolution toward a more aggressive phenotype. This new interpretation is reflected in the results of the R2-ISS and in the data of Mina et al. and is biologically coherent with the association between this CA and the APOBEC mutational signature. The study aimed to evaluate the prognostic impact of t(14;16) in the real-life setting as a way to dissect the clonal evolution of t(14;16) patients over time as opposed to those harbouring other CAs. **Methods:** 69 active MM patients carrying t(14;16), diagnosed between 2010 and 2025 were included. Clinical and biological characteristics at diagnosis, treatments received, and survival outcomes were collected. Patients were compared with 150 SR patients according to the R-ISS classification. **Results:** Median age was 67 years in the t(14;16) cohort and 68 in the SR cohort ($p = 0.634$). Patients with t(14;16) more frequently presented with ISS stage III disease ($p = 0.003$), elevated LDH levels ($p = 0.007$), and +1q abnormalities ($p < 0.001$). Del17p was detected in 16/69 patients (23%), while 18/69 (26%) harboured at least two additional HRCAs. Isolated t(14;16) was identified in 13 patients. Exposure to anti-CD38 therapy occurred in 70% of t(14;16) and 76% of SR patients ($p = 0.399$), with first-line anti-CD38 use in 42% and 43%, respectively. Autologous stem cell transplantation was performed in 42% and 43% of patients($p > 0.999$). Patients with t(14;16) showed inferior OS compared with SR patients (75 vs 110 months, $p = 0.027$), whereas no significant PFS difference was observed ($p = 0.162$). Isolated t(14;16) cases also demonstrated reduced OS compared with SR patients without +1q abnormalities or del1p (44 vs 150 months, $p = 0.045$), again without significant PFS differences ($p = 0.692$). Among patients treated with anti-CD38-based regimens, isolated t(14;16) showed a trend toward longer PFS compared with t(14;16) associated with additional HRCAs (77 vs 17 months, $p = 0.080$), with survival curves showing clear separation. No OS difference emerged ($p = 0.392$). **Conclusions:** Our data are consistent with previous literature results. t(14;16) seems to behave more similarly to a SR CA in terms of PFS while resembling HR CA with

respect to OS. This could be a glimpse of his biological role. This driver CA even when isolated may fuel clonal evolution leading over time to a more aggressive phenotype.

PA-310

M-Protein Kinetics After BCMA CAR-T Therapy Using Clonotypic Peptide Mass Spectrometry (M-inSight)

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Introduction: Cilta-cel CAR-T therapy can induce rapid and profound responses in multiple myeloma, with bone marrow minimal residual disease (MRD) negativity achieved within weeks in some patients. However, serum M-protein kinetics after CAR-T remain poorly characterized. Circulating monoclonal immunoglobulin may persist after marrow clearance, reflecting immunoglobulin half-life, delayed biochemical response, or residual production. Patient-specific clonotypic peptide LC-MS/MS enables highly sensitive longitudinal quantification of the M-protein in serum and may complement bone marrow MRD assessment. **Methods:** This study includes 34 patients treated with Cilta-cel CAR-T therapy and 271 collected serum samples. Samples were annotated by treatment timepoint, including screening/baseline, day 0, high-frequency early post-treatment visits, monthly follow-up, and yearly follow-up. Early sampling included blood draws every few days during the first post-treatment month in several patients, with follow-up extending up to 3 years. At baseline, patient-specific clonotypic peptides were identified from the monoclonal protein, and follow-up serum samples were quantified by M-inSight (clonotypic peptide mass spectrometry Sebia). BM-MRD status was assessed by next-generation flow cytometry (NGF). Serum M-protein kinetics were compared descriptively with BM-MRD status and clinical response. A serum threshold of 12.5 mg/L, previously associated with outcome stratification, was applied to evaluate blood-MRD status. **Results:** Ig patient specific clonotypic peptides were identify in 33 of 34 patients, (97%). Longitudinal serum profiles demonstrated often rapid M-protein decline after cilta-cel. In one representative patient, serum M-protein decreased from 0.520 g/L at day 0 to 0.014 g/L at day 28, corresponding to a 98% reduction within the first month, and reached 0.005 g/L at 3 months. This patient remained BM- MRD-negative by NGF and maintained Blood-MRD during subsequent follow-up. Dense early sampling captured rapid changes occurring over days, while extended follow-up showed sustained suppression of clonotypic M-protein in several patients with persistent BM-MRD negativity. In other patients, detectable serum M-protein persisted despite BM-MRD negativity, supporting the hypothesis that serum clearance may lag behind marrow response after highly effective cellular therapy. Importantly, these patients continued to show a downward M-protein kinetic profile over time, suggesting ongoing biochemical response rather than stable or progressive residual disease. **Conclusions:** High-frequency serum sampling combined with clonotypic peptide LC-MS/MS enables detailed characterization of M-protein kinetics after cilta-cel CAR-T therapy. These data suggest that BM- MRD negativity may occur before complete serum M-protein clearance and that blood-based clonotypic monitoring can provide complementary information on biochemical response and long-term disease suppression after CAR-T-cell therapy.

PA-311

Multicentric Evaluation of SPIRIT IT: Artificial Intelligence to Detect and Characterize M-Protein

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Introduction: Interpretation of immunotyping (IT) profiles for monoclonal protein detection remains challenging and subject to significant inter-operator and intra-operator variability. Artificial intelligence (AI) may help standardize interpretation and support laboratories facing increasing workload and limited expertise. SPIRIT IT is an AI-based software designed to assist clinicians and laboratory professionals in IT interpretation. **Methods:** SPIRIT IT software relies on a supervised, non-self-learning artificial intelligence algorithm intended to aid in the interpretation of immunotyping curves for the detection and the characterization of monoclonal proteins. The categories thus created depend on the absence or presence of a single monoclonal peak (Ig A Kappa, Ig A Lambda, Ig G Kappa, Ig G Lambda, Ig M Kappa or Ig M Lambda) or category "other" such as, for example, an increase of the polyclonal background, or the observation of biclonal, triclonal or oligoclonal profiles. SPIRIT IT suggests an interpretation of the results along with an associated confidence level. A result is considered highly confident when the prediction confidence exceeds 90%, relatively confident when it falls between 70% and 90%, and low confidence when it is below 70%. To assess the concordance between SPIRIT IT predictions and user interpretations, a multicentric study was conducted across international sites including 6,745 IT results obtained on CAPILLARYS 3 systems. SPIRIT IT predictions were compared with interpretations from routine laboratory users and Sebia experts. **Results:** SPIRIT IT generated an interpretable prediction in 62% of cases, while 12% showed low confidence and 26% had no reliable prediction. Among interpretable samples, concordance reached 87% with user interpretations and 93% with expert interpretations. Performance was highest for monoclonal profiles, with concordance rates of 95–100%, while lower agreement was observed for heterogeneous "other" profiles, reflecting their intrinsic complexity. Overall, results were consistent across multiple sites, instruments, and geographic regions, supporting the robustness of the model. **Conclusions:** SPIRIT IT demonstrated high

concordance with expert interpretation and reduced variability compared with routine users, supporting its ability to standardize IT interpretation. By providing consistent classification and confidence levels, it may enhance reliability and support decision-making in routine practice. SPIRIT IT is a reliable AI-based decision-support tool for immunotyping interpretation, showing high agreement with experts and potential to improve consistency and efficiency in clinical laboratories.

PA-312

Multi-Modal Single-Cell Profiling of MRD-Negative Patients Identifies Early Immune Signatures Predicting Prolonged Response or Relapse in Multiple Myeloma

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Introduction: Sustained MRD negativity (MRD-) is among the strongest prognostic indicators in multiple myeloma (MM), yet a subset of MRD- patients ultimately relapse. Predictive tools to identify patients at risk for relapse versus durable remission remain limited. Here, we identified bone marrow (BM) immune microenvironment features distinguishing future converters from sustained responders. **Methods:** We profiled paired bone marrow scRNA-seq and scTCR-seq with MRD- lasting at least 24 months at both an early MRD timepoint (T1) and a median of 39 months later (T2), either with ongoing sustained MRD- (MRD-S, n = 5) or at MRD conversion preceding relapse (MRD-R, n = 6). Unsupervised compositional analysis using Bayesian beta-binomial modeling identified emerging cell states which were further characterized with pseudobulk differential expression, immune-program scoring, ligand-receptor analysis, and T cell receptor (TCR) clonotype mapping to transcriptional states. All findings were cross-validated across multiple orthogonal analytical frameworks with leave-one-out sensitivity analysis to minimize tool-specific bias and confirm result stability. **Results:** MRD-R patients showed expansion of CD8+ T cells at both timepoints (FDR< 0.001) compared to MRD-S patients. At T1 MRD-R patients were enriched for activated effector/inflammatory CD8+ T cell subsets, including HLA-DR+ CD8+ Teff cells and IFN+ CD8+ effector memory (EM) T cells, and loss of antigen-presenting cells (APC), including cathepsin Shigh CD14+ monocytes (FDR< 0.05). By T2, this pattern deepened along with accumulation of stressed/apoptotic CD8+ T cells (FDR = 0.004) and further loss of APC subtypes, such as cathepsin Shigh, S100high, and IFN-stimulated CD14+ monocytes and conventional type 2 dendritic cells. Pseudobulk differential expression across CD8+ subsets in MRD-R patients showed upregulation of exhaustion and TNF/NF-kB programs with concurrent loss of IFN-response and proliferative signatures. MRD-R patients showed persistently elevated myeloid-to-CD8+ signaling through Galectin and MIF pathways, driven by inflammatory monocyte subsets. TCR diversity in MRD-R patients at T2 was significantly reduced (Shannon entropy p = 0.045) and showed greater clonal dominance (top-10 clone fraction p = 0.031). Within the GZMK+ CD8+ central memory (CM) T cell compartment, expanded clones showed loss of lymph node homing receptor CCR7 and Mal, T cell differentiation protein, alongside upregulation of cytotoxic effectors GZMH and KLRF1. **Conclusions:** Patients with subsequent relapse harbored a distinct BM immune profile marked by expanded but dysfunctional CD8+ T cells, immunosuppressive myeloid-to-CD8+ signaling, and diminished TCR diversity with clonal differentiation from the CM toward an EM state. This signature was detectable at early MRD-, suggesting a permissive rather than reactive immune state. Prospective immunophenotyping during sustained MRD- may identify patients at risk of conversion and inform safer discontinuation of therapy.

PA-313

Multi-Omics Profiling Unveils Exclusive Molecular Signature of Multiple Myeloma Cells Harbouring Differential TP53 Genetic Perturbations

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Introduction: 17p(del) multiple myeloma(MM) remains a major unmet clinical need. Loss of functional TP53, a key tumour suppressor(TS) on chr17p, through monoallelic deletion(WT/-), biallelic deletion(-/-) or double-hit events(mut/-), consistently associated with inferior outcome. However, these observations are largely based on heterogeneous patient cohorts and remain predominantly associative, not supported by biological evidence. Mechanistic studies, particularly in isogenic systems, are indeed scarce. We hypothesised that monoallelic and biallelic TP53 loss drive distinct biological programmes that contribute differently to disease pathogenesis. **Methods:** Via CRISPR-Cas9 and single-cell cloning, we generated an isogenic MM model from NCI-H929(n = 2 clones/genotype) representing TP53 WT/WT, WT/-, and -/- states to recapitulate the clinical paradigm of TP53 abnormalities, i.e. from TP53-intact to monoallelic deletion and double-hit TP53 disease. Genotypes were confirmed by NGS and cleavage assays. Functional assays were done to assess their oncogenic potential. Validated clones underwent bulk RNA-seq and ATAC-seq, followed by integrative bioinformatic analyses. **Results:** Stepwise TP53 loss progressively increased oncogenic potential. TP53 -/- cells showed the highest proliferation, followed by WT/- and WT/WT cells, consistent with

cell-cycle and colony-forming capacity. Drug perturbation studies using genotoxic(doxorubicin, melphalan) and non-genotoxic(nutlin-3) agents demonstrated TP53 haploinsufficiency, with a progressive reduction in drug sensitivity from WT/WT to WT/- to -/- cells. At the molecular level, RNA-seq and ATAC-seq revealed broadly similar transcriptional and chromatin landscapes across all genotypes, consistent with their common parental origin. Nevertheless, each TP53 state also displayed distinct gene expression and chromatin accessibility signatures. Several genes exhibited progressive expression changes across the TP53trajectory(WT/WT→WT/-→-/-), suggesting direct TP53 regulation. Canonical MM drivers(IRF4, KRAS, IL6R/STAT3, ADAR1) were upregulated in both WT/- and -/- cells relative to WT/WT cells, indicating enhanced oncogenicity following TP53 loss regardless of copy number. More importantly, WT/- and -/- cells also exhibited distinct molecular programmes independent of the TP53 trajectory. Pathways involving E2F, MYC, cellular metabolism, and immune responses were among the major differentiators between monoallelic and biallelic TP53 loss. Although ATAC-seq revealed a complex chromatin landscape, promoter-TSS accessibility changes supported the pathway enrichments identified by RNA-seq. **Conclusions:** Our preliminary findings suggest that TP53 abnormalities in MM involve more than just loss of its TS function. The extent of TP53 copy-number loss is also crucial as it contributed to distinct biological states that may drive MM through different mechanisms. Ongoing work aims to define the functional relevance of pathways uniquely associated with specific TP53abnormalities in MM.

PA-314

Multiple Myeloma in World Trade Center-Exposed Individuals: Evidence for a High-Risk Clinical and Cytogenetic Phenotype

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Introduction: Twenty-five years after the September 11, 2001 World Trade Center (WTC) attack, the cancer burden among exposed individuals continues to be high. Multiple myeloma (MM) is recognized as a WTC-related malignancy, but it remains unknown whether WTC exposure is associated only with excess disease occurrence or also with distinct clinical and molecular features. This is biologically plausible because WTC dust contained carcinogenic exposures capable of inducing DNA damage, inflammatory signaling, and epigenetic remodeling. Studies of other WTC-associated cancers, including thyroid and prostate, have linked the exposure to high-risk molecular features and aggressive clinical behavior. We therefore evaluated whether WTC-exposed MM is associated with a distinct clinical and cytogenetic phenotype. **Methods:** We performed a retrospective cohort study comparing WTC-exposed MM patients (n = 108) with non-WTC-exposed institutional controls with available baseline cytogenetic data (n = 2,097). WTC exposure was ascertained through clinical documentation and program records. Cytogenetic abnormalities were classified using 2025 IMS/IMWG high-risk criteria. Prespecified outcomes were age at MM diagnosis, high-risk cytogenetics, and secondary malignancy. Multivariable models adjusted for age, sex, and race with Benjamini-Hochberg correction were performed. Sensitivity analyses included 1:10 propensity-score matching. **Results:** The WTC-exposed cohort was predominantly male (74.1% vs 53.7% in controls), consistent with the WTC-responder population. Racial distribution was similar between groups. MM was diagnosed a median of 16.3 years after WTC exposure (range, 3.6–24.0 y). WTC-exposed patients were significantly younger at diagnosis than non-WTC MM controls (mean 58.0 vs 62.5 years; adjusted Δ −4.43 years, 95% CI −6.54 to −2.33; P < 0.001). They also had more adverse cytogenetic features: high-risk cytogenetics were significantly enriched in WTC-exposed MM (21.3% vs 14.8%; ORadj 1.65, 95% CI 1.02–2.67; P = 0.04), with del(17p)/TP53 loss accounting for much of this signal (12.0% vs 7.9%; ORadj 1.71, 95% CI 0.93–3.15; P = 0.08). Secondary malignancies were significantly more frequent in WTC-exposed MM (31.5% vs 18.7%; RRadj 2.03, 95% CI 1.52–2.73; P < 0.001), with prostate (n = 6) and breast (n = 5) as the most common tumors. All prespecified findings remained significant after FDR correction, and propensity-score matched analyses confirmed the directionality of the associations. **Conclusions:** In this single-center cohort, WTC-exposed MM was associated with earlier onset, enrichment of high-risk cytogenetics driven in part by higher rates of del(17p)/TP53 loss, and increased secondary malignancy burden. Together, these findings support WTC-exposed MM as a potential exposure-associated phenotype marked by earlier onset and adverse genomic features, and provide a foundation for prospective molecular and exposomic studies of environmental influences on plasma cell evolution, risk stratification, and surveillance.

PA-315

MY.13: A Canadian-Led Non-Inferiority Phase III Trial in Progress Integrating Equity Principles in Transplant-Ineligible (TIE) Newly-Diagnosed (ND) Multiple Myeloma (MM)

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Introduction: Anti-CD38 monoclonal antibodies (CD38mAbs), are given indefinitely as standard of care for patients with newly diagnosed multiple myeloma, ineligible for stem cell transplant. The need for continuous administration is unclear. Studies suggest increased infection risk with prolonged CD38mAbs use, alongside substantial costs (E.g., ~$8000 CAD/month for daratumumab administration), supporting evaluation of fixed-duration therapy. **Methods:** MY.13 (NCT06182774) is an academic, phase III non-inferiority trial. After 18–20 cycles of standard of care triplet or quadruplet frontline therapy including lenalidomide, CD38mAbs (daratumumab or isatuximab) and steroids, patients are randomly assigned 1:1 to discontinue their CD38mAb therapy, or to continue all standard of care therapy. Patients in the fixed duration CD38mAbs arm continue to receive lenalidomide ± steroids as per local practice. Inclusion criteria: Partial response or better to frontline therapy as per International Myeloma Working Group (IMWG) 2016, ECOG performance status 0–3. The primary endpoint is progression-free survival (PFS), with the study designed to rule out a hazard ratio of 1.37 comparing fixed-duration with continuous CD38mAbs, associated with a non-inferior PFS margin of 9.1% at 3.5 years. Secondary endpoints include overall survival, response rates, toxicity, time to next treatment, post-protocol therapy, quality of life, and health economics. Exploratory endpoints include optional bone marrow minimal residual disease and peripheral blood mass spectrometry, correlated with outcomes. The innovative design embeds equity principles being inclusive of the frail elderly, people living with controlled HIV and renal failure. Ethnic origin data is collected. Decentralized trial conduct includes options for remote consent, virtual visits and treatment at satellite centers. Patient advocates provide input in study design and conduct. **Results:** As of May 2026, 99 of 570 planned participants have enrolled from 7 Canadian provinces. The 28 sites range from academic quaternary referral centers to community centers serving remote, rural and Indigenous populations. Among patients enrolled, median age is 77 years (range 61–88); 87% are ≥70 years-old; 60% male sex at birth; 90% ECOG 0–1; 73% self-identify as Caucasian; 7% Canadian; 3% South Asian; 2% Indigenous; and 15% from other diverse backgrounds. **Conclusions:** This pragmatic phase III trial in progress evaluates fixed duration compared with continuous CD38mABs in older adults with TIE ND MM. The study is designed to maximize patient accessibility and generalizability of results. Incorporation of patient reported outcomes, health economics, and laboratory correlative studies, highlight the strategic opportunity taken to answer questions that matter to patients, clinicians and health care systems. Accrual continues with work underway to expand internationally.

PA-316

Neoantigen Viral Vector Vaccination Provides Effective and Durable Tumor Control in an Aggressive Multiple Myeloma Model

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Introduction: Multiple myeloma (MM) progresses through well-defined precursor stages, providing a unique window of opportunity for cancer interception/prevention strategies. Neoantigen(nAgs)-targeted vaccination represents a promising approach particularly in the preventative and early treatment settings. Among available platforms, viral vector–based vaccines are highly effective in inducing robust and long-lasting antigen-specific T cell responses and are clinically validated. Here, we evaluated a viral vector multiepitope neoantigen vaccine in the well characterized immunocompetent Vk*MYC mouse model of MM to assess its anti-tumor activity. **Methods:** Whole genome and RNA sequence analysis of the Vk*MYChCRBN Vk32908 multiple myeloma transplantable line was performed to identify tumor neoantigens for vaccine selection. 47 nAgs were selected by VENUS proprietary bioinformatic pipeline and encoded in a great ape adenovector (GAd). Vaccine immunogenicity was evaluated in C57BL/6 wild type mice and confirmed in hCRBN mice. Vaccine induced CD8+ T cell response were quantified by ex-vivo IFN-γ ELISpot (C57BL/6 mice) and by intra-cellular flow cytometry in PBMC collected seven days post tumor challenge and stimulated ex-vivo with peptide pools overnight (hCRBN mice). Efficacy was evaluated in hCRBN recipient mice vaccinated 14 days prior to Vk32908 tumor challenge. M-spike levels (gamma/albumin ratio) and overall survival were evaluated overtime and compared to unvaccinated mice. **Results:** Single injection of the GAd vector in wild type mice induced robust and polytopic T-cell responses measured by ex-vivo IFN-γ ELISpot using peptide pools. Deconvolution analysis enabled the identification of several reactive epitopes inducing $CD8^+$ T cell responses. Presence of T cell response was associated with vaccine efficacy, with 100% of vaccinated animals remaining tumor free during the entire observation period (more than 70 days post transplantation), whereas all but one unvaccinated mice succumbed to rapidly progressing myeloma (median survival 41 days). **Conclusions:** Our results show that vaccination targeting tumor neoantigen can be highly effective in a clinically predictive model of multiple myeloma with anti-tumor responses and prolonged survival observed in all treated animals bearing our most aggressive tumor line, establishing proof-of-concept for a preventive neoantigen vaccine-based approach in MM.

PA-317

Neutrophils Promote Multiple Myeloma Progression via Activation of PAD4

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Introduction: The bone marrow (BM) microenvironment plays a critical role in promoting myeloma progression and therapeutic resistance. Myeloid cells, particularly neutrophils, represent the largest cellular population within the BM. We have previously shown that myeloid cells promote myeloma progression and resistance; however, the mechanisms underlying neutrophil-mediated effects remain unclear. Neutrophils can produce neutrophil extracellular traps (NETs), a process dependent on peptidylarginine deiminase 4 (PAD4). Here, we investigated the role of neutrophil PAD4 in myeloma progression. **Methods:** Mouse neutrophils were isolated using anti-Ly6G MicroBeads and MACS technique. Human neutrophils were isolated by Percoll gradient centrifugation. PAD4 expression and activation were assessed by qPCR and Western blotting. NET formation was evaluated using a Nikon TE300 inverted microscope, and images acquired with Nikon NIS-Elements AR software. Cell-free DNA (cfDNA) was quantified using SYTOX® Green Nucleic Acid staining. Confocal microscopy assessed intracellular cfDNA localization. The impact of PAD4 inhibition on myeloma progression was evaluated in vivo using syngeneic DP42 and 5TGM1 mouse models. **Results:** Myeloma cells activated PAD4 in BM neutrophils inducing NET release. This effect was mediated by soluble factors, including myeloma-derived Syndecan-1 and HMGB1, as inhibition of either abrogated NET formation. NETs were the main source of cfDNA. NET-derived cfDNA levels were significantly elevated in myeloma-bearing mice compared to tumor-free controls. Similarly, human myeloma cells induced NET formation in human neutrophils, and cfDNA levels were increased in BM plasma from patients versus healthy donors. Mechanistically, NET-derived cfDNA was internalized by myeloma cells via endocytosis and subsequently localized within the cytoplasm. Both NETs and internalized cfDNA have the capacity to bind anthracycline agents, thereby reducing their effective intracellular availability and contributing to tumor cell resistance to this class of drugs. Pharmacological PAD4 inhibition significantly suppressed myeloma growth in vivo. Targeting cfDNA with Pulmozyme or inhibiting PAD4 abrogated neutrophil-mediated protection and restored sensitivity to doxorubicin and melphalan. **Conclusions:** Our findings identify activation of neutrophil PAD4 as a result of myeloma-neutrophil interaction driving NET formation and cfDNA release as a novel mechanism of BM microenvironment-mediated myeloma progression and drug resistance. Targeting this pathway through PAD4 inhibition suppresses myeloma growth and restores therapy sensitivity, highlighting a promising therapeutic strategy in multiple myeloma.

PA-318

New Versus Old: Clinical Outcomes Using 2025 IMS/IMWG vs R-ISS/R2-ISS High Risk Definitions in Newly Diagnosed Multiple Myeloma With TP53 Mutation Status

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Introduction: Risk stratification in newly diagnosed multiple myeloma (NDMM) is critical for prognostic and therapeutic purposes. The Revised International Staging System (R-ISS) and its update R2-ISS are widely used to identify high-risk disease, but not fully capture prognosis in the era of novel therapies. In 2025, the international Myeloma Society (IMS) and International Myeloma Working Group (IMWG) published new criteria for high-risk MM, incorporating TP53 mutations via next generation sequencing (NGS), concurrent with updated cytogenetic abnormalities. Early validation studies have confirmed the prognostic value of these criteria; however direct comparison across all three systems evaluating multiple clinical endpoints remain limited, and many validation cohorts lack universal TP53 status. We compared clinical outcomes across all three risk stratification systems R-ISS, R2-ISS, and IMS/IMWG classification in a real world NDMM cohort with TP53 mutation status. **Methods:** We retrospectively analyzed 140 NDMM patients, all with NGS-based TP53 mutation testing. Patients were classified by R-ISS (I-II vs III), R2-ISS (I-III vs IV), and IMS/IMWG (standard vs high risk) criteria. Response rates and MRD negativity were compared using Fisher's exact test. Progression free survival from first line (PFS1), overall survival (OS), and time to next treatment (TTNT) were estimated by Kaplan Meier methods with log rank testing and Xox proportional hazards regression. **Results:** Median age was 66.3 years (64% M/36% F); median follow up was 23.2 months. NGS identified TP53 mutations in 35 patients (25%). 2025 IMS /IMWG classified 54% as high risk (75/140, none from b2MG alone) versus 28% by R-ISS stage III (39/140) and 21% by R2-ISS stage IV (30/140) respectively. Sixty-four percent received quadruplet induction; 46% underwent first line ASCT. For PFS1, only IMS/IMWG significantly differentiated outcomes: median 29.6 vs 67.8 months for high vs standard risk (HR 1.78, 95% CI 1.02–3.09; p = 0.041), while R-ISS (HR 1.41, p = 0.22) and R2-ISS (HR 1.57, p = 0.12) did not reach significance. Similarly, TTNT was significantly shorter for IMS/IMWG high risk patients (median 29.9 vs 76.3 mo; HR 2.23, 95% CI 1.22–4.07; p = 0.009). For OS, R2-ISS provided the strongest discrimination (median 45.4 vs NE months;

HR 2.84, p = 0.004), followed by R-ISS (HR 2.33, p = 0.019), while IMS/IMWG showed a trend (HR 1.95, p = 0.09). MRD negativity was significantly lower for R2-ISS stage IV (36% vs 69%, p < 0.01). **Conclusions:** In this NGS-annotated real world cohort, the IMS/IMWG high risk definition was the only classification to significantly differential PFS1 and TTNT, identifying a broader high risk population with distinctly inferior early outcomes. Conversely, R-ISS and R2-ISS provider stronger OS discrimination. These complementary prognostic profiles suggest that integrating newer genomic-based and established staging may optimize risk adapted treatment strategies in NDMM. Prospective validation in larger cohorts is warranted.

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Next Generation Flow (NGF) Identifies Peculiar Aberrant Subtypes of Clonal Plasma Cells in Newly Diagnosed Multiple Myeloma Patients: A Single Center Experience on 293 Patients

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Introduction: Complete remission (CR) is a prerequisite for long term responses, PFS, OS and cure. In the era of novel agents, many MM patients can achieve stringent CR (sCR). Most of these patients will relapse and minimal residual disease (MRD) detection will play a crucial role. Since 2017 two 8 colours tubes panel developed by the EuroFlow Consortium can detect MRD with an increased sensitivity (≥ 1 in 105 cells) and can be applied as standardized method to study MM patients. Minimal residual disease status measured both by multi parametric-FLOW cytometry (next generation flow) or next generation sequencing is a consolidated new prognostic parameter in multiple myeloma trials (threshold at 10–5 according to IMWG guidelines). We report our decennial experience on MRD on 363 MM patients studied with multi -flow (293 with NGFand since diagnosis). **Methods:** At the Hematology, University of Siena, AOUS Policinico Le Scotte, we applied Multi-flow technique to the study of bone marrow aspirates since 2016. Euroflow standardized protocol was introduced in our Lab in 2019. Specimens were processed within 12 h of collection, with a fix and perm protocol, staining an high numbers of cells with 2- tubes optimized 8-colours antibody panel (One Flow PCST e PCD BD Biosciences), acquisition was considered adequate when a significant PC population was detected or a minimum of 2 × 106 cells was acquired. Discrimination between phenotypically aberrant (aPCs) and normal (nPC) was also acquired and upon the recommendations of the European Myeloma Network. **Results:** 363 multiple myeloma patients were studied (70 from January 2016 and December 2018; 293 since January 2019 and May 2026). The latter one were newly diagnosed MM patients studied with NGF protocol. Median age was 69 (range 38–90). Male/Female 172/121. PC populations were identified by gating on cells with CD138 positivity and strong CD38 expression. CD45 and light scatter properties were also examined, to exclude debris, doublets and lymphocytes. nPCs and aPCs are defined based upon a normal or abnormal pattern of expression of others antigens. The median percentage of Plasmacells was 7(range 0.01–77). We observed heterogeneity of the plasma cell immunophenotype at diagnosis: CD45 was pos in 255/293 (87%); CD19 in 283/293 (97%); CD56 Pos/DIM in 215/293 (73%). CD28 Pos in 118/293 (31%). CD81 in 2152/293 (52%) and CD117 Pos in 127/293 (43%). All clinical and genetic data at diagnosis were available and correlations are underway. **Conclusions:** In a 10 years experience NGF was applied to 293 MM patients at diagnosis and as MRD evaluation after therapy. An heterogeneity of the diagnostic immunophenotype was found with aberrant peculiar cases. Clinical and laboratory data will be showed.

PA-320

NSD2 Induces Global Chromatin Changes to Potentiate IL-6 Signaling in Multiple Myeloma

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Introduction: The t(4;14) translocation causes overexpression of NSD2 in ~12% of patients with multiple myeloma (MM) and is associated with poor clinical outcomes. NSD2 catalyzes dimethylation of histone H3 lysine 36 (H3K36me2), which is dramatically increased in t(4;14) MM. How NSD2 expression and subsequent H3K36me2 promote malignant transformation of plasma cells is poorly understood. **Methods:** A panel of six t(4;14) MM cell lines were treated with the catalytic NSD2 inhibitor KTX-1031 (K36; hereafter NSD2i; 1 μM) or its inactive enantiomer (KTX-1030; 1 μM) as a control. CRISPR/Cas9 was used to knock out the translocated allele of NSD2 in multiple single-cell clones of KMS11 and KMS18. Cell growth in RPMI-1640 media, media supplemented with IL-6, or in 15% HS-5 stromal cell conditioned media was assessed by flow cytometry after 7 days. In KMS11, KMS18, and NCI-H929, global chromatin composition was assessed by mass spectrometry, transcriptomics by RNA sequencing (Kapa), and epigenetic changes by Cleavage Under Targets and Tagmentation (CUT&Tag; Epicypher). CoMMpass data were provided by MMRF/TGEN. **Results:** NSD2i treatment globally depleted H3K36me2 to ~5% of histone H3 in all cell lines tested, down from as much as ~60% in control cells (p < 10e-6). Conversely, the repressive mark H3K27me3 increased 2–4-fold (p < 10e-6). Chromatin profiling revealed an enrichment of H3K36me2 at enhancer elements, and 10%–20% of all enhancers lost H3K27ac (FDR< 0.05) following

NSD2i, indicating NSD2 maintains enhancer activity. NSD2i reversed the t(4;14) gene expression signature observable in patients ($p < 0.05$) and resulted in widespread gene repression, including of AP-1 transcription factors JUN and ATF3 (FDR< 0.05). Results of NSD2i treatment were largely reproduced by genetic ablation of the translocated NSD2 allele. NSD2i treatment impaired cell proliferation in a subset of t(4;14) lines (KMS11, LP-1, KMS34; $p < 0.05$) but did not affect growth in others (NCI-H929, KMS28-BM, KMS18). Analysis of public transcriptomic data indicated that cells that were growth-impaired by NSD2i had higher expression of genes related to IL-6 signaling. Adding IL-6 or conditioned media to non-responsive cell lines induced a proliferative boost to these cells that was abrogated by NSD2i ($p < 0.05$). Finally, t(4;14) patients in CoMMpass showed upregulation (FDR< 0.05) of IL-6 signaling components (IL6, IL6R) and AP-1 transcription factors (JUN, ATF3). **Conclusions:** Here, complementary pharmacologic and genetic approaches demonstrate that NSD2 maintains a globally euchromatic, permissive epigenome which becomes more heterochromatic and repressive upon NSD2 disruption. Furthermore, NSD2i was sufficient to impair cell growth in the context of high IL-6 related signaling. We propose that NSD2 promotes permissive chromatin primed to transduce IL-6 signals into proliferative responses, which is pharmacologically reversible. These results have implications for t(4;14) biology and ongoing clinical trials targeting NSD2 in MM (NCT05651932).

PA-321

NSDHL Drives Glycolytic Reprogramming and Cell Proliferation in Multiple Myeloma Through c-Myc Stabilization

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Introduction: Multiple myeloma (MM) is a highly heterogeneous plasma cell malignancy characterized by frequent relapse and drug resistance. Metabolic reprogramming plays a critical role in MM progression, yet the key regulators involved remain incompletely understood. NAD(P)-dependent steroid dehydrogenase-like protein (NSDHL), a key enzyme in cholesterol biosynthesis, has been implicated in several solid tumors, but its role in MM remains unclear. **Methods:** NSDHL expression and prognostic significance were analyzed using GEO datasets and the MMRF-CoMMpass cohort and validated by Western blotting in clinical bone marrow samples. Stable NSDHL knockdown and overexpression MM cell lines were established to assess proliferation, cell cycle progression, and apoptosis using CCK-8 assays and flow cytometry. Transcriptomic sequencing, untargeted metabolomics, glucose consumption and lactate production assays, and Seahorse metabolic flux analysis were performed to investigate the role of NSDHL in glycolytic regulation. qRT-PCR, Western blotting, immunofluorescence, nuclear-cytoplasmic fractionation, cycloheximide (CHX) chase assays, MG132 treatment, and dual-luciferase reporter assays were used to explore the molecular mechanism underlying NSDHL-mediated regulation of c-Myc and PKM2. Rescue experiments were conducted to verify the role of c-Myc in NSDHL-driven glycolysis and proliferation. **Results:** NSDHL was significantly upregulated in MM samples and associated with advanced ISS stage and poor prognosis. Functional assays demonstrated that NSDHL knockdown inhibited MM cell proliferation, whereas NSDHL overexpression promoted proliferation, without significantly affecting apoptosis or cell cycle distribution. Multi-omics analyses revealed a strong association between NSDHL and glycolytic metabolism. NSDHL knockdown reduced glucose consumption, lactate production, extracellular acidification rate, and expression of glycolytic enzymes including HK2 and PKM2, while NSDHL overexpression showed opposite effects. Mechanistically, CHX chase assays showed that NSDHL depletion shortened the half-life of c-Myc protein, while MG132 partially restored c-Myc levels, indicating involvement of the ubiquitin-proteasome pathway. NSDHL increased c-Myc Ser62 phosphorylation and decreased Thr58 phosphorylation, thereby stabilizing c-Myc. Dual-luciferase assays confirmed that c-Myc transcriptionally activates PKM2. Rescue experiments further demonstrated that c-Myc overexpression partially reversed the inhibitory effects of NSDHL knockdown on glycolysis and proliferation. **Conclusions:** NSDHL is highly expressed in MM and correlates with disease progression and poor prognosis. By stabilizing c-Myc and activating the c-Myc/PKM2 axis, NSDHL promotes glycolytic reprogramming and MM cell proliferation. These findings identify a novel oncogenic role of NSDHL in MM and suggest that the NSDHL–c-Myc–PKM2 pathway may represent a potential prognostic biomarker and therapeutic target.

PA-322

Open-Label, Single-Arm Phase Ib/II Study of Immune Combination Therapy with Belantamab Mafodotin and Elotuzumab in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Belantamab mafodotin plus elotuzumab [Bela-Elo] (NCT05002816) is an ongoing phase Ib/II trial evaluating safety, tolerability and preliminary efficacy of the unique combination of

these two agents in patients with relapsed/refractory myeloma (RRMM). We report data from early follow-up of this trial. **Methods:** This single-arm phase Ib/II study has enrolled patients with triple-class refractory RRMM. Patients with prior progression after BCMA-targeted therapy are included. Elotuzumab is administered via IV infusion at an established dose of 10 mg/kg on days 1, 8, 15, 22 every 28 days for cycles 1 and 2; followed by 20 mg/kg on day 1 of each cycle, cycles every 28 days. Belantamab mafodotin is administered via IV infusion with the starting dose of 1.9 mg/kg IV at every 4-week interval, with subsequent dose-reduction based on toxicity. Descriptive statistics were used to summarize patient demographics and safety and efficacy outcomes. **Results:** As of data cut-of (Apr 30, 2026), 24 subjects were enrolled and received treatment, 3 subjects remain on study treatment. Median age of patients was 66 years (range 50–81), 71% (17/24) were male, 17% were Black or African American, 4% were Asian. The patient population was heavily pretreated. All patients were triple class-refractory, with 8 prior median lines of therapy (range 2–17). A substantial number of patients, 38% (9/24), were relapsed/refractory to a prior BCMA-targeted T-cell redirection therapy [TCRT] (25% had a prior chimeric antigen receptor T (CART) cell therapy, 25% had a prior bispecific TCRT [BITE], 12.5% had received both CART and BITE). Phase I part of the study was previously reported. Thirteen DLT events were observed in 9 patients. Eight serious adverse events were observed related/likely related to the study treatment, including grade 3–4 pneumonia (n = 2), grade 4 sepsis (n = 1). Ocular keratopathy developed in 14 (58%) of patients. All keratopathy events were grades 1–2, except for 1 (4%) grade 3 event. All keratopathy events resolved upon discontinuation or dose-reduction of the study treatment. Grade 3–4 hematologic toxicity included lymphopenia 50%, anemia 8%, thrombocytopenia 12.5%. Clinical efficacy was noted with cumulative overall response of 34.7%, including partial responses (PR) in 5 (22%), VGPR in 3 (13%). Stable disease was noted in additional 11 (47.8%) patients. Median PFS was 3.8 months (95% CI: 2.0 to 5.6). Among the 9 patients who were refractory to prior BCMA-targeted TCRT, one achieved partial response (PR) (11%), stable disease was observed in 6 (67%). **Conclusions:** Conclusion: The combination immune therapy of belantamab mafodotin and elotuzumab appears to have an encouraging safety profile and a promising activity in patients with heavily pretreated RRMM, including in those with prior failure of BCMA-targeted T-cell redirection therapy. Funding and Product for this study was provided by GSK NCT05002816.

PA-323

Opposing Effects of Prevotella Species in Multiple Myeloma are Driven by Distinct Molecular Mechanisms

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Introduction: We previously showed that in transgenic Vk*MYC mice, the human commensal Prevotella heparinolytica (P.h.) promotes a pro-tumorigenic Th17 response, whereas Prevotella melaninogenica (P.m.) delays smoldering multiple myeloma (mSMM) progression and synergizes with anti-PD-L1 immunotherapy. However, the cellular and molecular mechanisms driving this protective immune reprogramming remains unknown. Here, we defined the distinct pathways through which P.m. dampens systemic inflammation and restrains MM progression. **Methods:** We performed transcriptomic profiling (RNA-seq) on mouse dendritic cells (DCs) stimulated in vitro with inactivated P.m. or P.h., or Escherichia coli (E.c.) as control. Receptor dependency was investigated using TLR4 knockout (TLR4-/-) DCs and TLR2-blocking antibodies. Findings were validated in human CD11c +/HLA-DR+ DCs. Implementing the in vivo t-VkMyc model, we evaluated how the two Prevotella strains alter host gut microbiota and metabolic profiles via 16S rRNA sequencing and targeted stool NMR metabolomics. **Results:** Volcano plot and transcriptomic cluster analyses revealed that P.h. and E. coli induce a highly overlapping pro-inflammatory gene signature in DCs. Conversely, P.m. suppresses these canonical inflammatory pathways, downregulating key response genes such as Cxcl10, Il12b, and Il23a, and upregulated genes belonging to sterol metabolism pathways. Mechanistically, while P.h. activation relied on both TLR2 and TLR4 pathways, P.m. acted exclusively through TLR2, driving a selective signaling cascade that avoids TLR4-mediated inflammation. Consequently, P.m.-stimulated DCs adopted a less inflammatory phenotype and produced lower levels of IL-1b and IL-6—pro-Th17 cytokines— than P.h.-stimulated DCs. In vivo, P.m. reshaped the gut microbiota, favoring the enrichment of short-chain fatty acid (SCFA) producers such as Lachnospiraceae and Bacteroidaceae. This microbial drift was functionally confirmed by targeted NMR, showing a marked expansion of luminal acetate and butyrate in P.m.-gavaged mice compared to controls. Finally, butyrate-conditioned DCs mirrored the P.m.-induced phenotype. **Conclusions:** We demonstrate that P. m. mitigates systemic pro-tumorigenic inflammation via an exclusive TLR2-dependent "silencing" signature in DCs—repressing IL-1b production across species—and actively shapes a beneficial gut ecosystem enriched in anti-inflammatory SCFAs. These findings pave

the way for targeted microbiome-based therapeutic strategies to intercept MM aggressiveness.

PA-324

Optimized Computationally Engineered CD70-Targeting Virus-Free CRISPR Knock-in CAR T Cells for High-Risk Multiple Myeloma

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Introduction: Multiple myeloma (MM) remains incurable despite major advances in immunotherapy. Although BCMA-targeted CAR T-cell therapies improve outcomes, patients with high-risk cytogenetic features frequently relapse and require additional options. CD70 is expressed in a subset of high-risk MM, including t(4;14) and gain 1q, and is associated with poor clinical outcomes, supporting its development as an alternative target. Virus-free CRISPR-mediated TRAC knock-in provides a controlled, non-viral engineering strategy that may reduce risks from random viral integration and improve manufacturability. **Methods:** We developed a computationally optimized CD27-based CD70-targeting CAR incorporating an N88A modification designed to enhance binder performance. Virus-free CAR-T cells were generated by CRISPR-mediated TRAC knock-in using Cas9 ribonucleoproteins and an ssDNA donor template. Dual sgRNAs were used to knock out endogenous CD70 and reduce T-cell fratricide. We compared CD28ζ, 4–1BBζ, and 1XX signaling backbones, alongside a TRAC/CD70 double-knockout control. Cells were expanded in G-Rex culture systems. Efficacy was evaluated using in vitro cytotoxicity assays and an LP1 t(4;14) high-risk MM xenograft model monitored by serial bioluminescence imaging and CAR-T cell expansion in peripheral blood flow cytometry along with memory and exhaustion phenotypes. **Results:** G-Rex culture promoted faster recovery and greater expansion of engineered CAR-T cells compared with traditional methods. All N88A anti-CD70 CAR-T constructs showed potent anti-myeloma activity in vitro and in vivo. In the LP1 model, a low dose of 50,000 CAR-T cells achieved tumor clearance across backbones, with robust in vivo expansion of CD27-based CAR-T cells. Among signaling domains, 1XX emerged as the lead candidate, achieving tumor control comparable to CD28ζ and 4–1BBζ while showing greater expansion. Bulk RNA-seq and cytokine profiling showed that 1XX CAR-T cells maintained a more memory-like transcriptional state and a more restrained cytokine profile than CD28ζ. We are now generating 1XX CAR-T cells using dsDNA Nanoplasmid donors, achieving efficient TRAC knock-in with robust CD70/TRAC double knockout, which simplifies the workflow and may reduce manufacturing time and cost. **Conclusions:** The optimized N88A anti-CD70 CAR-T cell represents a potent strategy for high-risk MM. Non-viral manufacturing is feasible using GMP-compatible devices, and the 1XX signaling backbone provides a favorable balance of efficacy, expansion, and phenotypic fitness for future clinical translation. Ongoing work is advancing dsDNA Nanoplasmid-based engineering along with mRNA spCas9 and GMP-scale manufacturing using G-Rex reagents.

PA-325

Optimizing Risk Stratification in Newly Diagnosed Multiple Myeloma, the role of NGS on the New Consensus Genomic Staging: A multicenter descriptive study.

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Introduction: Although survival in multiple myeloma (MM) has improved substantially, clinical outcomes remain heterogeneous and traditional staging systems such as the Revised International Staging System (R-ISS) fail to fully capture genomic risk in the era of novel agents. To address this, the International Myeloma Society (IMS) and the International Myeloma Working Group (IMWG) proposed the Consensus Genomic Staging (CGS) for high-risk MM, defined by at least one of the following: del(17p) with clonal fraction >20% and/or TP53 mutation; IgH translocations [t(4;14), t(14;16), or t(14;20)] combined with 1q gain and/or del(1p32); monoallelic del(1p32) with 1q gain or biallelic del(1p32); and β2-microglobulin ≥5.5 mg/L with preserved renal function. This study evaluates CGS in a real-world cohort and examines the added value of NGS in risk stratification. **Methods:** Multicenter retrospective and descriptive study of bone marrow samples from newly diagnosed MM (NDMM) patients at referral hospitals in Alicante, Spain (March 2023–April 2024). From 60 collected samples, 11 were excluded (uncertain diagnosis or loss of follow-up), yielding a final cohort of 49. FISH was performed on CD138-selected plasma cells (MACSprep™ CD138 MicroBeads, Miltenyi Biotec) to detect IgH translocations, del(17p), 1p/1q abnormalities, and ploidy changes. Genomic profiling used NGS on the Illumina NextSeq 1000 platform. Risk redistribution between R-ISS and CGS was assessed by cross-tabulation and a Sankey diagram. **Results:** A total of 49 patients were evaluated (median age 63.7 years; 57.4% male). The CGS was applicable to 41 patients, classifying 25 (61%) as low-risk and 16 (39%) as high-risk. Comparative analysis between R-ISS and CGS (n = 40) revealed a global concordance of 65%, with 35% of cases being discordant. Specifically, 27.3% of R-ISS stage I and 39.1% of R-ISS stage II patients were upgraded to high-risk CGS. Conversely, 33.3% of R-ISS stage III patients were

downgraded to low-risk CGS. Regarding TP53 status, 10.2% of patients carried an isolated del(17p), 4.1% harbored a double-hit profile, and 12.2% presented exclusively with a TP53 mutation. Biologically, pathogenic mutations grouped via NGS were predominantly concentrated in two primary axes: the DNA damage response (DDR) and cell cycle regulation pathway (36%, led by ATM and TP53) and the mitogenic MAPK/ERK signalling cascade (28%, driven by KRAS, NRAS, BRAF, and FGFR3). **Conclusions:** The implementation of the CGS identifies 39% of NDMM patients in our cohort as high-risk. Integrating NGS testing into routine clinical practice offers substantial utility, successfully capturing the 12.2% of patients with isolated TP53 mutations who would otherwise be misclassified as low risk by standard FISH testing. Finally, genomic vulnerability in raw MM sample events remains heavily concentrated within the DDR/cell cycle and MAPK/ERK molecular networks, highlighting potential targets for risk-adapted therapeutic strategies.

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Outcomes of ≥3 BCMA-Directed Therapies in Relapsed/Refractory Multiple Myeloma: A Case Series from the Retrospective, Multicenter Real-Word SEQ-BCMA Study

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Introduction: BCMA-directed CAR T-cells (CAR T), bispecific antibodies (bsAb) and antibody-drug conjugates (ADC) have transformed the management of relapsed/refractory multiple myeloma (RRMM), but most patients (pts) eventually relapse. Pts relapsing after a BCMA-targeting therapy (BCMA-Tx) represent an unmet medical need, and evidence on BCMA re-challenge beyond two lines of BCMA-Tx is scarce. We analyzed pts from the multicenter SEQ-BCMA cohort who received ≥3 sequential BCMA-Tx. **Methods:** SEQ-BCMA is a retrospective, multicenter, real-world analysis of RRMM pts that had received ≥2 BCMA-Tx, regardless of the number of interim treatment lines. For this case series, we included pts who received ≥3 BCMA-Tx. Baseline characteristics, response (IMWG) and safety were summarized descriptively. Progression-free survival (PFS) was estimated using Kaplan-Meier (KM), median Follow-up (mFU) by reverse KM. **Results:** Of 180 pts from 21 centers in Germany, Austria, and Switzerland that were included in the SEQ-BCMA study, 12 pts met criteria of ≥3 lines of BCMA-Tx (7 with 3 BCMA-Tx, 5 with 4 BCMA-Tx). Median age at 2nd BCMA was 67.5 years (range 43–75); 67% were male. Pts were heavily pretreated at initiation of 3rd BCMA-Tx with median 9 prior lines (range, 4–12; 100% post-ASCT; 100% triple-class, 75% penta-drug and 42% hepta-drug refractory). Baseline extraosseous extramedullary disease was present in 17% and high-risk cytogenetics according to R-ISS in 33%. The 1st BCMA-Tx was CAR-T in 42%, bsAb in 25% and ADC in 33%; ORR was 78% in 7/9 evaluable pts with ≥nCR in 2/9 (22%). The 2nd BCMA-Tx was bsAb in 42%, ADC in 25% and CAR T in 33% with an ORR of 78% in 7/9 evaluable (ev.) pts; and ≥CR in 3/9 (29%). In 2nd BCMA-Tx, infections occurred in 3/11 (27%), no ICANS and only low-grade CRS in 4/11 (36%). BCMA expression was assessed in only 1/9 ev. pts before 2nd BCMA-Tx. At the 3rd BCMA-Tx (CAR-T 50%; bsAb 42%, ADC in 8%), ORR was 5/10 (50%) and ≥nCR reached in 3/10 (30%) ev. pts. Adverse events were more frequent: CRS in 6/12 (50%, 1x G3), ICANS in 2/12 (17%, 1x G3), infections in 5/12 (42%, 2x G3). 5 patients proceeded to a 4th BCMA therapy (4x CAR-T, 1x bsAb+CD38; 2x VGPR, 2x SD, 1x PD). Median PFS was 5.8 months (mo, 1st BCMA-Tx), 5.7 mo (2nd), 3.5 mo (3rd) and 1.9 m (4th, n = 5). At a median follow-up of 45.4 mo from 1st BCMA-Tx (95% CI, 04.62 to NR), OS was 58% (7/12 pts). **Conclusions:** In this case series of heavily pretreated RRMM pts, a third BCMA-Tx was feasible and yielded clinically meaningful responses in a subset of pts, while infections were increasingly frequent and the majority of pts progressed within months. All pts received at least one cross-class BCMA construct switch, and CAR-T was the most frequently selected 3rd- and 4th-line BCMA-Tx. These descriptive observations highlight an unmet need and support further investigation of biomarker-guided sequencing strategies for late-line BCMA retreatment.

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Outcomes of Multiple Myeloma Patients with del17p with Coexistent Trisomy/Tetrasomy 17

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Introduction: IMS-IMWG consensus identified del17p with a cutoff of ≥20% clonal fraction, TP53 mutation, or both as one of the criteria for high-risk myeloma. However, limited data exists on outcomes of myeloma patients with del17p with coexistent trisomy/tetrasomy 17. In a 21-patient series with del17p with trisomy/tetrasomy 17, their progression free survival (PFS) and overall survival (OS) were shown to be similar to the general del17p cohort. In this large retrospective analysis, we have evaluated long-term outcomes of myeloma patients with del17p with trisomy/tetrasomy 17. **Methods:** Among the 421 myeloma patients with del17p identified at Emory from 3/1/1999 until 6/30/2021, 164 patients with de novo and 171 patients with acquired del17p were included in this analysis. Descriptive analyses were performed within the del17p cohort, including evaluating associations with trisomy/tetrasomy 17. Survival outcomes were estimated using Kaplan–Meier method and compared with log-rank tests. Univariate and multivariate Cox proportional hazards models were used to assess associations with PFS and OS. Statistical analyses were performed using SPSS version 31.00, with significance set at $p < 0.05$. **Results:** In the overall evaluable cohort of del17p patients (N = 388), with a median follow-up of 105 months for PFS and 141 months for OS, median PFS and OS were 31 months (95% CI 26.3–35.6) and 74.2 months (95% CI 63.3–85.1) respectively. Median PFS and OS for de novo del17p were 27.4 months (95% CI 22.8–31.9) and 56.6 months (95% CI 43.3–69.9) and for acquired del17p, were 33.4 months (95% CI 26.9–39.7) and 89.9 months (95% CI 78.5–101.4), respectively. 125 (76%) patients in de novo and 117 (68%) patients in acquired cohorts respectively had del17p with ≥20% clonal fraction. For ≥20% vs < 20%, de novo - median PFS 24.5 vs 51.0 ($p = 0.087$) and median OS 43.9 vs 116.3 ($p = 0.002$); acquired - median PFS 30.4 vs 44 ($p = 0.003$) and median OS 83.1 vs 122.0 ($p = 0.012$), thereby validating IMS-IMWG criteria with unfavorable outcomes for del17p with ≥20% clonal fraction. Within the de novo cohort, 42 (26%) and in acquired cohort 47 (28%) had coexistent trisomy/tetrasomy 17. For patients with trisomy/tetrasomy 17 vs none, de novo - median PFS and OS were 40.9 vs 24.5 ($p = 0.161$) and 116.3 vs 49.3 ($p = 0.003$) respectively; acquired - median PFS and OS were 29.1 vs 36.1 ($p = 0.61$) and 106.1 vs 86.3 ($p = 0.15$), respectively. In de novo cohort, univariate analysis revealed inferior OS in del17p with clonal fraction ≥20% [HR 2.11, 95%CI 1.2–3.8; $p = 0.014$], and superior OS with trisomy/tetrasomy 17 [HR 0.49, 95%CI 0.3–0.9, $p = 0.012$]. **Conclusions:** De novo del17p patients with coexistent trisomy/tetrasomy 17 have significant superior OS in this dataset suggesting that these patients may not have the same adverse outcomes as other del17p patients. This is the first time this prognostic finding has been reported. We also validated IMS-IMWG high risk criteria for del17p patients with clonal fraction of ≥20% with inferior OS.

PA-328

Outcomes of Multiple Myeloma with an Isolated Bone Lesion and Limited Marrow Involvement Treated with Localized Radiotherapy Alone

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Introduction: By the 2014 IMWG definition, a solitary bone plasmacytoma with minimal marrow involvement (SBPmm) is a biopsy-proven solitary bone lesion of clonal plasma cells (cPCs), with cPCs in the bone marrow (BM) comprising < 10% of marrow cellularity, without CRAB features or further lesions on comprehensive imaging. SBPmm is treated with local radiotherapy (RT) to the lesion to achieve durable control, yet high risk of progression to multiple myeloma (MM) remains. Occasionally, patients otherwise similar to SBPmm meet criteria for MM with 10–20% cPCs in their BM; herein, we refer to this entity as low-burden MM (LB-MM). While upfront systemic therapy is standard for newly diagnosed MM, select LB-MM patients may receive localized RT alone to their solitary lesion due to patient-specific conditions, akin to SBPmm. We offer the first report of the outcomes in such cases. **Methods:** We included SBPmm patients and LB-MM patients seen at our institution from 2010 to 2025 who received RT monotherapy to their SBP. FISH was performed on cPCs from either BM aspirate or lesion biopsy. High risk (HR) FISH included t(4;14), t(14;16), t(14;20), del(17p), and 1q gain or amplification. Pearson Chi-Squared and Fishers Exact Tests were utilized. Time to progression (TTP) was analyzed using Kaplan-Meier method by log-rank test. **Results:** A total of 105 patients were included; 93 had SBPmm and 12 had LB-MM. Median age at diagnosis was 63 and 71 years respectively ($p = 0.015$). Median BMPCs were 3% for SBPmm and 15% for LB-MM. At diagnosis, 70 (75%) SBPmm and 11 (92%) LB-MM patients had measurable

serum M protein (p = 0.29). No LB-MM patients met IMWG criteria for HR Smoldering MM. FISH cytogenetics were known for 85 patients (81%) of which 35% and 20% were HR respectively. The median RT dose was 40 Gy vs 33 Gy respectively (p = 0.013). Six months (mos) after RT, 36 (45%) SBPmm and 5 (63%) LB-MM patients still had an M protein > 0.5 mg/dL (p = 0.46). At a median follow-up of 58 mos, 67 (72%) SBPmm patients and 9 (75%) LB-MM patients had progressed, requiring systemic therapy. Median TTP to MM was not significantly different: 18 mos (IQR: 8–46) in SBPmm versus 24 mos (IQR: 11–48) in LB-MM (p = 0.89). Of these, 30 (32%) SBPmm and 2 (17%) LB-MM patients progressed within 12 months of diagnosis. Among 9 LB-MM progressions, 8 had new out-of-field bone lesions and 1 met SLIM criteria with elevated light chains. None experienced MM progression after a median 11 mos following start of systemic therapy. **Conclusions:** This is the first report of outcomes in LB-MM patients treated with localized RT in a manner akin to SBPmm. While most patients ultimately required systemic therapy, TTP did not differ between LB-MM and SBPmm, suggesting in select cases where immediate systemic therapy is not feasible, localized RT to the isolated bone lesion may serve as a temporary management strategy. Of note, with limited follow-up, no early relapses were observed following systemic therapy in LB-MM patients first managed with RT alone.

PA-329

Outcomes of Outpatient Step Up Dosing (SUD) of Teclistamab (Tec) and Talquetamab (Tal) in Relapsed/Refractory Multiple Myeloma (RRMM): Findings from Academic and Community Practices in the USA

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Introduction: Tec and Tal are first-in-class bispecific T-cell engagers approved in the US for RRMM and use SUD to mitigate the risk of CRS and ICANS. The USPI recommends inpatient (IP) administration with 48-hour observation for Tec SUD1/SUD2 and for all Tal SUD; Tec first treatment dose may be outpatient (OP). To expand access and reduce healthcare resource utilization (HCRU), SUD is increasingly initiated in fully OP or hybrid (HY; patients [pts] may have a mix of IP and OP SUD doses) settings. This study evaluated safety outcomes and HCRU across OP, IP, and HY settings for Tec and Tal SUD. **Methods:** Electronic medical record data from a consortium of US academic and community centers (Consortium) and a large network of US community oncology practices (Community) were analyzed for pts (≥18 years) with RRMM receiving Tec (from Oct 2022) or Tal (from Aug 2023). Pts were categorized by SUD setting: OP, IP, or HY. Baseline characteristics, frequency/severity of CRS and ICANS, hospitalization rates and length of stay (LOS) were summarized descriptively. **Results:** The Consortium cohort had 312 pts (OP: 52; IP: 217; HY: 43) and the Community cohort had 151 pts (OP: 41; IP: 60; HY: 50) with comparable baseline characteristics. Median age (OP/IP/HY) was 72.5/68/66 years (Consortium) and 70/71/69.5 years (Community); median prior lines was 5 in Consortium and 4 in Community. In the Consortium cohort, the 14-day CRS rates were 23.1% in OP pts (IP: 53.9%; HY: 55.8%); no grade (G) ≥3 CRS events in OP and HY (3 G3 events in IP). Prophylactic toci and dex were used in 7.7% and 9.6% of OP pts, respectively (IP: 4.6%/6.0%; HY: 2.3%/0%). The 14-day ICANS rates were 1.9%, 10.1%, and 9.3% among OP, IP, and HY pts, respectively; all G1/2 among pts with known grading. All CRS and ICANS resolved and all pts completed SUD. All-cause hospitalization was captured only during SUD due to data availability and occurred in 7.7% of OP pts, with the shortest median LOS of 5.5 days (IP: 9; HY: 6). Among Community pts, 14-day CRS rates were similar across settings (OP: 46.3%; IP: 45%; HY: 58%) and primarily G1/2 with 1 G3 CRS in the OP. The 14-day ICANS rates were low among OP and IP pts (OP: 2.4%; IP: 5%; HY: 14%) and primarily G1/2 except 1 G4 event in the IP. All CRS and ICANS resolved; SUD was completed by most OP (97.5%; 1 pt moved to hospice) and HY pts (96%; 1 pt had ICANS; 1 pt had infection), and all IP pts. No prophylactic toci or dex were used. All-cause hospitalization within 14 days of treatment initiation occurred in 29% of OP pts with a median LOS of 3 days (IP: 9; HY: 2). **Conclusions:** Across practice settings, OP SUD for Tec and Tal resulted in CRS rates comparable to IP SUD, with fewer hospitalizations and shorter LOS. ICANS may be overreported in the real world, as certain symptoms (such as mild tremor, confusion, etc.) occurring more frequently in the elderly may be misclassified. These findings support OP SUD as a practical pathway to broaden pt access and reduce HCRU.

PA-330

Outcomes Of Patients Treated With Isatuximab Based Regimens For Relapsed Refractory Multiple Myeloma From British Columbia

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Introduction: Isatuximab (Isa)-based regimens are widely used in treating anti-CD38 sensitive relapsed multiple myeloma. Funded combinations include those with carfilzomib and dexamethasone (Isa-Kd) and pomalidomide and dexamethasone (Isa-Pd). There is limited real-world evidence on the safety and efficacy of these regimens, especially in the setting of lenalidomide refractory patients. This study aimed to evaluate real-world outcomes of Isa-based regimens with a focus on first relapse. **Methods:** We conducted a retrospective cohort study of adult RRMM patients treated with Isa-based combinations from October 2020 to February 2026. Clinical data were extracted from the provincial database and electronic medical records. The main outcomes examined were response rates, progression-free survival (PFS), and overall survival (OS). **Results:** The analysis included 124 patients (92 on Isa-Kd and 32 on Isa-Pd). The median age was 65 and 72 respectively. Both cohorts had a median of 1 prior line of therapy (1–7). High-risk disease, defined by IMWG criteria, was present in 30% of both Isa-Kd and Isa-PD patients. Prior autologous stem cell transplantation was more common in the Isa-Kd group (77% vs. 48%). Prior exposure to lenalidomide was noted in 98% in Isa-Kd and 100% in Isa-Pd, with len-refractory disease in 87% and 78% respectively. Among patients treated with IsaKd, 71% had received one prior line of therapy, compared with 56% treated with IsaPd. Primary refractory and functional high-risk (FHR) disease (defined as progression within 24 months of initial therapy) was seen in 49% of Isa-Kd patients and 40% of Isa-Pd patients. The overall response rate (ORR) for Isa-Kd was 87% (61% very good partial response (VGPR) or better), and 75% (47% VGPR or better) for Isa-Pd. After a median follow up of 19.2 months for IsaKd and 28.2 months for IsaPd, the median PFS (mPFS) was 24.6 months and 17.5 months (P = 0.63), respectively. The median OS (mOS) was not reached in either treatment arm (p = 0.57). In patients treated after one prior line, the mPFS for IsaKd and IsaPd were 24.6 and 23.8 months, respectively (p = 0.97). The mOS was 31.5 months with IsaKd and 45 months with IsaPd (p = 0.86). For those with FHR disease the mPFS between IsaKD and IsaPD was 17 months and 15.9 months, respectively (p = 0.98). The mOS was NR with IsaKd and 32.8 months with IsaPD (p = 0.71). The mOS after progression on Isa-based therapy was 8.63 months. In the Isa-Kd group, 13 (14%) patients discontinued treatment due to toxicity compared to 2 (1%) patients in the Isa-Pd group. **Conclusions:** In this real-world cohort of predominantly len-exposed and refractory patients, both regimens demonstrated high response rates and clinically meaningful disease control. No significant PFS or OS differences were observed. Overall, these findings support the use of both regimens in relapse and particularly in 2nd line lenalidomide exposed patients.

PA-331

Outcomes of Triple-Class Exposed Relapse/Refractory Multiple Myeloma Patients Treated with Carfilzomib-Based Regimens: Real-World, Single Center Study

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Introduction: Real-world data on the efficacy of carfilzomib (K) in triple-class exposed (TCE) relapse-refractory multiple myeloma (RRMM) patients (pts) remain scarce. **Methods:** This retrospective, single-center cohort study included all consecutive TCE RRMM pts (defined as progressed after proteasome inhibitor [PI], Immunomodulatory agent [IMiD] and daratumumab [DARA]) who received ≥1 dose of K, either with dexamethasone alone (Kd) or in triplet combinations. The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety, overall response rate (ORR), and overall survival (OS). Frailty was assessed using the simplified International Myeloma Foundation frailty score (age, ECOG, Charlson Comorbidity Index). **Results:** One-hundred and thirteen pts (50% female), treated from September 1st 2015 to May 1st 2026, were included. Median age was 68 (range, 46–89; 19% >75) years. Nineteen percent were frail. Pts received a median of 2 prior lines (range, 1–6); refractoriness rates to PIs, IMiDs and DARA were 69%, 75% and 89%, respectively. Fifty-four percent were triple-class refractory (TCR), and 58% undergone autologous stem cell transplantation. Median follow-up was 41.5 (95% CI 32.0–41.0) months. K regimens included Kd monotherapy (27%), Kd+ cyclophosphamide (KCyd, (30%), Kd+ pomalidomide (KPd, 25%), Kd+DARA (11%), and others (selinexor, lenalidomide, venetoclax). ORR was 64% (sCR 4%, VGPR 27%, PR 33%). Lower ORR was associated with higher ISS (p = 0.03) and K dose ≤45 mg/m^2 (p = 0.04). Combination therapy had no advantage over K monotherapy (p = 0.24). KPd, KCyd and Kd showed no difference in ORR (p = 0.16) Median PFS was 6.7 (95% CI, 3.9–9.4) months. In a univariate analysis, inferior PFS was associated with higher ISS and R-ISS, Charlson score >1, frailty, prior PI refractoriness, prior IMiD refractoriness, TCR, K given as ≥4th line, and K dose ≤45 mg/m^2. Combination therapy had no advantage over K monotherapy (p = 0.27). In a multivariate analysis (MVA), predictors of shorter PFS were lower K dosage (hazard ratio [HR] 0.29, 95% CI 0.7–2.3, p < 0.001), frailty (HR 1.99 95% CI 1.0–4.0, p = 0.05), higher R-ISS (HR 2.50, 95% CI 1.4–4.3, p = 0.001) and prior IMiD refractoriness

(HR 2.7, 95% CI 1.3–6.0, p = 0.01). Prior PI refractoriness had no effect on PFS in the MVA models. Median OS was 38.6 months (95% CI, 27.3–49.9). Pts achieving PR or better had median OS of 47.1 (95% CI 34.9–59.3) months, compared to non-responders (23.7 months [95%CI 0.0–47.9], p = 0.04). One-hundred and four patients (92%) had at least one adverse event (AE). Thirty-one percent had grade≥3 AE, including anemia (12.4%), neutropenia (10.6%), pneumonia (6.2%), thrombocytopenia (4.4%), peripheral edema (0.9%) and seizure (0.9%). No fatal AEs were reported. **Conclusions:** K-based therapy was safe and effective in TCE RRMM pts. R-ISS score, lower K dose, frailty and prior IMiD refractoriness predict shorter PFS. Combination had no advantage over monotherapy. Larger studies are warranted to define the optimal K-based regimen.

PA-332

Outpatient Administration of Bispecific Antibody Therapy for Multiple Myeloma in Community Oncology Practice

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Introduction: T cell-engaging bispecific antibodies (BsAbs) have demonstrated remarkable efficacy in relapsed/refractory multiple myeloma (RRMM). However, step-up dosing (SUD) requirements to mitigate cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) have largely confined these agents to academic centers, creating significant access barriers. We report the feasibility of a fully outpatient SUD protocol at a community oncology practice. **Methods:** A multidisciplinary BsAb team developed standardized outpatient administration and toxicity management protocols, supported by mandatory pre-treatment checklists. Patients and caregivers completed a 60-minute education session and received medical alert bracelets and home monitoring equipment. Eligibility required continuous caregiver availability, residence within 60 miles of a designated site with tocilizumab access, and absence of significant comorbidities. Nurse-led assessments were conducted every 6 hours during SUD. Prophylactic measures included intravenous hydration, dexamethasone 16 mg (pill-in-pocket), and antipyretics for home use. CRS and ICANS were managed per predefined escalation algorithms. **Results:** Seven RRMM patients underwent outpatient SUD (teclistamab n = 3, talquetamab n = 3, elranatamab n = 1) from March 2025 to February 2026. Four patients (57%) experienced CRS after the first SUD dose: three grade 1 and one grade 2. One patient developed ICANS (grade 1). Three patients were managed at home (acetaminophen in three; dexamethasone in one). Four were managed in the outpatient clinic (acetaminophen in two; oral steroids in one; intravenous steroids in one; tocilizumab in one; intravenous fluids in three). Two patients required hospitalization; only one was attributable to CRS/ICANS. The other hospitalization was due to pneumonia and pain. One upper respiratory infection was noted. No additional infectious complications occurred. **Conclusions:** This experience demonstrates the feasibility of fully outpatient BsAb SUD in a community oncology setting. Most adverse events were manageable at home or in the outpatient setting. Multidisciplinary protocols, caregiver education, and defined eligibility criteria were central to safe implementation. Expanding outpatient BsAb administration to community practices is a critical step toward broadening access to these paradigm-changing therapies. Prospective studies are warranted to validate this approach.

PA-333

Outpatient Desensitisation for iMiD-Induced Delayed Hypersensitivity: Pharmacist- and Nurse-Led Retrospective Case Series

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Introduction: Immunomodulatory drugs (iMiDs) are cornerstone therapies in multiple myeloma; however, cutaneous hypersensitivity reactions occur in approximately 27% of patients receiving lenalidomide and may result in treatment interruption or discontinuation. Desensitisation may facilitate continued therapy in selected patients, but inpatient pathways are resource intensive, whereas outpatient experience is limited. We evaluated the feasibility, safety, and outcomes of a structured pharmacist- and nurse practitioner-led outpatient desensitisation pathway for patients with suspected iMiD-associated delayed hypersensitivity reactions. **Methods:** A single centre retrospective case series was conducted at Peter MacCallum Cancer Centre. Adult patients with myeloma who underwent outpatient desensitisation for suspected delayed iMiD-associated cutaneous hypersensitivity between June 2025 and May 2027 were included. Patients with immediate hypersensitivity reactions or severe cutaneous reactions were excluded. The protocol included graded dose escalation, premedication with prednisolone and cetirizine, patient education and close monitoring via a pharmacist- and nurse practitioner-led outpatient service with haematologist oversight. Outcomes included protocol completion, continuation of iMiD, breakthrough reactions and reasons for discontinuation. **Results:** Five patients underwent outpatient iMiD desensitisation. Reactions ranged from grade 1 rash to extensive eruptions involving >80% body surface area, including one case of DRESS syndrome attributed to co-trimoxazole in the setting of concurrent lenalidomide therapy. Three patients (60%) successfully completed desensitisation and continued iMiD therapy. Breakthrough cutaneous reactions occurred in three patients during dose escalation which did not preclude rechallenge. Two patients discontinued desensitisation due to intercurrent clinical factors, including infection and disease progression, rather than refractory hypersensitivity. **Conclusions:** A

pharmacist- and nurse practitioner-led outpatient desensitisation pathway was feasible and enabled most patients with iMiD-associated delayed hypersensitivity reactions to safely continue treatment without recurrent hypersensitivity reactions. Preliminary findings suggest this approach preserved access to iMiD therapy in most patients, with breakthrough reactions remaining manageable and treatment discontinuation occurring primarily due to intercurrent clinical factors rather than refractory hypersensitivity. By preventing premature discontinuation, this practical ambulatory model may help maintain access to an important therapeutic class. Larger prospective studies are warranted to further evaluate efficacy, safety, and predictors of successful desensitisation.

PA-334

Outpatient Step-Up Dosing of Teclistamab or Talquetamab with Prophylactic Tocilizumab in Patients with Relapsed/Refractory Multiple Myeloma: Real-World Evidence from a Large US Cancer Center

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Introduction: Teclistamab (Tec) and talquetamab (Tal) are widely used T-cell-engaging bispecific antibodies (BsAbs) approved for RRMM. The USPI recommends inpatient (IP) step-up dosing (SUD) to manage CRS and ICANS for SUD 1/2 for Tec and all SUD for Tal. To expand patient (pt) access and reduce resource use, a large U.S. academic center implemented fully outpatient SUD with prophylactic tocilizumab (OP-toci) and hybrid model with IP SUD, toci-managed CRS, and early discharge (Hybrid [HY]). This study describes pt characteristics, 14-day CRS/ICANS rates, and 14-/30-day CRS/ICANS/infection-related hospitalization or readmission, among RRMM pts receiving Tec or Tal SUD. **Methods:** This retrospective chart review included adults with RRMM initiating Tec after October 25, 2022 or Tal after August 9, 2023. OP-toci pts received prophylactic toci [8 mg/kg] within 10 hours of SUD1. HY cohort pts initiated SUD IP; pts who developed CRS received toci and were discharged after resolution to complete SUD OP. OP eligibility for both cohorts required a caregiver, absence of cytopenias requiring transfusion or growth factor, and no significant co-morbidities. **Results:** This study included 45 RRMM pts: 23 in OP-toci cohort (Tec = 7, Tal = 16) and 22 in HY cohort (Tec = 4, Tal = 18). Across OP-toci and HY cohorts, 34.8% and 36.4% were ≥75 years, 13% and 18.2% were Black, 61% and 59% had high-risk cytogenetics, 95.6% and 100% were triple class refractory, 73.9% and 77.3% were penta-drug exposed, and 30.4% and 18.2% had extramedullary disease, respectively. The median prior lines of therapy were 4 (Tec) and 4.5 (Tal) in the OP-toci cohort, and 4.5 (Tec) and 5 (Tal) in the HY cohort. In the OP-toci cohort, no CRS occurred within 14 days of Tec or Tal initiation. Only one Tal pt experienced Grade (G) 1 ICANS within 14-days that resolved with pocket dexamethasone; no recurrent ICANS occurred. Two Tal pts were hospitalized within 30 days: one for dysgeusia-related failure to thrive; one for renal failure. All OP-toci pts successfully completed SUD without Tec or Tal discontinuations. In the HY cohort, 1 Tec pt developed G1 ICANS with concurrent CRS and later had recurrent G1 ICANS, and 1 Tal pt developed G2 ICANS. G1 ICANS was managed with dexamethasone, while G2 was treated with dexamethasone and anakinra per institutional SOP. All CRS and ICANS resolved prior to discharge, and all but one Tec HY pt successfully completed SUD OP. One Tec HY pt was readmitted within 30-days for infection; no 14- or 30-day readmissions occurred in the Tal HY cohort. Interpretation of the Tec HY may be limited due to the small sample size. **Conclusions:** OP SUD can broaden pt access to Tec and Tal and reduce healthcare resource utilization. OP SUD using prophylactic toci can reduce hospitalization with Tec and Tal while a hybrid model facilitates rapid discharge of pts to complete their treatment in the OP setting. Both strategies facilitate broad medical adoption of Tec and Tal across practice settings.

PA-335

Overall Survival in Multiple Myeloma is Improving but Rates of Attrition Remain Unchanged

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Introduction: The classic relapsing and remitting nature of myeloma (MM) is well known. Historically duration of response has shortened with each subsequent line of therapy, with only 15% of patients reaching 4th line treatment (Yong 2016). The myeloma treatment landscape has undergone a groundbreaking evolution in the last decade, and novel therapeutic options including CAR-T and T-cell engagers are breaking the paradigm for patients with relapsed, refractory MM. An updated understanding of rates of attrition, sequencing and clinical trajectories is needed to guide clinical decision making; we derive this from a high-fidelity real world patient cohort. **Methods:** The Haematological Malignancy Research Network tracks all patients diagnosed with a hematological malignancy in Yorkshire and the Humber since 2004, linking laboratory data from a

centralized diagnostic laboratory with medical records, national data on death and cancer registration, area based demographic data and Hospital Episode Statistics. We used the cohort to examine lines of therapy in 3608 patients commencing first line therapy for MM diagnosed 2005–2023. This timeframe predates introduction of front line daratumumab and the routine use of T-cell engagers in UK clinical practice. **Results:** Overall survival has improved across all age groups between 2005 and 2023, with a median survival of 2.7 years (95%CI: 2.3–3.3) for those diagnosed between 2005–2007 and 4.9 years (4.1-NR) for those diagnosed between 2020–2023. Median follow-up 13.7 years (95% CI: 11.6-NR) using reverse KM method. Of the 3608 patients who started first line therapy 1614 (44.7%) have commenced second line therapy, 935 (25.9%) are alive and off treatment without yet requiring second line therapy, 681 (18.9%) died from MM, 315 (8.7%) died from other causes prior to receiving second line therapy, and 63 (1.7%) remain on first line therapy. Overall 426 (12%) of patients have received 4th line therapy, 1318 have died from MM and 453 from other causes prior to receiving 4th line therapy. Just 5% started 5th line therapy. When censored for patients alive but not yet having required next line of therapy, 62% received 2nd line therapy, 38% received 3rd line therapy and 19% received 4th line therapy, closely mirroring the figures reported by Yong et al in 2016. **Conclusions:** Despite substantial gains in overall survival in MM in the last 10 years the proportion of patients reaching later lines of therapy has not substantially changed. This not only implies that gains in survival are driven by therapies received early in the disease course, but underscores that clinical trial data in relapsed refractory MM derive from the very small and therefore atypical subgroup of patients who reach that point. This information is useful for service planning for cellular therapies at later lines of treatment and also crucially highlights the importance of bringing novel therapies earlier in the treatment pathway to maximise their impact.

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Patient Characteristics and Initial Real-World Dosing Experience With Belantamab Mafodotin-Based Combinations for Relapsed/Refractory Multiple Myeloma

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Introduction: Patients (pts) with multiple myeloma (MM) are often initially treated with triplet/quadruplet regimens comprising proteasome inhibitors, immunomodulators, and anti-CD38 therapies (tx). Most pts subsequently experience progression. For pts with relapsed/refractory MM (RRMM), BCMA-directed tx have shown deep, durable responses, with efficacy benefits vs standards of care (SoC). The DREAMM-7 and DREAMM-8 studies showed robust efficacy of anti-BCMA antibody-drug conjugate belantamab mafodotin (belamaf) + bortezomib + dexamethasone (BVd) and belamaf + pomalidomide + dexamethasone (BPd) vs SoC triplets for pts with RRMM who had received ≥1 prior line of tx. A global managed access program was started to facilitate pt access to BVd/BPd. Belamaf gained regulatory approval (UK, April 2025; EU, July 2025). We show pt characteristics and dosing in pts with RRMM who were treated with BVd/BPd outside a clinical study. **Methods:** A retrospective, multi-country chart review examined pts treated with BVd/BPd (Brazil, Italy, UK), in the global managed access program. Pts who received care upon UK market authorization were also included. Data were captured on pt demographics, disease/clinical characteristics, and treatment history. The belamaf treatment period was January 2025–March 2026. **Results:** In total, 106 pts were included; 87 (82%) were treated with BVd and 19 (18%) with BPd. Median treatment period was 154 (interquartile range [IQR] 112–212) days at data cutoff. Median age was 71 (IQR 63–79) years and 12/71 (17%) pts with data available had high cytogenetic risk. Before starting BVd/BPd, pts received a median of 2 (IQR 1–2) prior tx, with 48 (45%) pts being refractory to anti-CD38 agents. At data cutoff, pts had received a mean of 4.4 (standard deviation, 2) doses of belamaf. Most (101/106 [95%]) pts started belamaf on a 2.5 mg/kg dose at planned schedules of Q3W (BVd) or Q4W (BPd, with planned reduction to 1.9 mg/kg Q4W from dose 2), and 5 (5%) pts started belamaf at 1.9 mg/kg. Dose reductions (56% of pts)/delays (72% of pts) were frequent, but 85% of pts remained on treatment. For pts treated with BVd, the median/mean time between doses increased from 3.7/4.0 weeks during the first 3 months of treatment to 6.1/8.7 weeks for Months 6–9. At data cutoff, 64 (97%) of 66 pts who received ≥4 doses were still on treatment. **Conclusions:** Similar to the clinical studies, physicians used extended dosing to improve belamaf tolerability and keep pts on treatment. Real-world belamaf use in earlier lines of tx signifies the unmet need for efficacious tx at first relapse. Funding: GSK (224207). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa. © 2026 European Hematology Association (EHA). Reused with permission. Parts of this abstract were previously accepted and presented at the 2026 EHA Annual Meeting. All rights reserved.

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Patient Experience, Satisfaction and Preference with Isatuximab Subcutaneous On-Body Injector from the Phase 3 IRAKLIA and Phase 2 IZALCO Clinical Trials

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Introduction: Subcutaneous (SC) delivery of isatuximab (Isa), an anti-CD38 monoclonal antibody, has been investigated in clinical trials using a novel on-body injector (OBI). The OBI facilitates hands-free administration through a small, hidden, retractable needle. Two key studies evaluated Isa SC OBI in patients with relapsed/refractory multiple myeloma (RRMM): the Phase 3 IRAKLIA trial (NCT05405166) compared Isa SC OBI with Isa intravenous (IV) plus pomalidomide (P) and dexamethasone (d), and the Phase 2 IZALCO trial (NCT05704049) compared Isa SC OBI with SC manual injection plus carfilzomib (K)-d. Both trials demonstrated the efficacy and safety of Isa SC OBI in MM patients. Here, we summarize available evidence of patient-reported outcomes (PROs) from IRAKLIA and IZALCO. **Methods:** In IRAKLIA, 531 adults with ≥1 prior line of therapy (LOT) were randomized 1:1 to receive Isa SC OBI (1400 mg) or IV (10 mg/kg) weekly in Cycle (C)1, then biweekly, with Pd. IZALCO enrolled 74 adults with ≥1 prior LOT who received Isa SC (1400 mg) via OBI or manually with Kd. In Part 1 of IZALCO, Isa SC was injected manually (C1–6). In Part 2, patients were randomized 3:1 to Isa SC manual (C1–3), then OBI (C4–6) or to Isa SC OBI (C1–3), then SC manual (C4–6). From C7, patients could choose either treatment method. PROs were a key secondary end point in both studies, patient satisfaction at C5 Day (D)15 in IRAKLIA and patient preference at C6D15 in IZALCO, with patient experience assessed during and at the end of treatment with 2 versions of the Patient Experience and Satisfaction Questionnaire (PESQ). Quality of life was evaluated with its specific domain from the EORTC–Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30). **Results:** PESQ completion rates at each cycle were high in both trials, ≥75% through C17 in IRAKLIA and ≥73.8% in IZALCO (except for C12D15, 54.5%). In IRAKLIA, at C5D15, fewer patients on Isa SC OBI reported discomfort (13.8%) and pain (6.9%) from the injection method vs those on Isa IV (discomfort: 16.3%; pain: 10.4%). More Isa SC OBI patients (83.1%) reported time savings with the injection method vs IV patients (32.7%). Throughout the study, higher satisfaction with the injection method was reported in Isa SC OBI vs Isa IV patients. Similarly, in IZALCO, at C6D15, fewer Isa SC OBI patients reported discomfort (0%) and pain (7.7%) vs SC manual patients (discomfort: 18.2%; pain: 18.2%). Most patients (74.5%) preferred Isa SC OBI at C6D15, and after experiencing both injection methods, 90.4% opted to continue or switch to Isa SC OBI from C7 onward. In both studies, global health status score (EORTC-QLQ-C30) remained stable relative to baseline, with no notable differences observed between any of the delivery methods. **Conclusions:** In IRAKLIA and IZALCO, Isa SC OBI recipients reported less injection discomfort and pain and greater satisfaction vs IV or SC manual injection recipients. The results support positive patient experience with Isa SC OBI in RRMM patients.

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Patient Insights on Side Effects from Different forms of Generic Lenalidomide

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Introduction: In October 2025, a Myeloma UK support group leader raised their concerns about the severe side effects many of the group were experiencing due to generic forms of lenalidomide they were taking as part of their myeloma treatment. Members of the group described horrific and debilitating side effects that restricted them leaving the house and living a normal life. We gathered further evidence from the Myeloma UK Advocacy Partner Panel and identified additional patients who were experiencing similar side effects from generic lenalidomide. **Methods:** Qualitative data on the side effects experienced from generic lenalidomide was collected from 8 patients in the support group and a further 9 patients during a focus group on the topic. Manual thematic analysis was undertaken to understand the different side effects and impact on quality of life caused by these treatments. **Results:** The themes of the qualitative data collected were the type of side effect, the severity of the side effect, how long the side effect lasted, the impact of the side effect on quality

of life, and how patients were trying to resolve the side effect. The majority of patients said that they had experienced gastrointestinal (GI) side effects from generic lenalidomide, with diarrhoea the most common side effect described. Skin rashes and fatigue were also reported. The severity of the side effects ranged from moderate to severe, and the most common word used to describe the diarrhoea was extreme. The duration of the side effects ranged from occasionally to days, with some patients describing them as constant, and one saying that the side effects contributed to 'probably the worst two years of my life.' All of the patients reported negative impacts on their quality of life because of the side effects. Many reported that the side effects prevented them doing things that they enjoy, like going for walks, swimming and on holidays. The GI side effects were related to responses from patients who told us that toileting was a problem and there was fear around losing control outside of the home. Some of the patients reported using bile acid sequestrant powders to relieve the GI side effects caused by the generic lenalidomide. They described the relief from the side effects as 'massively life-changing' and 'my life changed overnight.' **Conclusions:** Significant side effects from generic forms of lenalidomide have been reported by patients who are taking this treatment to control their myeloma. These range from diarrhoea and constipation to skin rashes and fatigue. They all have a negative impact on quality of life. The myeloma community need to come together to empower patients to speak about these side effects and their impact and identify solutions to manage these side effects to allow patients to be regain normality in their lives.

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Patient Perspectives on Progression Risk and Treatment Trade-offs in High-Risk Smoldering Multiple Myeloma: A Qualitative Interview and Thresholding Study in the US and Europe

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Introduction: While approximately 50% of patients with high-risk smoldering multiple myeloma SMM (HR-SMM) progress to active multiple myeloma (MM) within 2 years, active monitoring remains the standard of care. As treatments (TXs) emerge to delay progression, understanding patients' tolerance of risk is critical. This qualitative study explored patient perspectives related to progression, the perceived benefits and risks of TX vs monitoring, and the minimum acceptable benefit (MAB) to justify a shift from monitoring to TX. **Methods:** Between Nov 2024 and June 2025, qualitative interviews were conducted with patients ≥ 18 years old with current or prior diagnosis of SMM/HR-SMM in the US and Europe. Interviews explored disease comprehension, perceived risk of progression, the benefit-risk profile of monitoring vs TX, and willingness to initiate TX. Acceptability of TX was evaluated using a thresholding exercise consisting of 4 choices between monitoring and TX. Each choice compared alternatives across dimensions of the risk of severe or mild/moderate health events, monitoring requirements, administration, and time to progression. Time to progression was fixed at 30 months for monitoring and varied for TX based on patient responses. Results were summarized descriptively. **Results:** Twenty-two patients completed the study (mean age 59 years and 13 female). A majority (15/22) reported receiving no specific physician communication regarding progression risk or time to progression. The primary benefits of monitoring identified by patients included reassurance of no progression and early detection of progression (20/22); a subset of patients described monitoring in terms of preventing progression. While most patients identified no risks associated with monitoring, some noted the burden of clinic visits and invasive monitoring. Benefits of TX were identified as delaying progression (21/22) and preserving quality of life (9/22). However, TX-related risks were poorly understood, with patients often conflating therapy side effects with symptoms of myeloma progression. In the thresholding exercise, 18/22 patients chose TX over monitoring in at least one scenario. Of these, 3 selected TX in all choices (MAB< 4 months) and 15 required an additional time to progression of 4–82 months to switch to TX. Four patients preferred monitoring in all scenarios (MAB >88 months). **Conclusions:** The results provide insights into patient perspectives into different approaches to managing HR-SMM. Patients conceptualize benefits of monitoring in terms of reassurance and of TX in terms of potential to delay progression to MM. Most patients would accept a TX that increases time to progression, indicating willingness to accept TX-related risks in order to obtain survival benefit. Limited understanding of the risk of progression reinforces the need for shared decision-making and patient-centric education to align clinical goals with patient preferences.

PA-340

POLB 001, An Oral p38 MAPK Inhibitor for the Prevention of Cytokine Release Syndrome

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Introduction: Cytokine Release Syndrome (CRS) is a potentially severe adverse effect of cancer immunotherapies including CAR T cell therapies and T cell-engaging bispecific antibodies (BsAbs) which carry black box warnings for CRS, and management of CRS requires close monitoring and can be severe if not recognised and treated promptly. Monitoring & management of patients with CRS places

significant strain on the healthcare infrastructure. Initial dosing typically requires inpatient admission, or outpatient care only where patients can remain near the clinical setting with a carer. Availability of a convenient and effective prophylactic could enable an expansion in outpatient delivery. As use of CRS-inducing immunotherapies expands across more indications and earlier lines of therapy improved management strategies are needed. POLB 001 is an oral p38 MAPK inhibitor in development for prevention of immunotherapy-induced CRS. POLB 001 has previously been evaluated in two Phase 1 trials: a first-in-human SAD/MAD PK/PD study and an LPS challenge study, both in healthy subjects. **Methods:** MHC I/II double knockout NSG mice were treated with a CD28 agonist or CD3xCD19 bispecific antibody to induce CRS; POLB 001 was dosed prophylactically. The effects of POLB 001 on T cell killing, proliferation and phenotype were investigated in in vitro models of BCMAxCD3 bispecific antibody induced tumour cell killing using human PBMCs. POLB 001 is being investigated in a non-randomised, single-arm, multi-centre, open label Phase I/II trial in patients with multiple myeloma eligible to receive the bispecific t-cell engager antibody, teclistamab, within its licensed indication. **Results:** In an in vivo CD3xCD19 BsAb-induced CRS model, POLB 001 reduced levels of all cytokines tested (TNF, IFNγ, IL-6, IL-10) at all timepoints, with significant decreases of peak levels ($p \leq 0.05$). In an in vivo CD28-induced CRS model, peak levels of all cytokines tested were reduced;TNF, IFNγ, MIP1A, IL-2, IL-4, IL-6, IL-8, IL-10 (IL-6 & IL-4, $p < 0.05$, IL-8 & MIP1A, $p < 0.01$, IL-2, IL-10, TNF & IFNγ, non-significant). In in vitro models of CD3xBCMA BsAb-induced tumour cell death with human PBMCs, POLB 001 had no significant effect on tumour cell death T cell surface markers (CCR7, 4–1BB, CD25 or CD45RO) or intracellular granzyme B;, a mild increase in CD45RA+ cells was observed in some donors. **Conclusions:** POLB 001 reduced key CRS-associated cytokines and clinical CRS scores in humanised mouse models without impairing BsAb anti-tumour efficacy in in vitro models and had no meaningful impact on T cell phenotype. A Phase I/II trial of POLB 001 in teclistamab-treated patients with multiple myeloma is now commencing.

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Patient-Reported Quality of Life and Real-World Outcomes with Use of Daratumumab Regimens in Newly Diagnosed and Relapsed/Refractory Multiple Myeloma: A Multicenter Study

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Introduction: Daratumumab (DARA), a monoclonal antibody targeting CD38, has transformed the therapeutic landscape for newly diagnosed (NDMM) and relapsed/refractory multiple myeloma (RRMM) due to its superior efficacy in landmark trials. However, there is a paucity of real-world, prospective data on health-related quality of life (HRQoL) with DARA regimens. **Methods:** We performed a prospective, multicenter, observational trial of patients with NDMM or RRMM on standard of care DARA regimens started within 30 days of study entry. The EORTC core quality of life questionnaire (QLQ-C30) was collected at baseline, 3, 6, and 12 months or end of DARA therapy if before 12 months. Mixed effects model was used to analyze changes in HRQoL. DARA combinations, International Myeloma Working Group response assessments, and adverse events of special interest (AESI) were recorded. **Results:** 152 patients enrolled across 4 US centers, 89 (58.6%) NDMM and 63 (41.4%) RRMM. Median age was 67 years (33–89) for NDMM and 71 years (48–90) for RRMM. 94 (61.8%) were male; 21 (13.9%) were Black and 7 (4.6%) were Hispanic or Latino. 19 (12.8%) had Eastern Cooperative Oncology Group performance status 2–3. In the NDMM group, 58 (69.1%) had Revised International Staging System stage II–III disease. In RRMM, median prior lines of therapy was 2 (1–5). 79 (52.7%) received DARA in triplet and 60 (40.0%) in quadruplet regimens.137 patients with QLQ-C30 at baseline and at least one later timepoint were included in HRQoL analysis. There was a significant linear improvement in global health status score from baseline (60.7) to 3 (66.3, $p = 0.006$) and 6 months (71.4, $p < 0.001$), exceeding a minimally important difference of 10. This was maintained at 12 months (69.4, $p < 0.001$) and seen in NDMM and RRMM. We observed significant improvement in all functional (physical, role, emotional, cognitive, social) scales and all symptom scales except for constipation, diarrhea, and financial difficulties. Patients with RRMM had a lesser increase in physical ($p = 0.03$) and role ($p = 0.02$) functioning at 3 months compared to NDMM, indicating earlier improvement in the NDMM group. The NDMM group had a larger decrease in pain at 3 months ($p = 0.009$). Overall response rate was 89.5% in NDMM and 64.2% in RRMM. 54 (71.1%) NDMM and 25 (47.2%) RRMM patients achieved a very good partial response or better. With a median follow-up of 11.6 months, 12-month progression rate was 8.6% in NDMM and 17.9% in RRMM; 12-month mortality rate was 3.9% in NDMM and 9.0% in RRMM. Anemia (64%, 4.7% grade 3) was the most common hematologic AE, followed by leukopenia (38.7%), and lymphopenia (33%). Infection rate was low at 3.3%. **Conclusions:** With ongoing therapeutic advancements and prolonged overall survival, our understanding of HRQoL impact with DARA regimens is critical. In this real-world trial, we saw clinically meaningful enhancement in global health status, functioning, and symptoms with DARA

regimens that were both efficacious and tolerable in patients with NDMM and RRMM.

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Perspectives on Cure in Multiple Myeloma: A Dual Survey of Physician (SAARC) and Patient (India) Perspectives

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Introduction: Background: The concept of 'cure' in multiple myeloma (MM) lacks a universally accepted definition and carries profoundly different meanings for physicians and patients. With therapeutic advances enabling deep and durable remissions, a systematic understanding of perspectives on cure among both providers and patients is needed, particularly in resource-constrained settings. Objectives: To characterize and compare how (1) physicians practicing across SAARC nations and (2) patients with MM in India conceptualize, operationalize, and aspire toward a cure. **Methods:** Two parallel, voluntary, anonymous cross-sectional surveys were administered by IMAGe in March 2026 via SurveyMonkey: (1) a 20-item physician survey targeting SAARC-region clinicians; and (2) a 15-item patient survey targeting MM patients from India. Descriptive statistics were used for all analyses. **Results:** Physicians (n = 106 complete responses; predominantly clinical hematologists; 80.6% from India) defined cure largely in biomedical terms, with sustained MRD negativity for more than five years (76.7%) and off therapy (67.9%) as the dominant thresholds. In contrast, patients (n = 175 complete responses) defined cure in functional and experiential terms: 45.0% cited 'living a normal life', and 43.9% cited 'disease never returning for many years' as their primary criteria for cure. Patients demanded high temporal thresholds: 45.4% required an entire lifetime free of relapse. Both cohorts agreed that treatment-free remission was a central component of cure. Affordability emerged as a critical shared concern: 86.4% of physicians cited affordable therapy as the primary practical priority, while 73.0% of patients rated cost reduction as very or extremely important. The single largest barrier to cure in the physician cohort was the cost of therapy (53.4%). **Conclusions:** A meaningful physician–patient gap exists in how cure is conceptualized in MM, with physicians emphasizing molecular endpoints and patients prioritizing functional normalcy and freedom from treatment. Bridging this gap through structured, personalized communication and integration of patient-reported outcomes into care pathways is essential. Health policy in the SAARC region must urgently address the structural barriers of cost and access that constrain the pursuit of a cure for both clinicians and patients.

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PFS2 Outcomes in DREAMM-8: Belantamab Mafodotin (Belamaf)-Pomalidomide-Dexamethasone (BPd) vs Pomalidomide-Bortezomib-Dexamethasone (PVd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: B-cell maturation antigen (BCMA)–directed therapies have transformed the treatment landscape in RRMM. Belamaf, a BCMA-targeting antibody-drug conjugate, in combination with Pd significantly improved progression-free survival (PFS) vs PVd (hazard ratio [HR], 0.52; 95% CI, 0.37–0.73; P < 0.001) in patients (pts) with RRMM in DREAMM-8 (median follow-up, 22 mo). This PFS benefit was maintained with extended follow-up (HR, 0.49; 95% CI, 0.36–0.67; median follow-up 36 mo); median PFS2 also favored BPd vs PVd (47.1 vs 21.7 mo, respectively; HR, 0.52; 95% CI, 0.38–0.70), indicating sustained clinical benefit over

time. We report PFS2 outcomes from DREAMM-8 in subgroups based on prior therapy to further understand the long-term impact of BPd and inform treatment sequencing. **Methods:** DREAMM-8 (NCT04484623) is a phase 3, randomized, open-label study evaluating BPd vs PVd in pts with RRMM with ≥1 prior line of therapy including lenalidomide (LEN). Pts could not have received prior BMCA-targeted therapy. PFS2 was defined as time from randomization to disease progression after initiation of subsequent antimyeloma therapy or death. PFS2 was assessed based on prior-treatment subgroups. **Results:** In the BPd arm (DCO: Jul 7, 2025; median follow-up, 36 mo), PFS2 benefit was maintained in all subgroups, including pts who were LEN refractory and anti-CD38 exposed/refractory. In LEN-refractory pts, BPd treatment led to almost a 3-fold median PFS2 improvement vs PVd (41.7 vs 15.0 mo). A total of 56/155 pts (36%) in the BPd arm and 93/147 (63%) in the PVd arm received any first subsequent therapy (FST) at data cutoff. Across both arms, 36% of pts received steroids, 28% received anti-CD38 therapies (>50% of pts with any subsequent therapy in each arm), and 23% received proteasome inhibitors as FST. Of pts receiving FST (n = 149), 21 (14%) received novel therapies (BPd, n = 6 [11%]; PVd, n = 15 [16%]), including BCMA-targeted bispecific antibodies (bsAbs), non-BCMA bsAbs, CELMoDs, venetoclax, and belamaf. Improved median PFS2 was observed in patients who had novel therapies as FST (n = 21) vs non-novel agents (n = 128) (26.0 vs 20.1 mo; HR, 0.61; 95% CI, 0.34–1.09). **Conclusions:** BCMA-directed therapy, BPd, resulted in improved PFS2 outcomes vs PVd, demonstrating sustained clinical benefit beyond initial belamaf therapy. This benefit was seen regardless of prior treatment, with LEN-refractory pts experiencing almost a 3-fold PFS2 benefit, and despite a higher proportion of pts receiving novel therapies as FST in the PVd arm. PFS2 benefit with high use of subsequent anti-CD38 agents supports sequencing of belamaf combinations early in the treatment paradigm prior to anti-CD38 agents. Sponsorship: GSK (study ID 207499) Copyright statement © 2026 American Society of Clinical Oncology, Inc. Reused with permission.

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Pharmacodynamic Immune Changes and Cell Type Correlates of Response, Cytokine Release Syndrome (CRS), and Infection Across Linvoseltamab (LINVO) Combination Regimens in RRMM (LINKER-MM2)

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Introduction: LINVO (BCMA × CD3) in combination with anti-CD38 monoclonal antibodies (mAbs), proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), immune checkpoint inhibitors (ICIs), and a gamma secretase inhibitor (nirogacestat) is being evaluated in relapsed/refractory multiple myeloma (RRMM; LINKER-MM2; NCT05137054). These combinations are hypothesized to exert anti-myeloma activity via direct and indirect immune-cell modulation and may synergistically activate T cells. In-depth immune-cell profiling was performed before and after monotherapy and combination therapy to identify baseline and on-treatment immune correlates of response and adverse events. **Methods:** Flow cytometry phenotyping of T, B, NK, and monocyte cell subsets in blood (n = 164) and bone marrow (BM; n = 131) was performed before/during treatment. Cytokines were quantified by MSD V-PLEX assay pre/post–LINVO infusion. Fold change (FC) in immune cell subsets was compared by time point or clinical response, CRS, or infection, and assessed by Wilcoxon rank-sum test ($p < 0.05$ reported). **Results:** LINVO monotherapy modestly induced CD4/8 T-cell activation/proliferation, increased $CD38^+$ relative to $CD28^+$ CD4 central memory/effector memory (EM) T cells, and depleted B cells after step-up dosing. IMiDs and ICIs induced earlier broad T-cell activation relative to other combinations. By Week 8, activated/proliferating CD8 EM ($Ki67^+HLA\text{-}DR^+PD\text{-}1^+CD45RO^+$; FC 1.5–14.1) were observed across regimens. Anti-CD38 mAbs strongly activated effector CD4/8 (>14-fold CD4 EM) and depleted $CD38^+$ cells; ICIs increased cytotoxic effectors with limited proliferative capacity ($CD57^+KLRG1^+HLA\text{-}DR^+$; FC 1.9–4.5); PIs induced CD4 activation (FC 2.3); and IMiDs induced ICOS costimulation, regulatory T-cell (Treg) activation, and CD8 dysfunction (FC 1.9–4.5) with persistent IL-8 elevation. At baseline, responders (n = 110) had higher activated cytotoxic CD8 EM/EM re-expressing CD45RA (EMRA; $CD27^-CD28^-CD38^+$; FC ≥3.3; blood). Nonresponders (n = 17) had more suppressive $KLRG1^+$ Tregs (FC ≥1.8; blood) and conventional CD4T cells co-expressing $CD38^+HLA\text{-}DR^+KLRG1^+CD57^+$ (FC ≥1.5; BM). On treatment, responders had expansion of cytotoxic CD8 EM/EMRA ($CD27^-CD28^-CD57^+$; FC ≥5.1; blood) and a trend toward higher IL-2, IL-8, and IFN-γ. Nonresponders had persistent $KLRG1^+$ Tregs (FC ≥1.5) with elevated IL-10, TNF-α, and IFN-γ. CRS was predominantly observed during monotherapy. Grade (G) 2–3 CRS was associated with higher baseline monocyte/T-cell activation (blood), $CD38^+/CD57^+$ T effector cells (BM), and proinflammatory cytokine inductions. G3–5 infection correlated with baseline CD8 effectors (blood), CD4 EM (BM), and on-treatment $CD57^+$ CD8 EM/EMRA elevations. **Conclusions:** LINVO combinations induce diverse T-cell activation patterns, including cytotoxic effector, differentiated, and senescent cells, with distinct features per regimen. Response was associated with more cytotoxic CD8 EM/EMRA prior to treatment; suppressive Tregs and $CD4^+$ T-cell dysfunction characterized nonresponse.

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Pharmacological Inhibitors of Mutant Ras: Preclinical Studies, Biomarkers of Response and Rational Design of Combination Regimens

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Introduction: KRAS or NRAS mutations are present in ~50% of MM patients at diagnosis and at higher frequency in relapsed/refractory disease. Pharmacologic Ras inhibitors are clinically active in select solid tumors. We thus evaluated the efficacy of inhibitors targeting specific KRAS mutants (e.g., G12C [MRTX-1257]; G12D [MRTX-1133]), a broader spectrum of KRAS mutants (BI-2865), or multiple mutant and wild-type RAS forms (e.g., RMC-6236 and RMC-7977) in preclinical models of MM. **Methods:** We examined anti-MM efficacy, determinants of sensitivity vs. resistance, and rational combination strategies. **Results:** We observed that MM cells respond in vitro to RAS inhibitors at clinically relevant concentrations. Sensitivity to RMC-6236 correlates with KRAS/NRAS mutation or CRISPR-confirmed dependency but can also occur in wild-type MM lines with upstream RAS-activating lesions (e.g., activating FGFR3 mutations). Ras inhibitor monotherapy in vivo (NSG mice) was active against diverse MM lines (XG7 and KP6 with mutant-specific KRAS inhibitors; MM1S and SKMM1 with RMC-6236) but tumor escape eventually emerged. To define escape mechanisms, we performed DNA-barcoding clonal tracking, co-culture studies with bone marrow stromal cells or IL-6, longitudinal RNA-seq and proteomic/phosphoproteomic analyses, and 36 genome-scale CRISPR knockout (KO) and activation (CRISPRa) screens across 10 MM lines. We also characterized mutations (WES) and response to in vitro (re-)treatment with Ras inhibitors for MM cells recovered after escape from in vivo treatment with the same Ras inhibitor. Collectively, these studies identified multiple, potentially cooperating mechanisms of escape, including treatment-induced non-genomic molecular "rewiring," microenvironment-derived protection, and genomic lesions. The CRISPR studies revealed heterogeneous, cell-line-specific, "resistomes," but also recurrent patterns: CRISPRa of upstream receptors, KRAS itself, or positive RAS-MAPK regulators, and CRISPR KO of negative regulators of RAS-MAPK, NF-κB, or PI3K/AKT signaling recurrently conferred resistance. Some CRISPR "hits" affected all three inhibitor classes, whereas others were class-selective (e.g., PPIA for RMC-6236). Many functional hits overlapped with KRAS inhibitor screens in solid tumors, whereas others appear to be MM-selective. Notably, most of the top differentially expressed genes after Ras inhibitor treatment (including known regulators of Ras pathway) were often not top CRISPR hits in the same MM line, underscoring the value of functional genomics to dissect treatment-induced molecular changes vs. regulators of response. Finally, using in vitro pharmacological screening, we identified sensitizers and confirmed in vivo (NSG mice) that RMC-6236 combined with lenalidomide is more active than either agent alone. **Conclusions:** These findings map the complex molecular landscape underlying Ras inhibitor responses and can inform personalized clinical development of these agents in MM. (* authors with equal contribution).

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Phase 1/2, Open-Label, Platform Study of Surzetoclax with Etentamig in Biomarker-Selected Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Multiple myeloma (MM) is a plasma-cell malignancy with complex cytogenetic abnormalities that contribute to its clinical heterogeneity. Overexpression of the B-cell lymphoma (BCL)-2 protein, which helps MM cells evade apoptosis, is notable in t(11;14)-positive patients (pts). Venetoclax, a first-in-class BCL2 inhibitor (BCL2i), has shown efficacy in RRMM. Surzetoclax (surze), a next-generation oral BCL2i, possesses sub-nM affinity for BCL2 and high selectivity, which translates into potent cytotoxicity in human tumor cell lines dependent on BCL2 for survival. Etentamig

(etenta) is a bispecific antibody (BsAb) targeting B-cell maturation antigen (BCMA) on MM cells and CD3 on T cells. Emerging evidence suggests potential synergy when combining a BCL2i with immunotherapy. Here we describe the methods of the surze + etenta substudy in biomarker-selected pts with RRMM. **Methods:** This substudy is part of a Phase 1/2 international, multicenter, open-label, platform trial (NCT06953960). The primary objectives are to characterize the safety, toxicity, and tolerability of surze + etenta, and determine the recommended combination doses. Eligible pts with RRMM must have documented evidence of progression; positive for the t(11;14) translocation and/or BCL2high status determined centrally; no prior BCMA BsAb or BCL2i exposure; and no autologous stem cell transplant (SCT) within 12 weeks or allogeneic SCT within prior 6 months. During dose escalation (DE), several dose combinations may be explored. Bayesian Optimal Interval design (BOIN) guidelines will be used to identify the optimal combination doses of surze + etenta. In DE, pts must be triple-class exposed (protease inhibitor [PI], immunomodulatory drugs [IMiD], anti-CD38) with 3–5 prior lines of therapy (PLoT) and no other appropriate treatment options available per investigator judgment. For dose optimization (DO) cohorts, pts must be triple-class exposed (PI, IMiD, anti-CD38) with 2–3 PLoT. Pts in DO will be stratified by biomarker status and randomized (1:1:1) into 1 of 2 surze + etenta cohorts or an etenta monotherapy cohort. The primary endpoint is dose-limiting toxicity of surze + etenta. Secondary outcome measures include efficacy data (overall response rate, progression-free survival, duration of response, time to progression, time to next treatment, minimal residual disease negativity, and overall survival). Safety assessments include adverse events, clinical laboratory parameters, vital signs, and physical examinations. **Results:** N/A. **Conclusions:** N/A.

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Phase 2 Study of Selinexor, Carfilzomib, and Dexamethasone in Early Relapsed or Refractory Multiple Myeloma Previously Treated with 1–2 Prior Lines of Therapy

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Introduction: Although selinexor-based combinations have demonstrated clinical activity in relapsed/refractory multiple myeloma (RRMM), limited data exist regarding the efficacy and safety of selinexor, carfilzomib, and dexamethasone (XKd) in patients (pts) with early RRMM. **Methods:** This multicenter, open-label, phase 2 trial (KCT0008467) evaluated XKd in pts with RRMM. Eligible pts had received 1 or 2 prior line of therapies (LOTs), including len and/or a proteasome inhibitor. Prior selinexor exposure was excluded, while prior carfilzomib exposure was allowed in pts with carfilzomib-sensitive relapse (>6 months after the last carfilzomib dose). Pts received selinexor 60 mg orally on days 1, 8, 15, and 22, carfilzomib 20/56 mg/m2 intravenously on days 1, 8, 15, and dexamethasone 40 mg weekly in 28-day cycles until disease progression, unacceptable toxicity, or death. The primary endpoint was 12-month progression-free survival (PFS) rate. **Results:** Between July 2023 and January 2025, 48 pts were enrolled. Median age was 67 years (range, 33–84), and 29 (60.4%) had received 2 prior LOTs. Len-refractory disease was present in 42 pts (87.5%), and 25 (52.1%) were refractory to both len and bortezomib. IMS/IMWG-defined high-risk cytogenetic abnormalities were observed in 15 pts (31.3%), revised-International Staging System (R-ISS) II/III in 35 pts (72.9%), and functional high-risk disease in 10 pts (20.8%). With a median follow-up of 17.5 months (IQR, 13.8–22.3), the 12-month PFS rate was 47.0% (95% CI, 32.3–60.4), and median PFS was 10.3 months (95% CI, 4.9–19.1). Among 46 evaluable pts, overall response rate was 69.6% (95% CI, 54.5–82.0), including ≥very good partial response (VGPR) in 19 (41.3%) and ≥complete response in 10 (21.7%). Median time to first and best response was 1.7 (IQR 1.1–2.0) and 2.9 (IQR, 1.9–6.3) months, respectively. Median duration of response was 17.8 months (95% CI, 9.2-N/A) among responders and 21.6 months (95% CI, 15.0-N/A) among pts achieving ≥VGPR. Grade (G)3/4 hematologic adverse events (AEs) included thrombocytopenia (n = 27, 56.3%), neutropenia (n = 19, 37.6%) and anemia (n = 12, 25.0%). G3/4 infections occurred in 11 (22.9%), with lung infection being the most common infectious AE (14.6%). Non-hematologic AEs, including nausea (50.0%), vomiting (33.3%), weight loss (33.3%), and fatigue (25.0%), were mostly G1/2, although G3 vomiting occurred in 5 pts (10.4%). Three pts (6.2%) discontinued treatment because of therapy-related AEs. In post-hoc subgroup analysis, inferior 12-month PFS was observed in pts with R-ISS II/III (32.6% vs. 84.6%, p = 0.030) and functional high-risk disease (20.0% vs. 54.3%, p = 0.29). **Conclusions:** XKd demonstrated clinically meaningful and durable responses with manageable AEs in early RRMM despite the high prevalence of len-refractory disease. Outcomes appeared more favorable in pts without adverse biologic or functional high-risk features, suggesting that risk

stratification may remain important for optimizing treatment outcomes even in early RRMM.

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Phase 3 MajesTEC-9: Teclistamab Monotherapy vs Pomalidomide, Bortezomib and Dexamethasone or Carfilzomib and Dexamethasone (PVd/Kd) in Chinese Patients with Relapsed Refractory Multiple Myeloma (RRMM)

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Introduction: Triplet and quadruplet regimens have greatly improved outcomes in newly diagnosed multiple myeloma, yet a high unmet need remains for more effective, broadly accessible treatments for anti-CD38- and lenalidomide- (Len) exposed/refractory RRMM. Teclistamab (Tec), a BCMA × CD3 BsAb, is widely used in heavily pretreated RRMM and has shown improved outcomes in earlier lines of therapy (LOTs). In MajesTEC-3, the synergistic Tec-daratumumab combination significantly improved progression-free and overall survival (PFS/OS) as early as first relapse. MajesTEC-9 (NCT05572515) is the first phase 3 study of Tec monotherapy in patients(pts) with 1–3 prior LOTs. Here, we report efficacy and safety results from the interim analysis of MajesTEC-9 study in Chinese pts. **Methods:** Pts with RRMM and 1–3 prior LOTs including anti-CD38 and Len were randomized 1:1 to receive 28-day cycles (C) of Tec (C1–2: 1.5 mg/kg QW [C1 preceded by the approved step-up doses schedule]; C3–6: 3 mg/kg Q2W or Q4W for very good partial response or better; C7+: 3 mg/kg Q4W) or investigator's choice of PVd/Kd (21/28-day C). Primary endpoint was PFS by IRC; secondary endpoints included OS, complete response or better (≥CR), and safety. **Results:** 65 Chinese pts were enrolled (Tec, n = 32; PVd/Kd, n = 33). Median (range) age: 61(37–79) yrs; median (range) number of prior LOTs: 2 (1–3); Len refractory: 83%; anti-CD38 refractory: 88%; refractory to last LOT: 97%. With 16.5-mo median follow-up, Tec significantly improved PFS vs PVd/Kd (HR, 0.35; 95% CI, 0.16–0.73); mPFS: NR vs 8.4 mo; 18-mo PFS rate: 67.7% vs 29.0%. OS showed consistent improvement with Tec vs PVd/Kd (HR, 0.62; 95% CI, 0.24–1.64). ≥CR rate was markedly higher with Tec vs PVd/Kd (65.6% vs 15.2%; OR, 10.69; 95% CI, 3.22–35.46).At data cutoff, 62.5% of pts remained on Tec vs 28.1% on PVd/Kd (safety set: Tec, n = 32; PVd/Kd, n = 32). TEAEs were similar for Tec and PVd/Kd (100% vs 100%). Grade (Gr) 3/4 TEAEs (96.9% vs 93.8%) were comparable with Tec vs PVd/Kd, whereas no Gr 5 TEAEs with Tec and 6.3% with PVd/Kd, noting the median treatment duration was nearly doubled with Tec (13.0 vs 7.6 mo). Treatment discontinuation due to TEAEs was lower with Tec vs PVd/Kd (3.1% vs 15.6%). Gr 3/4 infections were higher with Tec vs PVd/Kd (65.6% vs 59.4%). Any-onset Gr≥3 infections decreased over time, consistent with disease control and supported by Ig prophylaxis guidance. CRS occurred in 75.0% of pts with Tec (Gr 1/2: 46.9%/21.9%) and no ICANS were observed. **Conclusions:** Consistent with the MajesTEC-9 overall population, Tec monotherapy significantly improved PFS and key secondary endpoints with manageable safety in Chinese RRMM pts with 1–3 prior LOTs. CRS and infections were generally manageable with established protocols. Results from phase 3 MajesTEC-9 study supports the medical adoption of Tec-based regimens in Chinese pts as early as second-line therapy regardless of prior anti-CD38/Len exposure.

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Phase 3 Randomized Trial of Anselamimab Demonstrates Improvement in All-Cause Mortality in κ Light Chain Amyloidosis

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Introduction: Light chain (AL) amyloidosis is a plasma cell dyscrasia (PCD) characterized by κ or λ Ig light chain amyloid fibrils that deposit in vital organs. Anselamimab is an investigational mAb designed to complement anti-PCD therapy through accelerated removal of amyloid fibrils. Cardiac Amyloid Reaching for Extended Survival (CARES) studies (NCT04512235 and NCT04504825) investigated the efficacy and safety of anselamimab compared with placebo, in addition to anti-PCD therapy. **Methods:** Alongside anti-PCD therapy with CyBorD (daratumumab was permitted) newly diagnosed patients with European modification of Mayo stage IIIa or IIIb AL amyloidosis were randomized 2:1 to receive anselamimab (1000 mg/m2) or placebo (normal saline) IV every 7 days for 4 weeks followed by every 14 days for the remainder of the blinded study (18 months after the last participant enrolled). The primary endpoint was a hierarchical combination of time to all-cause mortality (ACM) and frequency of adjudicated cardiovascular hospitalizations (CVH) using the Finkelstein-Schoenfeld test and win-ratio in the combined study population. Subgroup analysis by involved κ or λ free light chain isotype was prespecified. **Results:** In these two trials, 406 patients were randomized to receive anselamimab (271) and placebo (135). Baseline characteristics were similar between treatment arms. The median duration of treatment was 21.4 months and 21.1 in the anselamimab and placebo arms, respectively. Daratumumab was used in 79.3% and 83.7% of the anselamimab and placebo arms, respectively. Among 406 randomly assigned patients, the primary end point win ratio for anselamimab versus placebo was 1.11 (95% CI, 0.83, 1.50; p = 0.332) and the hazard ratio (HR) for ACM was 0.80 (95% CI, 0.57, 1.13; P = 0.290). CVH rates in the anselamimab and placebo groups were 0.59 (95% CI, 0.42, 0.83) and 0.89 (95% CI, 0.55, 1.43), respectively (P = 0.145). Among patients with κ isotype (n = 72), the primary end point win ratio was 2.06 (95% CI, 0.98, 4.31; P = 0.100). Anselamimab treated patients with κ isotype had a 62% reduction in ACM (HR = 0.38; 95% CI, 0.17, 0.86; nominal P = 0.012) and a 71% reduction in risk for CVH (estimated CVH rate ratio = 0.29; 95% CI, 0.10, 0.87; nominal P = 0.028). Patients with λ isotype had a 10% reduction in risk for CVH; none in ACM. Safety data were comparable between both treatment arms. In anselamimab-treated patients, safety findings were similar between κ subgroup and full population. **Conclusions:** Anselamimab, a κ light chain–directed anti-fibril monoclonal antibody used alongside anti-plasma cell dyscrasia therapy, offers a first-in-class, new therapeutic option for patients with newly diagnosed κ AL amyloidosis.

PA-350

Phase 3, Randomized Study of Talquetamab (Tal) Plus Daratumumab (D) ± Pomalidomide (P) vs D Plus P and Dexamethasone (DPd) in Relapsed/Refractory Multiple Myeloma (RRMM): MonumenTAL-3

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Introduction: Tal (anti-GPRC5D bispecific antibody) has shown deep responses and durable efficacy in late line RRMM with a favorable infection profile. A B-cell sparing mechanism facilitates combination with D and P, enabling potential synergistic efficacy in earlier lines. We report efficacy and safety of Tal+D+P (Tal-DP) and Tal+D (Tal-D) vs DPd in pts with RRMM and ≥1 prior line of therapy (LOT) at the MonumenTAL-3 (NCT05455320) interim analysis. **Methods:** Phase 3 study randomizing pts with RRMM and

≥1 prior LOT including lenalidomide (R) and a proteasome inhibitor 1:1:1 to Tal-DP, Tal-D, or DPd. Primary endpoint was progression-free survival (PFS) by IRC for Tal-DP and Tal-D vs DPd. Secondary endpoints included overall response, complete response or better (≥CR), minimal residual disease (MRD)-negative ≥CR (10–5, NGS), overall survival (OS) and safety. **Results:** 864 pts were randomized (Tal-DP, N = 287; Tal-D, N = 287; DPd, N = 290). Baseline characteristics were balanced across arms (median age, 64.0 y [range 30–88]; median prior LOT, 2 [range 1–8]; 11.8% anti-CD38 exposed; 85.1% and 93.4% refractory to R or last LOT, respectively; 30.9% had high risk cytogenetics). At 24.6 mo median follow-up, Tal-DP and Tal-D significantly improved PFS vs DPd (HRs [95% CI]: 0.28 [0.20–0.40], P < 0.0001 and 0.33 [0.24–0.46], P < 0.0001), with consistent benefit across subgroups. 24-mo PFS rates (95% CI) favored Tal-DP (81.3% [75.8–85.7]) and Tal-D (77.6% [71.7–82.5]) vs DPd (51.2% [44.8–57.1]). ORRs (88.2%, 88.5%, 77.6%), ≥CR rates (71.1%, 69.0%, 34.5%) and MRD-negative ≥CR rates (52.3%, 46.3%, 15.9%) were significantly higher for Tal-DP and Tal-D vs DPd. OS HRs (95% CI) vs DPd were 0.47 (0.30–0.73; P = 0.0006) for Tal-DP and 0.51 (0.33–0.78; P = 0.0015) for Tal-D. At data cutoff, 70.3% (Tal-DP), 69.7% (Tal-D) and 47.3% (DPd) of pts remained on study tx. Adverse events (AEs) were manageable; overall AE rates (gr 3–4, gr 5): Tal-DP (96.7%, 1.8%), Tal-D (78.8%, 4.0%), and DPd (95.8%, 4.6%). AEs leading to discontinuation of all study tx occurred in 10.5% (Tal-DP), 8.0% (Tal-D), and 6.7% (DPd). Gr 3–4 cytopenia rates were 87.7% (Tal-DP), 51.8% (Tal-D), and 89.0% (DPd). Infection rates (gr 3–4, gr 5) were: Tal-DP (37.0%, 0.7%), Tal-D (27.7%, 1.5%), and DPd (41.0%, 1.8%). With Tal-DP and Tal-D, CRS (any gr: 67.8%; 58.4%) and ICANS (any gr: 2.9%; 1.8%) were mostly gr 1–2. Any gr GPRC5D-related AEs with Tal-DP, Tal-D and DPd included taste changes (72.8%; 74.8%; 3.9%) and decreased weight (45.7%; 38.3%; 7.4%); most events were gr 1–2. Ataxia/balance disorders (gr 1–2, gr 3) with Tal-DP (11.6%, 2.9%), Tal-D (10.2%, 2.2%) and DPd (0.4%, 0%) were primarily low gr (none gr ≥4). **Conclusions:** Tal-DP and Tal-D demonstrated a significant PFS benefit vs DPd, clinically meaningful OS improvements and gr ≥3 infection rates similar to or lower than DPd. Tal was combinable, with low rates of tx d/c. Tal-D ± P represents a new standard of care for RRMM as early as 2L across all practice settings.

PA-351

Phase II Study of Daratumumab, Clarithromycin, Pomalidomide, and Dexamethasone (D-ClaPd) in Multiple Myeloma Patients Previously Exposed to Daratumumab

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Introduction: As a majority of relapsed/refractory multiple myeloma (RRMM) patients (pts) are daratumumab (dara)-exposed by early relapse, investigation of dara re-exposure in combination with immunomodulatory (IMiD)-based regimens in the second and later lines deserves further study. Clarithromycin (Cla) potentiates glucocorticoid activity and may modulate immune resistance via IL-6 suppression and CYP3A4 inhibition. A prior phase 2 study of Cla, pomalidomide (pom), and dexamethasone (dex) (ClaPd) in RRMM (median 5 prior lines) showed ≥VGPR 23% with median(m) PFS of 7.7 months (mos) and mDoR 9.3 mos. Given potential for CD38 re-expression in prior dara-exposed pts and CD38 upregulation by IMiDs, we hypothesized that dara combined with ClaPd (D-ClaPd) will yield deep responses with superior VGPR or better rates to pom/dex in this dara-exposed, RRMM population. **Methods:** Single-center, non-randomized phase II study (NCT04302324) of RRMM pts with ≥1 prior line and prior dara exposure. Dara refractory was defined as progression within 60 days of receiving dara or < PR achieved on prior dara-based therapy. Induction given q28 day(D) cycles(C): C1–8 dara 1800 mg SC D1, cla 500 mg BID D1–28 continuous until VGPR or 8 cycles, pom 4 mg D1–21, dex 40 mg weekly(qwk) C1–6; 20 mg qwk C7–8. Maintenance given C9+ q28D if ≥PR, up to 24 mos: dara 1800 mg SC D1, pom 4 mg D1–21, dex 20 mg qwk. 1° endpoint: ≥VGPR rate within 8 cycles. KM analysis was used to compute PFS and OS. **Results:** 9 pts were enrolled from 2021 to 2024 with further enrollment held due to slower than anticipated accrual. Median age was 65 years (40–83) w/ 6/9 (66%) high-risk by updated IMWG criteria, including 5/9 with del17p. Median prior lines was 2 (1–6); 78% had prior ASCT. All patients were prior dara and lenalidomide (len)-exposed, w/ 3/9 (33%) dara-refractory and 7/9 (78%) len-refractory. Seven of 9 (78%) had prior bortezomib exposure and 3/9 (33%) were bortezomib-refractory. Median time from last dara was 18.4 mos (1.8–56.2). At 30.5 mos median f/u, ORR was 67% (6/9), ≥VGPR 33% (3/9); a CR was achieved in 11% (1/9) which was MRD-negative. Two of 3 (67%) dara-refractory pts achieved PR. Median time to best response was 2.8 mos with mDoR 10.6 mos. mPFS was 12.5 mos w/ 12- and 24-mos PFS rates 55% and 33%, respectively. mOS was not reached and 24-mos OS was 88% w/ 8/9 pts who remain alive and 1 pt who died on subsequent therapy. Most common grade (gr)≥3 hematologic AEs were neutropenia (88%) and lymphopenia (44%). Non-hematologic gr≥3 AEs of note include (1 each): COVID-19 pneumonitis, atrial fibrillation, small bowel obstruction, and retinal detachment. No treatment-related deaths occurred. **Conclusions:** D-ClaPd demonstrated moderate efficacy with deep responses observed in previously dara-exposed RRMM pts, w/ ORR 66.7% (≥VGPR 33%; CR 11%), mPFS 12.5 mos and 24-mos OS of 87.5%. The demonstrated efficacy with CD38 retreatment along with a

manageable toxicity profile supports D-ClaPd as a tolerable and effective treatment option in this population.

PA-352

Phase III Randomized Evidence for BCMA-Directed CAR T-Cell Therapy Versus Standard Regimens in Relapsed/Refractory Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy has demonstrated substantial activity in relapsed/refractory multiple myeloma (RRMM), but randomized phase III comparative evidence remains limited. We performed a systematic review and meta-analysis of randomized phase III trials evaluating BCMA-directed CAR-T therapy versus standard regimens in RRMM. **Methods:** We searched PubMed/MEDLINE, Embase, ClinicalTrials.gov, and major hematology conference proceedings through May 2026 for eligible randomized phase III trials comparing BCMA-directed CAR-T therapy with standard regimens in adults with RRMM. Primary outcome was progression-free survival (PFS). Secondary outcomes included overall survival (OS), overall response rate (ORR), complete response (CR) or better, minimal residual disease (MRD) negativity, and treatment-related toxicities. Hazard ratios (HRs) were pooled using inverse-variance models. Because CARTITUDE-4 used a weighted protocol-specified PFS analysis due to early curve crossing, a harmonized sensitivity analysis using conventional unweighted HRs was prespecified. **Results:** Two phase III randomized trials met eligibility criteria: KarMMa-3 evaluating idecabtagene vicleucel versus investigator's-choice standard regimens and CARTITUDE-4 evaluating ciltacabtagene autoleucel versus pomalidomide-based standard regimens, comprising 805 randomized patients overall. Other BCMA CAR-T studies were excluded because they evaluated single-arm therapy, earlier-phase combinations, newly diagnosed disease, regional cohorts, or lacked publicly available comparative efficacy results. BCMA-directed CAR-T therapy significantly improved PFS across both trials. KarMMa-3 reported a PFS HR of 0.49 (95% CI, 0.38–0.65), while CARTITUDE-4 reported an unweighted sensitivity HR of 0.40 (95% CI, 0.29–0.55). In the harmonized pooled analysis, BCMA-directed CAR-T therapy reduced the risk of progression or death by 55% (pooled HR 0.45; 95% CI, 0.37–0.55), with no observed statistical heterogeneity. Both trials demonstrated higher ORR, CR or better, and MRD negativity rates with CAR-T therapy. Updated OS favored ciltacabtagene autoleucel in CARTITUDE-4; interpretation of OS in KarMMa-3 was limited by crossover from standard therapy to idecabtagene vicleucel. Cytokine release syndrome and neurotoxicity were common but predominantly low grade. **Conclusions:** Published phase III randomized evidence demonstrates a substantial progression-free survival benefit for BCMA-directed CAR-T therapy compared with standard regimens in RRMM. These findings support earlier integration of BCMA-directed CAR-T therapy in appropriately selected patients with relapsed/refractory disease.

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PHF19 Drives IMiDs Resistance by A Reciprocal Epigenetic-Transcriptional Adaptive Circuit in Multiple Myeloma

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Introduction: Immunomodulatory drugs (IMiDs) are standard in multiple myeloma (MM) therapy, but resistance limits long-term remission. Epigenetic dysregulation promotes MM progression, yet it is unknown whether specific chromatin regulators actively reprogram oncogenic dependency to drive IMiD resistance. **Methods:** We performed RNA-seq on primary CD138+ cells from MM patients with divergent responses to IMiD-based induction, then functional/epigenomic analyses via shRNA-mediated PHF19 knockdown in MM lines, including a lenalidomide-resistant model. Chromatin architecture was assessed by ChIP-seq (EZH2, H3K27me3) and ATAC-seq; protein interactions by co-immunoprecipitation and chromatin fractionation. **Results:** RNA-seq of IMiD non-responders showed significant activation of MYC, E2F, and G2/M checkpoint programs. Cross-cohort integration identified PHF19 as a top-ranked epigenetic regulator associated with treatment failure. High PHF19 expression significantly correlated with poor IMiD response, supporting its utility as a predictive biomarker. Functionally, PHF19 depletion sensitized intrinsically resistant cells and re-sensitized acquired lenalidomide-resistant MM.1S cells to IMiD treatment. Downregulation of MYC and IRF4 proved critical for IMiD-mediated cytotoxicity. Transcriptomic profiling of PHF19-KD cells revealed collapse of MYC target genes and IRF4-dependent transcription. Consistently, MYC and IRF4 were reduced at mRNA and protein levels following PHF19 loss. Western blot showed further suppression of MYC and IRF4 upon IMiD treatment in PHF19-KD cells, whereas levels remained stable in controls. Mechanistically, Co-IP/MS showed PHF19-associated proteins enriched for PRC2 components. However, PHF19 depletion did not destabilize core PRC2 complex (EZH2/SUZ12/EED) interaction or chromatin binding. Integrative epigenomic mapping revealed that PHF19 deficiency reprogrammed chromatin architecture by enhancing EZH2 and H3K27me3 deposition, which reduced chromatin

accessibility at transcription start sites, including those of MYC and IRF4. A total of 881 overlapping peaks were identified; motif analysis pinpointed ETV4 as a significantly affected transcription factor. ETV4 is known to drive lenalidomide resistance. Integrating ETV4 ChIP-seq data, we found that 306 genes epigenetically regulated by PHF19 were also transcriptionally regulated by ETV4, including MYC. Strikingly, PHF19 itself was regulated by ETV4. CoMMpass dataset analysis revealed a positive expression correlation between ETV4 and PHF19. **Conclusions:** PHF19 is a central epigenetic driver enforcing IMiD resistance through a reciprocal adaptive circuit with ETV4. PHF19 sustains ETV4 chromatin binding by modulating PRC2 recruitment and catalytic precision, while ETV4 transcriptionally activates PHF19. PHF19 expression predicts clinical outcome and IMiD response, positioning it as both a therapeutic vulnerability and a biomarker-guided strategy to overcome drug resistance in MM.

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Plasma Cell Density Gradients Reveal Angiogenic, Stromal, and Cytotoxic Immune Niches During Multiple Myeloma Progression

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Introduction: In the bone marrow, coordinated hematopoietic and stromal niches are disrupted during multiple myeloma (MM) progression. Despite therapeutic advances, relapse remains common, highlighting the need to define altered cellular interactions within the spatial context to uncover targetable vulnerabilities. **Methods:** We performed spatial transcriptomics using the Xenium platform on 92 MM patients, including 43 newly diagnosed (NDMM), 18 first relapse (FRMM), and 31 multiple-relapse (MRMM) cases and 4 longitudinal specimens, alongside with 22 normal bone marrow (NBM) samples from healthy donors. We supplemented the assay with a custom panel including myeloma-relevant genes and mutation-specific probes targeting recurrent alterations (KRAS p.G12V/D, NRAS p.Q61R/H/K and BRAF p.V600E). The cohort includes MM patients with diverse demographics and recurrent genomic alterations. **Results:** We captured over 10 million cells including progenitor and stromal populations, often underrepresented in dissociative single-cell studies. Probe-based spatial mapping of oncogenic mutations verified malignant PC identity and demonstrated subclone-specific transcriptional programs. MM marker expression was positively correlated with tumor burden and decreased along disease progression, possibly due to reduction of PC density in relapse samples. By stratifying PC regions into concentric density layers, we observed increased expression of KRAS and NRAS across PC layers from the periphery to tumor core. In MM samples, plasma cell (PC) niches were uniformly enriched for endothelial cells, supporting active angiogenesis, as well as mesenchymal stromal cells (MSCs), the dominant source of CXCL12 ligands anchoring PC subsets within the BM via CXCR4. Only the lowest-density PC niche (N1), observable in NBM as well as all MM timepoints, was significantly infiltrated by antigen presenting cells and cytotoxic T cells, suggesting immune exclusion in higher-density tumor pockets. Despite the ubiquity of N1, T cells within N1 of NDMM samples had significantly higher expression of cytotoxic markers (GZMA, GZMK, KLRK1) than those from either NBM or relapsed disease, suggesting enhanced local immune activation at disease onset. At diagnosis, T cells are more transcriptionally engaged across many programs, including activation, cytotoxicity, checkpoint/exhaustion, proliferation, and inflammatory signaling. We also observed increased abundance in relapse samples of proliferative erythroid niches, which were significantly depleted in NDMM, suggesting post-treatment erythropoietic recovery. **Conclusions:** These findings suggest that myeloma progression is marked by malignant plasma cell expansion, displacement of myeloid and erythroid populations, and stromal remodeling that may support tumor persistence. NDMM retains a more active T cell microenvironment compared to relapsed disease, highlighting the role of localized tumor-microenvironment interactions in disease evolution and relapse.

PA-355

POEMS Syndrome Outcomes: A Series of 3 Patients

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Introduction: POEMS syndrome is a paraneoplastic syndrome, the diagnosis of which is based on having both polyradiculoneuropathy and the monoclonal plasma cell disorder, and at least 1 of the other 3 major criteria (Castleman disease, sclerotic bone lesions, or elevated VEGF) and at least one minor criterion. Prompt treatment directed at the underlying plasma cell clone produces dramatic responses in the majority of patients. Durable benefit has been described with auto SCT based approaches; however, treatment approaches that are best informed by disease biology and variable clinical presentation have not been fully optimized. **Methods:** We present a case series of three patients diagnosed with POEMS syndrome at a single academic center, highlighting variation in clinical presentation, diagnostic workup, treatment approach, and outcomes. **Results:** Patient 1 was a 57-year-old male who presented in late 2016 with severe demyelinating polyradiculopathy. Clinical features

included IgA lambda protein and clonal plasma cells on bone marrow exam (9–10%), sclerotic bone disease, elevated VEGF; and other features such as thrombocytosis, skin changes, and hypocortisolism. He was treated with VCD plus pegylated liposomal doxorubicin followed by MEL200/ASCT. CR at day 105 with neurologic response at day 147. He then experienced rising VEGF and IFE-detectable M-spike in 2022, treated with dara KD and maintenance daratumumab through May 2024. He now remains off treatment with no evidence of progression. Patient 2 was a 45-year-old male who presented in mid-2025 with progressive bilateral leg numbness and weakness, initially misdiagnosed as CIDP. IgG lambda M-spike (0.4 g/dL), 3% clonal PC on bone marrow exam. Other clinical features included sclerotic bone disease, hepatosplenomegaly, ascites, pleural effusions, glomeruloid hemangiomas, and mild hyperprolactinemia. PET/CT identified a plasmacytoma. He was initiated on daratumumab/lenalidomide/dexamethasone with concurrent radiation therapy. He achieved PR at day 70 with neurologic response by day 105 and resolution of volume overload by day 98. PFS to date is 118 days. Patient 3 was a 47-year-old female who presented in 2020 with acrocyanosis and neuropathic symptoms. She was diagnosed with POEMS syndrome in 2021 following identification of an IgA lambda elevation, 14% clonal PC, sclerotic femoral lesion and elevated VEGF, hepatosplenomegaly, lymphadenopathy, and thrombocytosis. She was treated with Dara VRD for 11 cycles, achieving CR at day 123, followed by maintenance daratumumab/VRD until early 2026, at which point she transitioned to daratumumab/lenalidomide. **Conclusions:** Patients with POEMS syndrome present with a complex conglomerate of symptoms, and signs, making the diagnosis, management, and follow-up a challenge. Early diagnosis, multidisciplinary disease and patient centric approach will inform of best treatment outcomes for patients.

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Patient-Reported Outcomes (PROs) of Teclistamab-Based Treatment (tx) in Relapsed/Refractory Multiple Myeloma (RRMM) after 1–3 Lines of Therapy (LOT)

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Introduction: Significant PFS and OS benefits were seen with teclistamab + daratumumab (Tec-Dara) in MajesTEC-3 (NCT05083169) and Tec monotherapy in MajesTEC-9 (NCT05572515) vs controls (Dara + dexamethasone [dex] + pomalidomide/bortezomib [DPd/DVd] in MajesTEC-3; pomalidomide + bortezomib + dex or carfilzomib + dex [PVd/Kd] in MajesTEC-9) in patients (pts) with RRMM and 1–3 prior LOT. These Tec-based regimens have well-characterized safety profiles, manageable with established CRS/infection protocols, are steroid-free from Cycle (C) 1 Day (D) 5, and dosed monthly in later cycles. We report PROs from MajesTEC-3/MajesTEC-9. **Methods:** PRO tools were Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q; 0–4 point scale), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; 0–100 point scale), and EuroQoL 5-Dimension 5-Level (EQ-5D-5L; 0–100 point scale). Changes from baseline (BL) were analyzed using mixed-model for repeated measures and are shown at the latest tx cycle with adequate sample size and stable estimates: C37D1 (MajesTEC-3)/C20D1 (MajesTEC-9). Time to worsening/responder analyses used distribution- (MajesTEC-9 MySIm-Q), anchor- (MajesTEC-3 MySIm-Q) or literature- (EORTC QLQ-C30) based methods. **Results:** 291 Tec-Dara and 296 DPd/DVd pts in MajesTEC-3 and 293 Tec and 293 PVd/Kd pts in MajesTEC-9 were evaluated. Compliance (% forms received/expected) was >85% at BL and >80% at most post-BL timepoints across groups in both studies. For MySIm-Q, LS mean change from BL in total symptom and impact scores improved with Tec-Dara vs DPd/DVd (difference: symptom −0.13 [95% CI −0.30, 0.05]; impact −0.16 [−0.34, 0.03]) and Tec vs PVd/Kd (−0.15 [−0.33, 0.03]; −0.23 [−0.46, 0.0]). Time to symptom/impact worsening was longer with Tec-Dara vs DPd/DVd (HR: symptom 0.50 [0.34, 0.72], P = 0.0002; impact 0.41 [0.29, 0.58]) and Tec vs PVd/Kd (HR: 0.50 [0.36, 0.71], P < 0.0001; 0.42 [0.30, 0.59]). In general, more pts achieved meaningful improvements with Tec-Dara and Tec vs controls. For EORTC QLQ-C30, LS mean change from BL in global health status (GHS) score improved with Tec-Dara vs DPd/DVd (difference: 5.17 [95% CI 0.32, 10.02]) and Tec vs PVd/Kd (4.94 [−1.28, 11.15]). Pain, fatigue, and physical functioning domains also improved for Tec-Dara and Tec. Tec-Dara and Tec delayed time to worsening in GHS (HR, 0.46 [0.32, 0.65] and 0.50 [0.36, 0.69]) and across domains vs controls. More pts achieved meaningful improvements with both Tec-Dara and Tec vs controls across domains. For EQ-5D-5L, change from BL improved with Tec-Dara and Tec vs controls. **Conclusions:** Tec-Dara and Tec improved HRQoL and significantly prolonged time to symptom worsening vs controls. Building on transformative PFS, OS, and safety data, PROs support pt-relevant benefits, complementing improved pt experience with monthly dosing and steroid-sparing regimens. Findings reinforce Tec-based tx as SoC in 2L+ RRMM across practice settings.

PA-357

Pomalidomide, Bortezomib, and Dexamethasone (PVD) Versus Daratumumab, Bortezomib, and Dexamethasone (DVd) for Newly Diagnosed Multiple Myeloma Patients with Renal Impairment: A Prospective, Multicenter Trial

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Introduction: Renal impairment (RI) is common in newly diagnosed multiple myeloma (NDMM) and is associated with poor prognosis. Bortezomib-based therapy is the backbone for MM patients with RI, yet the optimal regimen remains undefined. Both pomalidomide and daratumumab have shown favorable tolerability in RI and promising activity in frontline NDMM. However, the comparative efficacy and safety of pomalidomide-based (PVD) versus daratumumab-based (DVD) induction therapy in NDMM with RI remain unclear. **Methods:** NDMM patients with RI (eGFR< 40 mL/min/1.73 m^2) were enrolled and assigned to PVD or DVD group in this ongoing, prospective, multicenter study (ChiCTR2400086035). Both regimens were administered in 28-day cycles and included bortezomib and dexamethasone. The PVD group received additional pomalidomide (4 mg po, days 1–21), whereas the DVD group received daratumumab (16 mg/kg iv, weekly (cycles 1–2), q2w (cycles 3–6), monthly thereafter). Eligible patients proceeded to autologous stem cell transplantation (ASCT). Drug acquisition costs were estimated based on the standard dosing schedules used in this study. The primary endpoint was renal overall response rate (ORR). Secondary endpoints included hematologic response, progression-free survival (PFS), overall survival (OS) and safety. **Results:** As of March 31, 2026, 45 NDMM patients with RI were enrolled (PVD, n = 26; DVD, n = 19), with a median age of 65 years. Baseline features were generally balanced except for a higher proportion of males in the DVD group (42.3% vs. 73.7%, P = 0.036).ISS stage III (96.2% vs. 89.5%), high-risk cytogenetics (30.4% vs. 14.3%) and baseline eGFR [19.4 (9.86–27.1) vs. 12.4 (10.1–15.1) mL/min/1.73 m^2] were comparable between groups. Median induction cycles were 5.0 (4.0–6.0) for PVD, and 4.0 (3.5–7.5) for DVD. 9 (34.6%) PVD and 3 (15.8%) DVD patients underwent ASCT. Among patients who completed 4-cycle induction (PVD, n = 24; DVD, n = 16), renal ORR after 4 cycles was comparable (70.8% vs. 75.0%, P = 0.772). Best renal ORR in the overall cohort was 73.1% vs. 84.2% (P = 0.481). Dialysis independence was achieved in 2/6 and 3/6 baseline dialysis-dependent patients, respectively. Hematologic responses were similarly favorable in both groups, with ≥VGPR rates of 79.2% vs. 81.3% and ORR rates of 91.7% vs. 87.5% after 4 cycles; best hematologic ORR was 100% in both groups (all P ≥0 .05). With a median follow-up of 16 months (9–33), median PFS and OS were not reached in either group (P = 0.826 and P = 0.511, respectively). The most common adverse event was infection (PVD:34.6%; DVD:21.1%, P = 0.321), with grade ≥3 infections in 26.9% vs. 15.8%, respectively (P = 0.600). Drug acquisition cost for a 4-cycle course was substantially lower with PVD than DVD (¥18,731 vs. ¥119,464, based on a 60-kg patient). **Conclusions:** Both PVD and DVD regimens show favorable efficacy and tolerability in NDMM patients with RI, with the PVD regimen being more economical. Larger-scale studies with prolonged follow-up are needed to confirm long-term benefits.

PA-358

Post-Infusion Immunophenotypic And Functional Characteristics Of Arlocabtagene Autoleucel (Arlo-Cel) In A First-In-Human (FiH), Phase 1 Trial In Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Arlo-cel (BMS-986393) is a GPRC5D-targeted CAR T cell therapy with deep, durable activity as evidenced in a FiH ph1 trial (NCT04674813) in patients (pts) with RRMM. In the ≥3 prior lines of therapy efficacy evaluable (EE) cohort (N = 79), mFU was 24.0 mo (range, 3.8–38.4), median (95% CI) DOR was 19.6 mo (13.3–23.0), and mPFS was 18.3 mo (11.8–23.7). ORR was 87.3%; 53.2% achieved a ≥CR. mOS (N = 84) was not reached. We report an exploratory biomarker analysis in these pts to define post-infusion arlo-cel phenotypic and functional features underpinning responder biology. **Methods:** Pts with ≥3 prior anti-myeloma regimens (PI, IMiD, anti-CD38) were eligible; prior BCMA-targeted therapy, including CAR T cell therapy, was allowed. Primary objective was safety; secondary objectives were IMWG criteria activity and pharmacokinetics. Exploratory objectives included characterizing post-infusion CAR T cells and associated soluble inflammatory factors. Peripheral blood mononuclear cells were phenotypically characterized using cytometry by time-of-flight at peak CAR T expansion (Tmax), and days 29 (D29) and D60 post-infusion. Plasma from pre- through ≤D60 post-infusion was assessed for inflammatory factors via multiplex immunoassay. **Results:** Among EE responders, available cytometry or immunoassay data (n = 69), inflammatory cytokines increased post-infusion with most peaks prior to CAR T Tmax, consistent with CAR T cell activation after target engagement (IFN-γ, TNF-α) and proliferation (IL-2). The levels of myeloid produced factors (GM-CSF, IL-6, MCP-1, IP-10, IL-12, and IL-15) that support T cell proliferation also increased post-infusion. These soluble factors decreased toward baseline levels by D60. Arlo-cel CAR T expansion involves CD4+ and CD8+ CAR T cells. CD8+ CAR T cells dominated at peak CAR T concentration, and both subsets contracted thereafter, with relative enrichment of CD4+ CAR T cells by D60. At Tmax, CD4+ and CD8+ CAR T cells were predominantly effector memory (EM) T cells. From Tmax to D60, the proportion of CD4+ central memory CAR T cells and CD8+ terminal EM (TEMRA) CAR T cells increased relative to the other memory subtypes within the respective parent populations. The percentage of CD27+ cells increased over this period in CD4+, but not in CD8+ CAR T cells. At Tmax, a greater percentage of CD8+ vs CD4+ cells expressed activation (CD38) and proliferation (Ki67) markers, although activation and proliferation of CD4+ and CD8+ CAR T cells decreased by D60. **Conclusions:** Arlo-cel phenotypic and functional characteristics suggest early anti-tumor activity, memory formation within the CD4+ CAR T cells, and resolution

of the inflammatory state after tumor clearance. Early arlo-cel activation, proliferation, and supportive cytokine production mediate tumor eradication. After tumor clearance, memory evolution in the CD4+ CAR T compartment may support arlo-cel anti-MM surveillance, while resolution of inflammation may indicate target specific arlo-cel activity.

PA-359

Preclinical Evaluation of β-Glucuronide Linker-Based BCMA ADCs with MMAF, proPBD, and TOP1 Inhibitor Payloads Support Differentiated Clinical Development Strategies

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Introduction: Belantamab mafodotin combination therapies have demonstrated the potential of BCMA-targeted antibody-drug conjugates (ADCs) in the multiple myeloma treatment landscape, yet are limited by the prevalence of ocular toxicity. We sought to improve the clinical utility of BCMA ADCs through linker-payload engineering designed to increase the therapeutic index and support a patient experience less tethered to regular ophthalmological assessment. To address this, we generated a series of BCMA ADCs using our second-generation β-glucuronide cleavable linker platform for evaluation of distinct payload mechanisms within a shared BCMA-targeted ADC architecture. Of these, the lead ADC LCB14-2524, uses the same conjugation and MMAF linker-payload platform as FS-1502/IKS014, which has demonstrated clinical efficacy and was not dose intensity limited by ocular toxicity. Beyond microtubule inhibition, we evaluated DNA crosslinking and topoisomerase 1 inhibition mechanisms. **Methods:** An Fc-modified and site-specific conjugation engineered anti-BCMA antibody was conjugated to either MMAF (monomethyl auristatin-F, microtubule inhibitor) LCB14-2524, proPBD (β-glucuronide prodrug pyrrolobenzodiazepine, DNA cross linker) LCB14-2516, or a novel TOP1i (topoisomerase 1 inhibitor) payload LCB43-10100. The resulting ADCs were compared across pre-clinical in vitro and in vivo cell line models to a belantamab mafodotin biosimilar. **Results:** LCB14-2524, LCB14-2516 and LCB43-101001 demonstrated robust activity across preclinical models compared to a belantamab mafodotin biosimilar with each ADC showing a differentiated profile. In the NCI-H929 model, LCB14-2524, LCB14-2516 and LCB43-101001 achieved 50%, 100%, and 100% complete responses respectively vs 38% for belantamab mafodotin biosimilar. In the MM.1S model, LCB14-2524, LCB14-2516 achieved 80% and 100% complete responses respectively compared to 60% for belantamab mafodotin biosimilar. LCB14-2516 and LCB43-101001 utilize the highly potent proPBD payload class and a novel TOP1i respectively, creating ADCs with either more or less potent payload classes than the microtubule inhibitor MMAF used in LCB14-2524. These differences in payload potency also impact tolerability, such that each ADC presents an alternating set of strengths and weaknesses. LCB14-2524 was well tolerated in a research cyno toxicity study while the expectation for the proPBD and novel TOP1i ADCs would be lower and higher tolerated doses respectively – mirroring their intrinsic potencies. **Conclusions:** LCB14-2524 (LBG-MMAF), LCB14-2516 (LBG-proPBD), and LCB43-101001 (Novel TOP1i) all demonstrated preclinical profiles supporting further development. LCB14-2524 has been prioritized for first clinical assessment based on the combination of pre-clinical profile and clinical experience with the platform linker-payload (FS-1502/IKS014). LCB14-2516 or LCB43-101001 provide differentiated follow-on opportunities to introduce new payload mechanism into the multiple myeloma treatment landscape.

PA-360

Predicting Cytogenetic Abnormalities in Multiple Myeloma from Gene Expression Data using Machine Learning

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Introduction: Multiple myeloma is an incurable blood cancer, defined by genetic abnormalities with important prognostic and treatment implications. Standard-of-care testing uses fluorescence in-situ hybridization (FISH), which captures information on limited cytogenetic abnormalities. Conversely, RNA sequencing (RNA-seq) provides a broader and more nuanced view of tumour biology. In this study, we investigate whether FISH information can be extracted from RNA-seq data. **Methods:** Bulk RNA-seq and cytogenetic data were obtained from the MMRF-CoMMpass study (Keats et al., 2013) and a Moffitt Cancer Center cohort (Sudalagunta et al., 2025). RNA-seq data was normalized to log2 counts per million and z-scored for cross-cohort comparisons. Binary classifiers were trained to predict five clinically relevant cytogenetic lesions: del(17p13), gain(1q21), t(11;14), t(14;16), and t(4;14). Features were selected after differential gene expression and gene set enrichment analyses to restrict inputs to lesion-relevant genomic loci and hallmark pathways. Three machine learning architectures were evaluated: random forest decision trees, extreme gradient boosting (XGB), and deep neural networks (DNN). Models were trained and on up to 703 CoMMpass patients using 4-fold cross-validation and externally validated on 677 Moffitt cohort patients. Copy number alteration (CNA) prediction was benchmarked against a fine-tuned RCANE model (Ge et al., 2025), an RNA-seq-based CNA prediction tool, using an 85/15 train/test split. **Results:** For translocation prediction, XGB models generalized best, achieving external validation F1 scores of 0.87 for t(4;14), 0.90 for t(14;16), and 0.92 for t(11;14). For copy number alteration (CNA)

events, DNN models performed best with external F1 scores of 0.86 for gain(1q21) and 0.71 for del(17p13), achieving similar performance to RCANE. Feature importance analysis confirmed lesion-specific biology in model predictions with CCND1, NSD2, and MAF overexpression driving t(11;14), t(4;14) and t(14;16) predictions respectively. For CNA events, the most important features were on or near the target gene locus. Misclassification analysis revealed that false negative del(17p13) samples (n = 13) had significantly higher log2CNA values from whole genome sequencing analysis ($p < 0.01$) and higher mean gene expression of genes from the 17p13 locus ($p < 0.01$), suggesting shallow deletions or subclonality. The opposite pattern was observed in false negative gain(1q21) predictions (n = 16). False positive t(4;14) samples (n = 7) had evidence of concordant biology with true positive cases with higher NSD2 expression and a trend of poorer overall and progression-free survival. **Conclusions:** Transcriptomic-based machine learning models can accurately predict cytogenetic lesions across independent myeloma cohorts, with the potential to augment standard FISH testing. Critically, the model may identify clinically significant abnormalities missed by conventional diagnostics, warranting further evaluation.

PA-361

Preemptive Tocilizumab in Patients with Relapsed-Refractory Multiple Myeloma Receiving Bispecific: A Case Series

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Introduction: Multiple myeloma is a plasma cell malignancy which expresses B cell maturation antigen (BCMA) and GPRC5D. Teclistamab (Tec), talquetamab (Tal), and elranatamab (Elra) are bispecific antibodies (BsAbs) approved for relapsed-refractory multiple myeloma (RRMM). These BsAbs target CD3 on T-cells and either BCMA or GPRC5D on the malignant plasma cells. BsAb toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and ICANS may result in increased frequency and duration of hospitalization for toxicity management. Tocilizumab (Toci), an interleukin-6 receptor antagonist, is a first-line treatment option for CRS. Some institutions have reported success in preemptive use of Toci for CRS prophylaxis; however, more real-world is needed to establish the role of Toci in this setting. **Methods:** A retrospective, single-center analysis of patients with RRMM who received preemptive Toci 8 mg/kg intravenously once 60 minutes prior to first step-up doses of Tec, Tal or Elra between December 2024 and March 2026. **Results:** Thirteen patients received preemptive Toci prior to Tec, Tal or Elra. Notable patient characteristics included 61% male sex (eight male and five female), median age 74 years (range 59–85 years) and median 5 prior lines of therapy (range 3–10). RRMM subtypes included two IgG Kappa, one IgG lambda, one IgA lambda, three IgA kappa, three kappa light chain and three lambda light chain patients. Pre-treatment monoclonal protein ranged from 500 to 6800 mg/dL and light chain from 104.73 to 4,106 mg/L. Eight patients received Tec only, one received Tec plus Dara, and four received Tal. All patients received antiviral and PJP prophylaxis throughout treatment. Additionally, patients were started on antibacterial prophylaxis for absolute neutrophil < 0.5 K/mcL. All patients received intravenous immunoglobulin to maintain functional IgG ≥500 mg/dL, filgrastim to maintain absolute neutrophil 1.00 K/mcL, epoetin alfa to maintain hemoglobin above 10 g/dL, and romiplostim to maintain platelets above 50 K/mcL. Four patients achieved a complete response, eight patients achieved a very good partial response and one patient achieved a partial response (PR). Average time to first response of PR or better was 1 month (range 1–2 months). Three patients progressed after an average of 8 cycles and the remaining 10 patients continue treatment. The median duration of continued response is 6.5 months (range 1–13 months). The only incident of CRS occurred with a single patient who developed grade 1 CRS on C1D3 which resolved after one dose of dexamethasone 10 mg. There was no incidence of ICANS or major infections. **Conclusions:** Preemptive Toci may decrease the incidence and severity of CRS in patients with RRMM receiving BsAbs, without compromising response. In this small observational analysis, no patients experienced prolonged hospitalization for management of CRS.

PA-362

Pre-existing CX3CR1$^+$ Cytotoxic CD4$^+$ T Cells Sustain Durable Responses to Bispecific Antibodies in Multiple Myeloma

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Introduction: Bispecific T-cell engagers (BiTEs) have significantly improved outcomes in relapsed/refractory multiple myeloma (RRMM), yet determinants of durable response remain undefined. We performed longitudinal single-cell transcriptomic and TCR/BCR profiling to identify cellular and clonal programs associated with durable response. **Methods:** We performed longitudinal single-cell RNA, TCR, and BCR sequencing on 23 paired bone marrow samples collected before and after BiTE therapy from 12 RRMM patients. Patients were stratified into long-term responders (LR, ≥18 months; n = 6) and short-term responders (SR, < 18 months; n = 6). **Results:**

After quality control, 171,485 cells were retained for downstream analysis. BiTE treatment induced expansion of CX3CR1$^+$ cytotoxic CD8$^+$ T cells (CD8 TE-CTL) in both LR and SR patients, without association with remission duration. In contrast, CX3CR1$^+$ cytotoxic CD4$^+$ T cells (CD4 TE-CTL) selectively expanded in LR patients and exhibited a terminally differentiated cytotoxic transcriptional program. Trajectory analysis revealed preferential differentiation of TCF7$^+$ stem-like CD4$^+$ T cells into non-exhausted TE-CTL cells in LR patients, whereas SR patients accumulated TCF7$^+$ stem-like cells without terminal effector differentiation. Single-cell TCR profiling further revealed that CD4 TE-CTL populations in LR patients were predominantly composed of shared clonotypes detected both before and after treatment; in contrast, SR patients were enriched for pre-treatment-only clonotypes. Shared clonotypes exhibited enhanced cytotoxic and interferon-response signatures, indicating functional reactivation of pre-existing effector populations during durable response. Concurrently, post-treatment myeloid subsets from LR patients exhibited coordinated IFN-response and antigen-presentation transcriptional programs, consistent with an IFN-driven T cell–myeloid interaction network associated with durable response. **Conclusions:** Durable responses to BiTE therapy are associated with reactivation and persistence of pre-existing CX3CR1$^+$ cytotoxic CD4$^+$ T-cell clonotypes together with IFN-mediated myeloid reprogramming. These findings identify a previously underappreciated CD4$^+$ cytotoxic T-cell axis supporting durable anti-myeloma immunity.

PA-363

Premedication Use and Infusion-Related Reactions in Patients Treated With Subcutaneous Isatuximab: A Pooled Post Hoc Safety Analysis

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Introduction: Premedication is recommended prior to administration of intravenous (IV) isatuximab (Isa), an anti-CD38 therapy for multiple myeloma, per the drug label. In IRAKLIA, 18.1% (931/5145) of Isa subcutaneous (SC) injections with the on-body injector (OBI) were given without premedication and did not lead to infusion-related reactions (IRRs). In this post-hoc analysis, we explored premedication use with Isa SC and Isa IV in the pooled IRAKLIA, IZALCO, and Phase 1b trials and the incidence of IRRs in Isa SC patients (pts) with relapsed/refractory multiple myeloma (RRMM). **Methods:** Pts with RRMM in IRAKLIA (Isa SC: n = 263; Isa IV: n = 264) and the Phase 1b TCD15484 trial (Isa SC dose-expansion cohort: n = 22; Isa IV: n = 12) received 1400 mg Isa SC OBI or 10 mg/kg Isa IV plus pomalidomide and dexamethasone (d). In IZALCO, pts with RRMM (n = 74) received 1400 mg Isa SC OBI or manual injection plus carfilzomib (K)-d. Isa was given over 4-week cycles, weekly for cycle (C)1 and biweekly for subsequent cycles. Premedications included montelukast (C1 only per protocol), steroids (excluding dexamethasone), acetaminophen, H1 antihistamines, and others. Pts without systemic IRRs after 4 consecutive administrations of Isa SC had subsequent premedication reassessed at the investigator's discretion. The time-to-first visit without premedications was estimated using the Kaplan-Meier approach. **Results:** 359 Isa SC pts and 276 Isa IV pts were included. More Isa SC pts (29.0%) had a visit without premedications vs Isa IV pts (20.3%). Median time to first visit without premedication was 21.5 mos for Isa SC and not reached for Isa IV. Overall, 1127/7023 (16.05%) SC and 742/5752 (12.90%) IV injections were given without premedication. No IRRs were reported with Isa SC injections without premedication. During C1, 94.2% of Isa SC and 90.9% of Isa IV pts received 3 unique premedications (primarily acetaminophen, diphenhydramine, and montelukast). In C2, most pts received 2 unique premedications, acetaminophen (Isa SC: 99.0%; Isa IV: 97.5%) and diphenhydramine (or equivalent) (Isa SC: 91.9%; Isa IV: 93.3%); some pts continued montelukast beyond C1, with use declining each cycle. Six (1.7%) Isa SC pts had 8 IRRs, all occurring with premedication at C1 and resolved. There were 5 pts with 1 IRR occurring after the first Isa injection and 1 pt with 3 IRRs at 1st, 2nd, and 3rd injections. Regarding time of onset, 4 IRRs occurred on the day of the injection, 2 occurred 1 day after injection, 1 occurred 2 days after, and 1 occurred 3 days after. IRRs were mainly grade (G)1 (6, 75%) with 1 G2 and 1 G3. The G3 IRR did not lead to drug interruption and resolved with corrective treatment on Day 4. The participant had prior history of infusion reaction. **Conclusions:** Isa SC injections without premedication were more frequent than Isa IV injections without premedication, and no IRRs occurred with Isa SC injections delivered without premedications. The results support Isa SC as a safe delivery option with low incidence of IRRs.

PA-364

Prior BCMA Exposure in Patients with Relapsed/Refractory Multiple Myeloma Treated with Teclistamab or Elranatamab from the IMWG Immunotherapy Registry

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Introduction: BCMA-targeted therapies (BCMA-TT) including CAR T cells (CART), bispecific antibodies (bsAb) and antibody-drug conjugates (ADC), have changed the treatment landscape of relapsed multiple myeloma (RRMM). However, patients (pts) still relapse with limited subsequent treatment options. Data on subsequent treatment with teclistamab (tec) and elranatamab (elra) after prior BCMA-TT is limited due to small cohorts. Here we analyzed the International Myeloma Working Group (IMWG) Immunotherapy Registry for RRMM ps treated with tec or elra after BCMA-TT. **Methods:** Pts with RRMM treated with tec or elra outside of clinical trials were enrolled. Response was assessed using the IMWG consensus criteria. Pt characteristics were summarized by proportion or median (interquartile range [IQR] or range), as appropriate. Kaplan-Meier methods and log-rank tests were used to summarize and compare ORR, PFS, and OS. **Results:** 439 pts from 9 countries (342 tec, 97 elra), of whom 136 received prior BCMA-TT were enrolled. Median follow-up was 11.8 months (mo) (range 0.2–42.1). In the entire cohort median age was 67 (range 32–95), 23% ≥75 years; 49% female; 55% with high-risk cytogenetics (HRCA); 33% with extramedullary disease (EMD). Pts received a median of 6 (IQR 5–8) prior lines of therapy (LOT) with 46% being penta-refractory. The prior BCMA-TT pts had a median age of 66 (range 33–88) with 13% ≥75, 40% female, 59% with HRCAs, 39% with EMD, median 8 (IQR 7–11) prior LOT, and 60% with penta-refractory disease. Prior BCMA-TT included 34% ADC alone, 43% CART alone, 4% bsAb alone, 13% ADC+CART, 2% CART+bsAb, and 4% with other. Median time from last prior BCMA-TT to commencing tec/elra was 8.3mo (range 0.5–77.1). For BCMA-TT, ORR for the last BCMA agent was 64% (44% ≥VGPR). ORR for the entire, BCMA naive and prior BCMA cohorts was 65% (57% ≥VGPR), 72% (64% ≥VGPR), and 48% (41% ≥VGPR). Median PFS (mPFS) was 9.6mo (95%CI 7.4–13.2), 16.1mo (95%CI 12–22), and 2.7mo (95%CI 2.1–5.0); mOS was 26.1mo (95%CI 19.8-not reached [NR]), NR (26.5-NR), and 13.6mo (10.4–17). ORR based on prior BCMA agent(s) was ADC: 58%, CART: 41%, bsAb alone: 33%, ADC +CART: 56% and ≥2 other combination group with last agent being bsAb: 25%. mPFS was ADC 4.9 mo (95%CI 2.5–9.6), CART 2.3 mo (1.2–5.1), bsAb alone 1.9 mo (0.8-NR), ADC+CART 2.5 mo (0.9–13.6) and ≥2 bsAb combinations: 0.9 mo (0.6-NR). mOS was ADC 15.1 mo (95%CI 11-NR), CART 13.0 mo (7.2-NR), bsAb alone 8.8 mo (0.9-NR), ADC+CART 16.9 mo (9.7-NR) and ≥2 bsAb combinations 1.8 mo (1.6-NR). mPFS differed by time from last BCMA to tec/elra: < 9 mo: 2.5 mo (95%CI 1.8–4.9) vs ≥9 mo: 3.4 mo (2.3–13.8) (P = 0.02) and mOS: < 9 mo: 11.5 mo (95%CI 8.5–17) vs ≥9 mo 16 mo (13.6-NR) (P = 0.08). **Conclusions:** Outcomes for patients receiving tec/ elra after prior BCMA were poor, particularly following BCMA bsAb. However, benefits were seen in prior ADC and CART cohorts, particularly with a ≥9-month interval between BCMA treatments. Additional data including safety after prior BCMA exposure will be presented at the meeting.

PA-365

Prognostic Impact of [18F] FDG PET/CT Before and After BCMA-Directed CAR T-Cell Therapy in Relapsed/Refractory Multiple Myeloma: A Multicenter Analysis

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Introduction: Depth of response is one of the most relevant prognostic markers in multiple myeloma (MM), as highlighted by minimal residual disease (MRD) data. Functional imaging such as [18F] FDG PET/CT has gained importance for assessing disease burden and response. However, its prognostic value in relapsed/refractory MM (RRMM) treated with BCMA-directed CAR T-cell therapy remains unclear. We aim to evaluate the prognostic utility of baseline and post-treatment [18F] FDG-PET/CT in this setting. **Methods:** We analyzed patients treated with BCMA-targeted CAR T-cell therapy (April 2018–January 2024) at Clínica Universidad de Navarra (Spain) and IRCCS Azienda Ospedaliero-Universitaria di Bologna (Italy). PET/CT scans at baseline, month 1, and month 3 post-infusion were assessed for focal lesions (FLs), paramedullary (PMD) and extramedullary disease (EMD), alongside metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Response was evaluated using Deauville criteria. Optimal cut-off values with the highest discriminative prognostic value for baseline and month 1 MTV and TLG were determined using the maxstat algorithm (categorized as high vs. low b-MTV, b-TLG, MTV-1, and TLG-1). **Results:** In total 75 patients received BCMA-targeted CAR T-cell therapy (61 Spanish & 14 Italian). ORR was 85%, with 45% achieving ≥CR, and 57% MRD negativity. Median PFS and OS for the entire cohort was 12 (95% CI, 8.8–15.2) and 24 months (95% CI, 15.9–32.3), respectively. Baseline scans were positive in 62 (83%) patients. A positive baseline scan was associated with inferior PFS (11.5 months [95% CI, 7.8–15.3]) compared to having a negative study (18.9 months [95% CI, 12.5–25.4]) ($p = 0.03$). Baseline EMD predicted shorter PFS (4.6 months [95% CI, 3.5–5.8] vs. 14.1 [95% CI, 10.4–17.7]; $p = 0.014$). Baseline high MTV (≥810 mL) and TLG (≥1640 g) predicted inferior PFS (5.6 vs. 15.6 months; HR 1,9; $p = 0.03$) and OS (11.4 months vs. not reached; HR 3.0; $p = 0.002$). At month 1, persistent hypermetabolic PMD trended toward shorter PFS (7.1 vs. 16.0 months; HR 1.8; $p = 0.058$), and significantly shorter OS: 11.7 vs. 42.3 months (HR 2.4; $p = 0.02$). Positive FLs in the absence of PMD and EMD had no significant impact on PFS ($p = 0.32$). At month 3, persistent hypermetabolic PMD was associated with shorter PFS (6.9 months [95% CI, 0.0–14.9] vs. 16 [95% CI, 10.8–21.2]; HR 3.6; $p = 0.006$) and OS (7.8 months [95% CI, 6.8–8.8] vs. 34.2 [95% CI, 10.9–57.1]; HR 3.7; $p = 0.01$). Deauville score 4 FLs trended toward shorter PFS (8 vs. 17 months) compared to Deauville score < 4. **Conclusions:** Baseline tumor burden by PET/CT, including high MTV/TLG and EMD, was associated with inferior outcomes after BCMA-directed CAR T-cell therapy. Early assessment at month 1 appeared suboptimal, as persistent FLs uptake without concurrent EMD/PMD was not associated with worse survival. In contrast, month 3 PET/CT provided the strongest prognostic discrimination, supporting this timepoint as the preferred assessment for post–CAR T response evaluation.

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Prognostic Impact of CDKN2C Mutations in Newly Diagnosed Multiple Myeloma Patients

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Introduction: Deletion of 1p32 (del(1p32)) is a known adverse feature in multiple myeloma (MM). Indeed, the combination of monoallelic del(1p32) with another intermediate risk factors – among 1q gain, t(4;14), t(14;16) or t(14;20) – defines high-risk patients according to the Consensus Genomic Staging (CGS). Moreover, double-deletion of 1p32 defines an ultra-high-risk entity and was also included in the high-risk criteria of the CGS. The putative target of del(1p32) is CDKN2C, which prevents cell cycle G1 progression. However the prognostic impact of CDKN2C mutations has never been assessed to our knowledge. The aim of this study is to assess the prognostic impact of CDKN2C mutations, heterozygous or associated with a monoallelic del(1p32). **Methods:** Clinical data were obtained from 3951 NDMM patients, followed up for ≥ 18 months or having died or progressed within 18 months post treatment. Informed consent was obtained for all included patients. Follow-up duration was estimated using reverse Kaplan-Meier method. Progression free survival (PFS) curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. Tests were two-sided, and $P < 0.05$ was considered significant. All analyses were performed using R version 4.5.3. **Results:** CDKN2C

mutations are rare events. Indeed, only 0.5% of our cohort (21/3951) harbor a mutation. 62% (13/21) of CDKN2C mutations were associated with a monoallelic del(1p32), leading to a biallelic inactivation of CDKN2C. Of note, the frequency of CDKN2C mutations is doubled at first relapse (1.2%). About 60% of mutations are missense variants distributed throughout the coding gene; while 40% are nonsense or frameshift mutations that introduce a premature stop codon, occurring predominantly in exon 1. After a median follow-up of 37 months, the PFS of patients harboring CDKN2C mutations was significantly shorter as the PFS of patients without mutation (20 and 55 months, respectively, P = 0.0005). In the univariate analysis, the risk of progression was increased for patients with CDKN2C mutation (HR: 2.3; 95%CI 1.3–4.1, P = 0.007). In the multivariate analysis (with age, del(1p32), del(17p), t(4;14) and 1q gain), the risk of progression was 1.9 times higher among patients with CDKN2C mutations (95%CI 1.1–3.2, P = 0.02). Patients with both del(1p32)/CDKN2Cmutation (n = 13) had a median PFS of 18 months, which was similar than the PFS of patients with double-deletion of 1p32 (n = 73; PFS = 19 months, P = 0.6). Interestingly, patients with CDKN2C mutation only (n = 8, PFS = 22 months) had a trend toward a lower PFS than patients with a monoallelic del(1p32) (n = 271, PFS = 37 months, P = 0.2), but not significantly due to the low frequency of this event. However, the PFS was significantly lower compared with patients without abnormality of 1p32 (22 vs 55 months, P = 0.009). **Conclusions:** In this study, we are showing for the first time the adverse prognostic impact of CDKN2C mutations, a rare genomic event in MM.

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Prognostic Impact of Echocardiographic Right Ventricular Systolic Pressure in Patients with Multiple Myeloma: A Retrospective Cohort Study

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Introduction: Pulmonary vascular and cardiopulmonary complications are increasingly recognized in patients with multiple myeloma (MM). Echocardiographic right ventricular systolic pressure (RVSP) provides a practical non-invasive estimate of pulmonary pressure, although it does not replace right-heart catheterization for the diagnosis of pulmonary hypertension. This study aimed to evaluate the prevalence, clinical correlates, and prognostic significance of elevated echocardiographic RVSP in patients with MM. **Methods:** We conducted a retrospective cohort study of adult patients diagnosed with MM at Taipei Veterans General Hospital between 2002 and 2025. Patients were included if they had available baseline transthoracic echocardiography. Elevated RVSP was defined as RVSP ≥ 40 mmHg. The primary outcome was overall survival (OS). Variables with $p < 0.1$ in univariate analysis entered multivariable Cox analysis with backward selection. **Results:** A total of 545 patients were included, with a median age of 68 years (range 23–96) and 55.1% were male. The median RVSP was 32.4 (interquartile range 26.0–42.0) mmHg, and 154 (28.3%) patients had RVSP ≥ 40 mmHg. Compared with patients with RVSP < 40 mmHg, those with RVSP ≥ 40 mmHg were older and more frequently had advanced ISS stage, atrial fibrillation, heart failure, pulmonary disease, anemia, hypoalbuminemia, hypercalcemia, elevated β2-microglobulin, and elevated lactate dehydrogenase. Patients with RVSP ≥ 40 mmHg had significantly inferior OS compared with those with RVSP <40 mmHg, with a median OS of 3.2 (95% CI 2.2–3.7) years versus 7.0 (95% CI 5.2–8.6) years, respectively ($p < 0.001$). In univariate analysis, RVSP ≥ 40 mmHg was associated with increased mortality risk (HR 1.88, 95% CI 1.43–2.48). After multivariable adjustment, RVSP ≥ 40 mmHg remained independently associated with worse OS (adjusted HR [aHR] 1.43, 95% CI 1.06–1.95). Other independent predictors of mortality included age ≥ 60 years (aHR 1.66, 95% CI 1.16–2.37), male sex (aHR 2.08, 95% CI 1.55–2.78), diabetes mellitus (aHR 1.42, 95% CI 1.02–1.99), platelet count < 100,000/μL (aHR 1.87, 95% CI 1.34–2.62), β2-microglobulin ≥ 5,500 ng/mL (aHR 1.51, 95% CI 1.12–2.04), lactate dehydrogenase ≥ 250 U/L (aHR 1.40, 95% CI 1.03–1.90), and left ventricular ejection fraction < 50% (aHR 1.47, 95% CI 1.01–2.13). **Conclusions:** Elevated echocardiographic RVSP was common among patients with MM and was associated with adverse clinical features and inferior survival. RVSP ≥ 40 mmHg remained an independent predictor of mortality after adjustment for clinical and laboratory risk factors. RVSP may serve as a practical cardiopulmonary risk marker in MM and support integrating echocardiographic assessment into baseline risk evaluation, particularly for patients with advanced disease burden or cardiac comorbidities. Prospective studies with standardized echocardiography, cardiac biomarkers, and confirmatory right-heart catheterization when clinically indicated are warranted.

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Prognostic Indeces in Multiple Myeloma: Merging Biological and Clinical Risk Factors – on the Brink of the New Prognostic Model

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Introduction: Risk stratification in newly diagnosed multiple myeloma (NDMM) patients (pts) has evolved substantially with introduction of R2-ISS staging system, reflecting disease-related biological risk factors. The IMWG Frailty Score has emerged as a validated tool for assessing patient vulnerability, yet its integration

with established biological prognostic systems remains insufficiently explored in real-world settings. The aim of study was to analyze the prognostic impact both R2-ISS and IMWG frailty score on the 5-years progression-free survival (PFS) and overall survival (OS) in NDMM patients and provide the basis for a novel integrated clinico-biological prognostic model. **Methods:** The single-center study included 371 NDMM pts (male/female 184/187 pts, median age 65 yrs, range 36–88 yrs), during period 2021–2025. The distribution according to the R2-ISS was: I 65 pts (18.6%), II 83 pts (23.8%), III 144 pts (41.3%), IV 57 pts (16.3%). Based on the IMWG Frailty Score, 114pts (30.7%) were fit, 156 pts (42%) intermediate-fit, and 101 pts (27.2%) were frail. Treatment with Bortezomib-based regimens was applied in 285 pts (76.8%), while autologous stem-cell transplantation was performed in 120/203 pts transplant-eligible (59.1%). The prognostic impact of R2-ISS scores (median 1.5, range 0–5), and total additive score incorporated in IMWG frailty web-calculator (median 3, range 1–5) were analyzed in accordance to the COX model, ROC analysis, and Youden index. **Results:** Treatment response (≥PR) was achieved in 275/340 pts (80.9%). Both R2-ISS and IMWG Frailty Score correlated with treatment response (R2-ISS: p = 0.027; IMWG Frailty Score: p = 0.000). R2-ISS system clearly stratified PFS outcomes (Log Rank: Chi-Square 27.424, p = 0.000), as well as OS (Log Rank: Chi Square 30.412, p = 0.000). The IMWG Frailty Score demonstrated strong prognostic value regarding both PFS (Log Rank: Chi Square 32.020, p = 0.000), and OS (Log Rank: Chi Square 72.682, p = 0.000). For 5-yrs survival, time dependent ROC analysis identified optimal cut-off values of R2-ISS score >1 (AUC = 0.638), and total additive score of IMWG frailty calculator >2 (AUC = 0.710), based on the maximum of Youden index. Total additive score >2 of IMWG frailty system is the most reliable tool for 5-yrs OS. Combining the R2-ISS score >1 and Total Additive IMWG Frailty score >2 into a unified prognostic model yielded a superior discriminative capacity (AUC = 0.786; Uno's C-index = 0.737) compared to either model alone. **Conclusions:** While both R2-ISS and IMWG Frailty Score independently provide strong prognostic value, their individual discriminative capacity for 5-yrs survival remains modest. Combining R2-ISS score >1 and Total Additive IMWG score >2, into a unified prognostic model yields a significantly superior and clinically robust tool for NDMM patient risk stratification with a consequent impact on the treatment approach.

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Prognostic Significance of Dynamic Minimal Residual Disease Trajectories in Newly Diagnosed Multiple Myeloma

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Introduction: Minimal residual disease(MRD) status accurately reflects myeloma tumor burden and serves as a sensitive prognostic biomarker superior to conventional response evaluation. Serial MRD monitoring, compared with isolated single-time detection, better delineates deep disease remission and clinical prognosis. This real-world study aims to investigate longitudinal MRD dynamics and their clinical significance in patients with newly diagnosed multiple myeloma(NDMM). **Methods:** This retrospective study included NDMM patients diagnosed after June 2018. Therapeutic responses were assessed after induction, 3 months post-transplantation/consolidation, and every 3–6 months during maintenance. For patients achieving CR or better, bone marrow MRD was detected by next-generation flow cytometry(NGF) with a negativity threshold of 10–5. Patients were divided into three groups: sustained MRD-(sustained for ≥12 months), persistently MRD+(never achieved MRD-), and MRD conversion(initial MRD- followed by subsequent MRD recurrence). ROC curve analysis was used to determine the optimal cut-off values for circulating plasma cell(CPC) at baseline and abnormal plasma cell proportion in total bone marrow plasma cells (abnormal PC/BMPC%) at MRD conversion, with the cut-off for both variables selected according to the maximum Youden index. For abnormal PC/BMPC%, the ROC endpoint was disease progression after MRD conversion. **Results:** A total of 231 NDMM patients achieving CR or better with ≥2 serial MRD detections were enrolled: 32(13.85%) never achieved MRD-, 88(38.10%) experienced MRD conversion, and 68(29.44%) sustained MRD- ≥12 months. Persistently MRD+ patients were older and had a lower transplantation rate than the other two groups(all P < 0.05). Median overall follow-up was 49(43, 60) months. Median PFS was 25 months (persistently MRD+), 39 months(MRD conversion), and not reached(sustained MRD-), with significant pairwise differences(all P < 0.05). Median OS was not reached in all groups; sustained MRD-patients had a higher OS rate than the other two groups (both P < 0.05), while OS did not differ between persistently MRD+ and MRD conversion groups(P = 0.163).MRD- independently predicted better PFS(HR = 0.222, P < 0.001) and OS(HR = 0.280, P = 0.019). Sustained MRD- ≥6 months improved OS(P < 0.001), and ≥12 months benefited both PFS and OS(both P < 0.001). Late MRD conversion, defined as MRD recurrence ≥12 months after first MRD negativity, showed OS comparable to patients with sustained MRD negativity(P = 0.339). Independent risk factors for post-conversion progression were elevated CPC at diagnosis(≥0.105%, HR = 3.761, P = 0.021), failure to achieve MRD negativity after induction (HR = 2.886, P = 0.037), and abnormal PC/BMPC% >31.9% at MRD conversion(HR = 4.091, P = 0.009). **Conclusions:** These findings demonstrate that sustained MRD- predicts favorable outcomes in NDMM. Dynamic MRD trajectories closely correlate with survival and post-conversion progression risk, supporting MRD-driven individualized therapy.

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Propensity Score Weighting Analysis of the KPD Regimen as Salvage Therapy in Newly Diagnosed Multiple Myeloma Patients With Suboptimal Response or Intolerance to V-Based Regimens

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Introduction: The aim of this study is to investigate the clinical efficacy and safety of the combination therapy of Carfilzomib, Pomalidomide, and dexamethasone (KPd) as a salvage treatment in newly diagnosed multiple myeloma (NDMM) patients with poor efficacy or intolerance to first-line bortezomib (V-base) regimen, and to compare it with continuing the original regimen or replacement chemotherapy drugs, providing real-world evidence for optimizing clinical treatment strategies. **Methods:** Retrospective analysis of NDMM patient data admitted to six prefecture level medical centers in Henan Province. The inclusion criteria are patients who have not achieved Partial Response (PR) after 2 cycles or failure to achieve Very Good Partial Response (VGPR) after 3 cyclestherapy with V-base regimen (VRd, VCd, orVd), or who have experienced ≥ grade 2 adverse reactions. According to the follow-up treatment strategy, they a re divided into an upgrade treatment group (converted to KPd regimen) and a maintenancetreatment group (continued with the original regimen or simply changed chemotherapy drugs). Using Propensity Score Weighting (PSW) to balance baseline characteristics (including gender, age, ISS,ECOG,etc.) between two groups. Primary comparisons included objective response rate (ORR) and the incidence of treatment-emergent AEs. **Results:** A total of 29 eligible patients were included. After PSW adjustment, baseline characteristics were well balanced between groups. Efficacy: CR was achieved in 41.2% (7/17) in the intensification group vs 0.0% (0/12) in the maintenance group ($P < 0.05$). VGPR was observed in 35.3% (6/17) vs 25.0% (3/12) ($P < 0.05$). PR occurred in 23.5% (4/17) vs 58.3% (7/12) ($P < 0.05$). SD was reported only in the maintenance group, 16.7% (2/12), with no SD in the intensification group ($P < 0.05$). Safety: hematologic toxicities (thrombocytopenia, neutropenia) and infections were more frequent in the intensification group ($P < 0.05$); anemia was less frequent, and heart failure did not differ between groups ($P > 0.05$). Patients receiving intensification presented more advanced disease (higher ISS/R-ISS, predominantly stage III), poorer performance status (higher ECOG), greater tumor burden (elevated β2M, LDH, Ca, Scr), and reduced renal reserve (lower CrCl), indicating a clinically high-risk, hard-to-treat population. **Conclusions:** For NDMM patients with poor efficacy or intolerance to first-line V-base regimen, early upgrading to KPd regimen can significantly improve the depth of remission and overcome refractory status. Although it is accompanied by high hematological toxicity and infection risk, it has significant clinical benefits under close monitoring. This strategy is particularly suitable for salvage treatment scenarios with severe baseline conditions and high-risk stages.

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Prophylactic Tocilizumab to Mitigate Cytokine Release Syndrome and Facilitate Dosing of Talquetamab (Tal) in all Practice Settings in Relapsed/Refractory Multiple Myeloma (RRMM): Results from MonumenTAL-1

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Introduction: Talquetamab is the first and only approved bispecific antibody targeting GPRC5D for the treatment of RRMM. In the phase 1/2 MonumenTAL-1 study, cytokine release syndrome (CRS) occurred in 75% (17% gr 2; 1% gr 3) of patients (pts) in the 0.8 mg/kg Q2W cohort without prophylactic tocilizumab (toci), with 37% receiving toci treatment for a CRS event. A prior analysis of the exploratory cohort D showed that a single dose of toci before Tal step-up dosing (SUD) reduced CRS incidence and severity. Here, we report CRS incidence from prospective exploratory cohorts of the phase 2 MonumenTAL-1 study: cohort D, with more pts and longer follow-up, and cohort E, with alternative SUD, in pts with RRMM. **Methods:** Pts in cohort D ($n = 30$) received the standard 3 SUDs (Tal 0.01, 0.06, and 0.4 mg/kg SC followed by 0.8 mg/kg Q2W), with the first 10 pts receiving SUDs and first full treatment dose in a hospital and subsequent pts treated as outpatients.

Pts in cohort E received 2 SUDs (0.06 and 0.4 mg/kg; n = 10) or 1 SUD (0.4 mg/kg; n = 10), all treated in a hospital setting. Toci 8 mg/kg IV was given ~3 hours before the first Tal SUD, along with other required pretreatments given before each SUD and first full treatment dose. 1 pt in cohort E (2 SUDs) did not receive the toci prophylaxis. Dexamethasone (dex; 8 mg PO or IV) was given daily for 2 days after each SUD and the first full treatment dose. Pts were then treated with Tal 0.8 mg/kg Q2W (Q4W cycle 7+). Pts had ≥3 (cohort D) or ≥1 prior lines of therapy (LOT) (cohort E) and all were triple-class exposed. **Results:** Median age was 66 y; 66% were male and 86% were White. Median prior LOT in cohorts D and E were 4 and 4 (1 SUD) and 3.5 (2 SUDs), respectively. Median follow-up was 12.3 mo in cohort D and 1.5 mo (1 SUD) and 4.0 mo (2 SUDs) in cohort E. CRS was reported in 26% of pts (all gr 1 except 2 pts in cohort E single SUD group with gr 2 events); neurotoxicity AEs and ICANS were reported in 36% and 6% of pts and were all gr 1/2. The most common AEs across cohorts (N = 50) were taste changes (72%), skin (60%) and nail (34%) AEs, dry mouth (34%), and rash (20%). Gr 3/4 AEs occurred in 66% of pts, of which neutropenia (20%) and lymphopenia (12%) were the most common. Infections occurred in 46% of pts (gr 3/4, 14%). No pts discontinued treatment due to AEs. Deaths occurred in 5 pts, all in cohort D (2 due to AEs and 3 due to disease progression). Furthermore, no CRS or ICANS have occurred in an additional ongoing outpatient cohort of 10 pts who received 2 SUDs (0.06 mg/kg and 0.4 mg/kg) + prophylactic toci. Further follow-up data, including response, will be presented at the congress. **Conclusions:** Use of prophylactic toci with Tal ± a modified Tal SUD schedule demonstrated a reduction in the incidence and severity of CRS and manageable safety profile. No increase in neutropenia or infection rates was observed. These results may support broader implementation of Tal with toci prophylaxis and postdose dex across all practice settings in pts with RRMM.

PA-372

Prophylactic Tocilizumab to Prevent Cytokine Release Syndrome in Patients with Relapsed and Refractory Multiple Myeloma Receiving Cilta-cel

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Introduction: Cilta-cel is commonly associated with immune effector cell (IEC) toxicities such as CRS (76–95%) and ICANS (21%). A single dose of tocilizumab (toci) reduces the risk of CRS in patients (pts) receiving bispecific antibodies. Here, we present a retrospective analysis to evaluate efficacy and safety of a single dose of prophylactic toci to mitigate the incidence and the severity of CRS and ICANS in RRMM pts receiving cilta-cel. **Methods:** Starting June 2025, a single dose of prophylactic toci (8 mg/kg, max 800 mg) was administered in all pts receiving cilta-cel per standard of care. Given a median time to CRS onset of 7–8 days in registrational studies, toci was planned on day 5 after cilta-cel infusion. **Results:** 68 consecutive RRMM pts (median age 65 years, range 42–81) undergoing cilta-cel, with planned prophylactic toci, between June 2025 and April 2026 were included in the analysis (intention-to-treat, ITT group). The median number of prior therapies was 3 (range 1–8); 81% of patients received bridging therapy and 64% had at least a partial response (PR). 57/68 pts (84%) received prophylactic toci on day 5 per protocol (PP) while 11/68 (16%) did not due to early CRS (day 1–5, median time to onset, 2 days). In the ITT group (n = 68), 29% of pts experienced CRS (grade 1, 21%; grade 2, 7%, grade 3, 2%) and 10% experienced ICANS (grade 1, 7%; grade 2, 2% grade 4, 2%). In the PP group, of pts who received prophylactic tocilizumab (n = 57), grade CRS occurred in 16% (grade 1, 11%, grade 2, 5%), with a median time to onset of 8 days (range 5–10) and duration of 1 day (range, 1–4 days). 8/9 pts with CRS in the PP group required ^{3}1 additional dose of toci and dexamethasone was administered in 3/9 pts. Only 1 grade 1 ICANS event occurred in the PP group and resolved in 1 day. Non-ICANS neurotoxicity occurred in 2 pts (3.5%, cranial nerve palsy, 1 cranial nerve palsy and GBS): no enterocolitis or hemophagocytic syndrome were observed. Any grade infection within 90 days from cilta-cel infusion occurred in 14% of pts (grade 1, 7%; grade 2, 7%). The overall response rate (^{3}PR) was 90% (sCR/CR, 49%; VGPR, 35%; PR, 5%). At the current median follow-up (9 months), 2 pts have died in remission and 2 pts have progressed. The average total ALC peak expansion within 30 days since cilta-cel infusion was 1.6 × 10^9/L (range 310–20,669); 39% of pts had ALC ≥ 3000 between day 10 and 14 and received prophylactic dexamethasone. **Conclusions:** In pts receiving cilta-cel, a single dose of prophylactic toci on day 5 resulted in a very low incidence and severity of CRS and ICANS with preserved CAR T-cell expansion and efficacy, comparing favorably to phase II/III trials. Our results support the adoption of prophylactic toci to improve tolerance and toxicity particularly in an older patient population as well as facilitate cilta-cel outpatient administration in selected patients.

PA-373

Prospective Study of Peripheral Residual Disease (PRD) Monitoring by Clonotypic Mass Spectrometry (EasyM) in patients with Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: Minimal residual disease (MRD) negativity correlates with improved outcomes and is a reliable biomarker of treatment efficacy. However, NGS (Next generation sequencing) and NGF (next generation flow)-based MRD assessments rely on serial bone marrow (BM) assessments, which is often limited by sample variability. EasyM, clonotypic mass spectrometry assay enables non-invasive peripheral residual disease(PRD) monitoring through quantitative tracking of serum M-protein using 'patient-specific peptide fingerprint'(Liyasova 2021). **Methods:** This prospective, multi-center study enrols transplant eligible (TE) and transplant ineligible (TI) newly diagnosed multiple myeloma patients(pts) within 4 months of treatment initiation. Pts with M protein of >2 g/L and/or involved free light chains (iFLC) of >200 mg/L undergo monthly conventional myeloma tests and PRD assessments with EasyM at screening (visit(v)1), and q3 months(v2+) for TI; post-induction (v2), at day100 post-ASCT; (v3) and q3 monthly (v4+) for TE pts. BM MRD by NGF (sensitivity 10–5) is done after achieving EasyM PRD- status. The primary objective is to compare conventional tests, EasyM PRD and BM MRD to establish the role of EasyM in clinical practice. **Results:** As of April 27, 2026, 70 pts were pre-screened. A unique clonotypic peptide was successfully identified in 69 pt- 1pt with iFLC level below assay detection threshold failed screening. Among 59 pts with measurable paraprotein, median screening M-protein concentration was 16.8 g/L(range 1.1–68.1); with IgG in 74% (n = 51), IgA in 10% (n = 7) and IgD in 1 pt. Eleven pts had light chain (LC) myeloma (14%; kappa = 6; lambda = 5), with median iFLC of 2493 (range 22.9–9381) mg/L. All 69 pts meeting eligibility criteria had successful baseline identification of clonotypic peptide, including 2 pts with M-protein < 2 g/L and 10 evaluable pts with LC MM. Forty-six (67%) pts were TE. At the time of analysis, 34 (49%) had completed ASCT (29 single, 5 tandem), 12 (17%) pts had started induction with ASCT intent, 15 pts (21%) were TI, and 4 pts were yet to start myeloma treatment. At a median follow up of 9.56 (range 1–22.6) mos, 64, 54 and 37 pts completed visits 2, 3 and 4, with ≥VGPR rates of 67% (43/64), 72% (39/54) and 97% (36/37), respectively. At the last follow up, 9 pts were PRD-by EasyM; 6 pts had concomitant BM MRD-, 1 pt was BM MRD+ (oligosecretory) and BM MRD is pending in 2 pts. In pts who underwent BM assessment outside this study, 6 showed concordant results [PRD+ MRD+], while 3 discordant results with MRD- but PRD+ (all IgG paraprotein) were observed. One subsequently turned PRD- at 6 months; follow-up for the remaining is ongoing. To date, 2 pts progressed (PD) within 1 month of treatment initiation, while 2 progressed by EasyM, without conventional evidence of PD; follow is ongoing. **Conclusions:** This prospective study evaluates EasyM as a sensitive, non-invasive serum-based method for longitudinal PRD monitoring and prediction of BM MRD status. Updated results will be presented.

PA-374

PROTAC-Mediated CBP/p300 Degradation Targets Myeloma Cell Survival and Overcomes Macrophage-Mediated Therapy Resistance in Multiple Myeloma

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Introduction: Multiple myeloma (MM) remains incurable, with disease progression driven by tumour-intrinsic mechanisms and protective interactions within the bone marrow microenvironment (BME). Tumour-associated macrophages (TAMs) promote MM survival and resistance to anti-myeloma therapies, including dexamethasone (Dex). CREB-binding protein (CBP) and p300 regulate oncogenic and pro-survival pathways, including c-MYC and STAT3 signalling. The CBP/p300 degrader CBPD-409 exhibits potent anti-myeloma activity in vitro and suppresses disease progression in vivo. However, its ability to overcome macrophage-mediated therapy resistance remains unknown.Aim: To determine whether CBPD-409 overcomes macrophage-mediated Dex resistance in MM and compare it's activity with the CBP/p300 inhibitor CCS1477/Inobrodib. **Methods:** MM1.S cells were cultured alone or co-cultured 1:1 with M2-polarised macrophages and treated for 72 h with DMSO, CBPD-409 (0.5 nM), Inobrodib (5 nM), Dex (100 nM), and combinations of Inobrodib or CBPD-409 with Dex. MM cell survival and apoptosis were quantified by Annexin V-FITC/PI flow cytometry. Data represent mean ± SEM from 4 independent experiments. RNA sequencing from six independent experiments compared transcriptional responses to CBPD-409 and Inobrodib. **Results:** Macrophages protected MM1.S cells from Dex-induced apoptosis, increasing MM cell survival from (41.6 ± 7.9%) to

(80.4 ± 2.2%) (n = 4). CBPD-409 retained anti-myeloma activity under macrophage-protective conditions, reducing survival to (37.4 ± 13.9%) and (42.1 ± 3.0%) in monoculture and co-culture. Combined CBPD-409 and Dex treatment produced the lowest survival, reducing viability to (5.0 ± 2.3%) and (10.9 ± 2.3%) in monoculture and in co-culture. In contrast, Inobrodib and Dex showed reduced synergistic activity in monoculture (29.7 ± 4.8%) in comparison to CBPD-409 when combined with Dex and further failed to overcome macrophage-mediated protection in combination with Dex (82.6 ± 2%). Macrophage viability remained largely unaffected, indicating selective targeting of MM cells. RNA sequencing demonstrated broader suppression of oncogenic and pro-survival programmes by CBPD-409 than Inobrodib, including greater downregulation of MYC, IRF4, CCND2, BCL2 and BCL2L1 (BCL-xL). Approximately 45% of genes suppressed by CBPD-409 were not significantly downregulated by Inobrodib. Notably, BCL2 and BCL2L1 were selectively repressed by CBPD-409. Given the role of BCL-xL in macrophage-mediated drug resistance, these findings suggest a potential mechanism underlying the activity of CBPD-409. **Conclusions:** CBP/p300 degradation exhibited greater anti-myeloma activity than CBP/p300 inhibition while overcoming macrophage-mediated Dex resistance. CBPD-409 directly targets MM cells while disrupting macrophage-driven BME resistance pathways, supporting further development of CBP/p300 degraders for MM.

PA-375

Proteogenomic Integration Reveals Predictive Signatures of Ibrutinib Response in Waldenström Macroglobulinemia

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Introduction: Over a decade ago, the BTK inhibitor ibrutinib (IBR) became the first approved agent for the treatment of patients Waldenström Macroglobulinemia (WM). Despite the high response rates and durable remissions, about a third of patients fail to respond to therapy while there is notable heterogeneity in the depth and timing of response. Clonal characteristics are important in elucidating the reasons for this heterogeneity, but peripheral blood biomarkers could be able to capture clonal and microenvironmental heterogeneity of the disease, providing new insights and prognostic tools. **Methods:** We conducted high-throughput plasma proteomic profiling using the Olink® Explore HT library. We profiled 84 peripheral blood plasma samples from 35 patients before (T1) and after (T2) IBR therapy, consisting of 21 responding (R) and 14 non-responding (NR) patients. Proteomic data were also integrated with single-cell RNA sequencing data from matched bone marrow (BM) samples to disentangle the relationship between BM gene expression and circulating plasma proteins. **Results:** Differential Protein Expression analysis between T1 and T2 in both groups identified over 350 proteins up-regulated at T1 primarily enriched by chemokines such as CXCL13, CXCL5 and CCL17. Feature selection using elastic net regression combined with principal component analysis identified key genes enriched in NR at T1, including AKT2, PPP2R5A, and RICTOR, mainly involved in AKT/mTOR signaling pathway. Integration analysis identified a cell–cell adhesion gene signature, comprising PCDH9, NEB, and CNTN5, that was driven by BM B cells and associated with increased plasma protein levels in R at T1 also associated with longer progression-free survival (PFS; $p < 0.05$). By applying linear models, we were able to infer the cell type of origin for key plasma proteins. Specifically, LTB, TNF, and PCDH9 were predominantly associated with malignant B cells, whereas LAG3, TIGIT, and CTLA4 were primarily derived from T cells. Furthermore, by incorporating IBR response as an interaction term in the linear models, we were able to identify the response group-specific cellular origin of these plasma proteins. Specifically, PCDH9 was predominantly derived from malignant B cells in the R group, whereas TNF and TIGIT originated primarily from malignant B cells and T cells in the NR group. To identify factors underlying shared variance between the two assays, we applied the MOFA-FLEX tool. We identified a latent factor (LF4) that differed significantly between the two response groups at diagnosis characterized by elevated protein expression of EIF4E and IRAK4 in the NR and increased gene expression of CD9, XBP1, and CHST15 in B cells of the R group; a signature also associated with shorter PFS ($p < 0.05$). **Conclusions:** In conclusion, our results highlight the identification of plasma biomarkers for WM and demonstrate shared programs between the two compartments that can be used to elucidate response status and predict progression.

PA-376

PTX Syndrome: A Novel Clinical Concept Explaining the Diagnostic Complexity of Plasma Cell Disorders with Cytopenia — A Single-Center Retrospective Study with Case-Based Analysis

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Introduction: Cytopenia is common in plasma cell disorders (PCD), but its etiology is often multifactorial and incompletely

understood. We observed that some PCD patients with cytopenia harbor additional hematopoietic or immune abnormalities. We therefore propose a novel clinical concept, "PTX syndrome," integrating Plasma cell disorder (P), T-cell abnormality (T), and with or without additional hematopoietic or immune abnormalities (X). **Methods:** We conducted a single-center retrospective study (2022–2026) of PCD patients with cytopenia who underwent extended etiologic evaluation. Clinical, morphologic, immunophenotypic, cytogenetic, and molecular data were analyzed. **Results:** Twelve patients met inclusion criteria (5 MGUS, 1 SMM, 6 MM). All patients (100%) exhibited T-cell abnormalities (T-LGLL or T-CUS). Autoimmune serologic positivity was observed in 41.7%, erythroid disorders in 33.3%, and MDS/pre-MDS features in 33.3%. In SMM/MM patients, CD38 monoclonal antibody–based therapy achieved ≥PR in 100% and hematologic recovery in 100%, outperforming non-CD38 regimens. In contrast, MGUS patients primarily treated with immunosuppressive or hypomethylating therapy showed limited hematologic improvement (20%), and some demonstrated clonal progression with one case progressing to active MM after six years. **Conclusions:** PTX syndrome represents a distinct and likely underrecognized clinical entity in PCD patients with cytopenia. Comprehensive multilineage evaluation is essential. CD38-directed therapy shows promising efficacy in SMM/MM, and targeting the JAK–STAT pathway may offer future therapeutic potential.

PA-377

Quadruplet Induction Followed by Teclistamab Consolidation and Doublet Maintenance in Patients with Primary Plasma Cell Leukemia (QUANTUM): A Prospective Randomized Phase 2 Study

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Introduction: Primary plasma cell leukemia (pPCL) is a rare and aggressive plasma cell neoplasm characterized by circulating plasma cells, frequent extramedullary disease, and inferior survival outcomes compared with multiple myeloma. Contemporary series report median overall survival ranging from approximately 18 to 36 months despite the use of proteasome inhibitor- and immunomodulatory drug-based approaches and autologous stem cell transplantation. Prospective studies in pPCL remain limited and outcomes remain poor despite intensified treatment strategies, highlighting a significant unmet need for novel therapeutic approaches. A prospective randomized study was developed to evaluate whether incorporation of B-cell maturation antigen (BCMA)-directed therapy into frontline management can improve outcomes in transplant-eligible patients with newly diagnosed pPCL. **Methods:** Alliance A062401 (QUANTUM; NCT07605416) is a prospective 1:1 randomized phase II study enrolling transplant-eligible patients with newly diagnosed pPCL. Eligible patients must have >5% circulating plasma cells at diagnosis, measurable disease according to International Myeloma Working Group criteria, fitness for autologous stem cell transplantation, and receipt of no more than one prior cycle of induction therapy. Participants are randomized to receive standard quadruplet induction followed by autologous stem cell transplantation with or without BCMA-directed consolidation, followed by doublet maintenance. The primary endpoint is overall survival. Secondary endpoints include safety and tolerability, response rates (overall response rate, very good partial response, complete response, stringent complete response), progression-free survival, time to response, time to progression, duration of response, and measurable residual disease (MRD) negativity at predefined treatment landmarks. Planned enrollment is 64 patients (32 per arm), providing ≥80% power to detect a hazard ratio of 0.50 using a one-sided α of 0.10. Correlative analyses include central pathology review of diagnostic bone marrow biopsies, aspirates, and peripheral blood smears, longitudinal circulating plasma cell assessment, genomic profiling, biobanking, and imaging-based evaluation at serial disease milestones. The clinical trial is supported by NCI U10CA180821, U10CA180882, Janssen. **Results: Conclusions:** pPCL remains a disease with poor outcomes and limited prospective evidence to guide management. This randomized phase 2 study evaluates a frontline strategy incorporating BCMA-directed consolidation into transplant-based therapy with the goal of improving survival and depth of response. Correlative analyses may further define mechanisms of resistance, disease biology, and predictors of durable remission in this high-risk population.

PA-378

Quantifying the Rise of Non-Cancer Mortality in Multiple Myeloma: A SEER Database Analysis (2000–2030)

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Introduction: The transformation of Multiple Myeloma (MM) into a chronic condition has exposed survivors to emerging non-cancer mortality risks. This study quantifies the modern burden of cause-specific deaths and projects future mortality trends to guide survivorship care. **Methods:** We identified 129,837 patients diagnosed with MM from 2000–2022 using SEER-17 registries. Patients were stratified by era: Pre-Novel (2000–06), Early-Novel (2007–14), and Modern (2015+). Median overall survival (mOS) and cumulative incidence function of death (CIF) were analyzed using Kaplan-Meier estimates and Gray's test, respectively. Fine-Gray competing risk regression was used to estimate sub-distribution hazard ratios (sHR) for non-cancer death. Non-cancer mortality burden was projected from 2021–2030 using linear regression models based on 2010–2021 trends. **Results:** Median Overall Survival (mOS) improved from 32 months (Pre-Novel era) to 49 months (Early-Novel era) and 63 months (Modern era) ($p < 0.001$). Modern-era patients had lower odds of dying from MM compared to the Pre-Novel era (OR 0.68, 95% CI 0.66–0.71, $p < 0.001$). The 5-year CIF of MM-specific death decreased from 46.5% (Pre-Novel) to 28.0% (Modern) while the non-cancer death remained stable (20.2% vs 20.7%). Among 82,585 total deaths recorded, Myeloma remained the primary cause (62.5%), while non-cancer causes accounted for 37.5%. Cardiovascular disease was the most common specific non-cancer cause, accounting for 11.4% (n = 9,383) of all deaths. Early decedents (< 3 years) had significantly higher odds of dying from Myeloma compared to late survivors (65.1% vs 58.5%;OR 1.32, $p < 0.001$). In contrast, late survivors (≥3 years) had significantly higher odds of death from cardiovascular disease (OR 1.16, 95% CI 1.11–1.21, $p < 0.001$) and Infections (OR 1.16, 95% CI 1.05–1.28, $p = 0.003$) as compared to early decedents. In Fine-Gray competing risk models, the modern era was associated with a reduced relative hazard of non-cancer death (sHR 0.80, $p < 0.001$). The population of MM is projected to grow by 34.5% (from ~47,200 to ~63,500) between 2022 and 2030 and annual Myeloma-specific deaths are projected to increase by 6.1% (~2,980) by 2030, annual non-Cancer deaths are projected to rise by 38.8% (~3,600). **Conclusions:** Novel therapies have nearly doubled MM survival, but a rising absolute burden of non-cancer deaths—projected to surge by 2030—narrows the mortality gap. Modern MM management must now mandate comprehensive, long-term survivorship care.

PA-380

Radiographic Response to Bridging Therapy is Predictive of efficacy post BCMA CAR T-cell therapy in relapsed/refractory multiple myeloma

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Introduction: BCMA CAR T-cell therapy produces deep responses in relapsed/refractory multiple myeloma (RRMM), yet most patients ultimately progress. Bridging therapy, though non-standardized, is routinely administered between apheresis and infusion for disease control, but its impact on post-CAR T outcomes is incompletely characterized. We examined the prognostic impact of radiologic and biochemical response to bridging therapy on CAR T outcomes. **Methods:** We analyzed 102 RRMM patients treated with ciltacabtagene autoleucel (2018–2024) who underwent serial FDG PET/CT. Three PET/CT timepoints were analyzed: pre-apheresis (80 scans, 307 lesions), pre-lymphodepleting chemotherapy (LDC) (98, 336), and first progression (PD) (102, 178). Radiologic response was assessed using Deauville-based criteria for changes in lesion maximum standardized uptake value. Biochemical response was assessed per International Myeloma Working Group criteria. Progression-free (PFS) and overall survival (OS) were estimated by Kaplan-Meier method, with groups compared by log-rank test. **Results:** The cohort (median age 66) was heavily pretreated (median 5 prior lines): all triple-class exposed, 65% penta-class exposed, 90% prior transplant, 26% with EMD, and 57% with high-risk cytogenetics. 83 patients received bridging therapy (68% systemic only, 10% systemic + radiotherapy (RT), and 4% RT only). Biochemical responses to bridging therapy (n = 98) were complete response (CR) or very good partial response (VGPR) in 15%, partial response (PR) in 7%, stable disease (SD) in 8%, and PD in 69%; radiologic responses (n = 75) were CR in 37%, PR in 7%, SD in 20%, and PD in 36%. Both biochemical and radiographic PD occurred in 31%. At median follow-up of 19 months, 24-month PFS and OS were 48% and 74%, respectively. Radiologic response to bridging (CR/PR vs /SD/PD) was significantly associated with PFS ($p < 0.001$) and OS ($p = 0.023$), whereas biochemical response (CR/VGPR/PR vs SD/PD) was not associated with either (PFS $p = 0.568$; OS $p = 0.918$). Combined stratification (both vs radiologic only vs biochemical only vs neither) was significantly associated with PFS ($p < 0.001$) and trended with OS ($p = 0.074$). Patients with biochemical but not radiologic SD/PD had PFS comparable to those who responded by both criteria ($p = 0.360$), while radiologic SD/PD was associated with markedly worse PFS even in patients with biochemical response ($p < 0.001$). Among biochemical non-responders, radiologic response remained associated with PFS ($p = 0.007$). **Conclusions:** Radiographic bridging response significantly predicted CAR T efficacy, and pre-CAR T PET/CT provided prognostic stratification beyond biochemical response. These findings suggest that combined modality approaches warrant strong consideration, as persistent radiographic disease, even with biochemical response, portends inferior outcomes. Routine PET/CT during bridging may identify high-risk lesions amenable to local therapy (e.g., RT) and inform post-infusion salvage/consolidation strategies.

PA-381

Rapid Clinical Whole-Genome Sequencing Provides Real-Time Risk Stratification and Immunotherapy Selection in Multiple Myeloma

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Introduction: The IMS/IMWG consensus genomic staging emphasizes the importance of identifying high-risk multiple myeloma (MM) at diagnosis and restaging at subsequent progression events. However, traditional fluorescence in situ hybridization (FISH) tests and panel sequencing tests can take weeks to complete, fail to fully capture structural variants, and can miss critical mutations affecting risk stratification and therapeutic targets. To address this unmet need, we validated the JAYseq clinical test, a rapid whole-genome sequencing (WGS) platform designed for comprehensive prognostication and risk-adapted therapeutic selection within 72 hours, at the TGen Clinical Laboratory. **Methods:** The JAYseq test couples CD138+ plasma cell enrichment from bone marrow aspirates with >118x PCR-free WGS analyzed by our custom analysis and interpretation algorithms to produce a clinically actionable, MM-specific report with a median turnaround time of ~58 hrs. By interrogating all 3 billion base pairs of the tumor genome, the workflow simultaneously assesses single-nucleotide variants (SNVs), INDELs, copy number alterations (CNAs), structural rearrangements (translocations, inversions, and deletions) in a single unified assay with sensitivity, specificity, and accuracy exceeding 95% for all variant types, and a limit of detection down to 6% variant allele frequency. **Results:** The platform directly resolves the IMS/IMWG "high-risk" diagnostic gap by FISH by identifying TP53 mutations along with CDKN2C and TP53 deletions down to single exon events. Furthermore, JAYseq evaluates the mutational status of therapeutic targets including cell-surface antigens (BCMA, CD38, CS1, GPRC5D) targeted by approved immunotherapies. It identifies mutations that block therapeutic agent binding along with mutations that prevent cell surface expression (nonsense or frameshift mutations, large or focal deletions, translocations, and inversions) all of which drive antigen escape. To date, we have provided reports for 39 patients: 54% (n = 21) are molecular high-risk, 44% (n = 17) are hyperdiploid, and 56% (n = 22) have predicted loss-of-function in immunotherapy target genes, including 21% (n = 8) with loss of BCMA. The comprehensive nature of this WGS test has identified clinically and biologically relevant events such as the likely high-risk t (8;14)/IGH::MAFA (n = 2), MYC rearrangements with a diverse array of plasma cell enhancers (IGH, IGK, IGL, NSMCE2, TENT5C, TXNDC5) (n = 11), and CCND3 rearrangements with IGK and IGL. **Conclusions:** Ultimately, JAYseq transitions WGS from a retrospective research platform into an actionable, real-time clinical tool. By combining new consensus on risk stratification with prognostic associations and rapid forecasting of immunotherapy resistance, this assay addresses core priorities for newly diagnosed and relapsed MM patient management, providing a scalable framework for precision hemato-oncology.

PA-382

Rapid Hemoglobin Recovery with Enarodustat in Newly Diagnosed Multiple Myeloma Patients with Anemia: A Single-Center Single-Arm Study with Historical Comparison

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Introduction: Anemia is a common complication in patients with Multiple Myeloma (MM), frequently accompanied by renal dysfunction and associated with impaired treatment tolerance and quality of life. Current therapies are limited by delayed hematologic recovery and safety concerns. Enarodustat is an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor and has demonstrated efficacy in renal anemia; however, evidence in MM-associated anemia remains limited. We evaluated the effectiveness of Enarodustat in promoting hemoglobin (Hb) recovery in newly diagnosed MM patients with anemia. **Methods:** This single-center, single-arm study included newly diagnosed MM patients with baseline anemia (Hb < 80 g/L) who received Enarodustat combined with standard anti-myeloma therapy. Hb levels were assessed longitudinally through week 20. The primary endpoint was absolute Hb change from baseline to week 20. Hemoglobin response rates, defined as Hb increases of ≥10 g/L, ≥20 g/L, and ≥30 g/L, were also analyzed. A matched historical cohort treated with standard anti-myeloma therapy alone was included for exploratory comparison. Changes in Hb over time were evaluated using mixed-effects modeling. **Results:** A total of 29 newly diagnosed MM patients receiving Enarodustat were included. For exploratory comparison, 65 matched historical controls were analyzed.Mean (SD) baseline Hb levels were 63.03 (11.34) g/L in the Enarodustat cohort and 69.63 (8.68) g/L in historical controls. Mean (SD) serum creatinine levels were 229.62 (239.09) μmol/L and 188.32 (161.11) μmol/L, respectively. Rapid and sustained Hb recovery was observed in the Enarodustat cohort, with separation of Hb response curves evident from week 4 onward. Median Hb increases from baseline at weeks 4, 8, and 12 were 29.5 versus 13.0 g/L (P = 0.001), 39.5 versus 25.0 g/L (P = 0.002), and 43.0 versus 36.5 g/L (P = 0.015) in the Enarodustat and historical cohorts,

respectively. At week 12, the proportions of patients achieving Hb increases of ≥10 g/L, ≥20 g/L, and ≥30 g/L were 95.7% versus 87.9%, 95.7% versus 75.9%, and 82.6% versus 58.6%, respectively. Mixed-effects modeling supported sustained hematologic improvement over time. Enarodustat was generally well tolerated, with infrequent thrombotic events and no unexpected safety signals observed. **Conclusions:** In this single-center single-arm study, Enarodustat was associated with rapid and sustained Hb recovery in newly diagnosed MM patients with anemia, including those with renal dysfunction. Exploratory comparison with matched historical controls suggested clinically meaningful hematologic benefit without an apparent increase in thrombotic risk. A prospective randomized double-blind placebo-controlled study is underway to further validate these findings.

PA-383

RAS and TP53 Mutations in Multiple Myeloma in Ecuador: A Preliminary Variant-Level Real-World Series

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Introduction: RAS-pathway and TP53 alterations are clinically relevant genomic events in multiple myeloma (MM), but data from Latin American populations remain scarce. We describe the frequency, clinical timing, and variant-level annotation of KRAS, NRAS, and TP53 mutations in a real-world Ecuadorian MM series. **Methods:** We performed a retrospective descriptive study using secondary data from a molecular biology service database. Adult patients with MM and available bone marrow targeted next-generation sequencing were included. Clinical status at molecular evaluation was classified as newly diagnosed or relapsed disease. KRAS and NRAS were grouped as RAS-pathway mutations; TP53 was analyzed separately. Variant interpretation used VarChat, ClinVar, GeneBe, Seshat, and the IARC TP53 database. Conventional cytogenetic/FISH data were unavailable during the study period, limiting integrated genomic risk stratification. **Results:** Fifteen patients were included. Median age was 68 years (IQR, 62–72; range, 32–81), and 7 were male (46.7%). Molecular evaluation was performed at diagnosis in 12 patients (80.0%) and at relapse in 3 (20.0%). ISS stage III disease was present in 9 patients (60.0%). RAS-pathway or TP53 mutations were identified in 5 patients (33.3%). RAS-pathway mutations were detected in 4 patients (26.7%): KRAS in 2 (13.3%) and NRAS in 2 (13.3%). Both KRAS-mutated cases, detected at diagnosis, harbored KRAS c.183A >C (p.Gln61His, rs17851045), a missense exon 3/Q61 variant. NRAS mutations included NRAS c.35G >A (p.Gly12Asp, rs121913237), detected at diagnosis, and NRAS c.38G >A (p.Gly13Asp, rs121434596), detected at relapse; both are missense exon 2 variants. CADD/REVEL scores were 23.4/0.644 for KRAS p.Gln61His, 24.7/0.783 for NRAS p.Gly12Asp, and 24.5/0.699 for NRAS p.Gly13Asp. These RAS variants were rare or very rare in gnomAD, with no homozygous individuals reported, and were annotated as pathogenic/likely pathogenic and/or oncogenic. One TP53 mutation was identified at relapse: TP53 NM_000546.6.395A >G (p.Lys132Arg, rs1057519996), a missense exon 5 variant with CADD 33.0, very rare in population datasets, and annotated as pathogenic/oncogenic with functional evidence consistent with impaired TP53 activity. Overall, RAS-pathway or TP53 mutations were present in 3 of 12 patients evaluated at diagnosis (25.0%) and 2 of 3 evaluated at relapse (66.7%). **Conclusions:** In this preliminary real-world Ecuadorian series, RAS-pathway mutations were identified in approximately one-quarter of patients with MM, whereas TP53 mutation was detected at relapse. Although limited by sample size and the absence of cytogenetic/FISH data, these findings support expanding molecular profiling in MM care in resource-constrained settings. Future cases will incorporate cytogenetic/FISH assessment when available to improve clinicogenomic interpretation.

PA-384

Real Life Data of Belantamab Mafodotin for Patients with Early Relapsed Multiple Myeloma

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Introduction: Belantamab mafodotin (BELA) was recently approved for patients with relapsed/refractory multiple myeloma (RRMM) who received at least one prior line, in combination with bortezomib (BOR) or pomalidomide (POM). Real-world data on the efficacy and safety of BELA treatment in early relapse are lacking. **Methods:** All consecutive RRMM patients (pts) who received at least one dose of BELA under an expanded access compassionate care program in 10 centers were included. Primary endpoint was progression free survival (PFS), secondary endpoints included overall response rate (ORR) and safety, with focus on ocular toxicity. **Results:** Fifty-six RRMM pts were allocated for BELA-based treatment between June 2025 and May 2026. Median age was 78.4 (range 52.2–93.4) years. Thirty pts (53%) were males, 43 (76%) were older than 75 years, and 8 (14%) had high-risk cytogenetic profile. Sixteen (28%) pts received BELA+proteosome inhibitor (PI) (14 BOR, 2 carfilzomib); 30 (52.6%) pts received BELA+immunomodulatory drug (IMiD) (26 POM, 4 lenalidomide (LEN)). Eleven (19.3%) pts received BELA monotherapy. Median follow-up of all pts was 7.0 (CI95% 6.5–7.5) months. Exposure rates to BOR, carfilzomib, LEN, POM and daratumumab were 85.9%, 15.8%, 75.5%, 24.6% and 92.0%, respectively. Thirteen (23%) were triple class refractory. In the BELA+PI cohort, median prior line of treatment (LOT) was 1 (1–2) and ORR was 43.8% (VGPR 31.3%, PR 12.5%). In the BELA+IMID cohort, median prior LOT was 2 (1–4) and ORR was 70% (CR 3%, VGPR 30%, PR 36.7%). In the BELA monotherapy cohort, median prior LOT was 3 (1–4) and ORR was 50% (VGPR 20%, PR 30%). Median PFS was 7.9 (CI95% 2.1–13.8) months, NR and 9.2 (CI95% not applicable) months for BELA+PI, BELA+ IMiD and BELA monotherapy, respectively. Gr3–4 non-ocular treatment emergent adverse events (TEAEs) occurred in 12 pts (21%). Hematological Gr3–4 TEAEs included thrombocytopenia (4) and anemia (2). Non-hematological Gr3–4 TEAEs included infections (3), febrile neutropenia (1), myocardial infarction (1), heart failure (3), CVA (2), diarrhea (1) and GI bleeding (1). Thirty-four (59.6%) pts had ocular toxicity, leading to dose delays in 17 pts, dose reductions in 10 pts and treatment discontinuation in 3 pts. Twenty-one (36.8%) pts had documented keratopathy (13 Gr3–4); all Gr3–4 improved to a lower grade (Gr0–1 in 10 pts and Gr2 in 3 pts). Twenty-eight (49.1%) pts had blurred vision (4 with Gr3, no Gr4). Of 4 pts with Gr3 blurred vision - 2 improved to Gr0 and 2 improved to Gr2 at the time of last follow-up. The reasons for dose delays were mainly ocular toxicity (52%), hematological toxicity (15.2%) and infection (10.8%). None of the pts discontinued BELA d/t non-ocular AE. No fatal AEs were documented. **Conclusions:** Belantamab mafodotin shows significant anti-myeloma activity in early RRMM pts with high rate of daratumumab exposure in a real-world setting with a manageable safety profile.

PA-385

Real-Time Single-Cell Profiling to Guide T-cell Redirecting Treatment Sequence in Multiple Myeloma

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Introduction: BCMA- and GPRC5D-targeted T-cell redirecting therapies, including T-cell engagers (TCEs) and CAR-T cells, have transformed the treatment of relapsed/refractory multiple myeloma (RRMM). However, one-third of patients exhibit primary resistance and most responders eventually relapse, with median progression-free survival around 12 months. Single-cell studies have identified multiple resistance mechanisms, including genetic or epigenetic target inactivation and T-cell dysfunction, which could critically inform subsequent treatment selection but are not yet accessible in clinical practice. **Methods:** We developed OneMAP, an end-to-end single-cell RNA-sequencing (scRNA-seq) workflow generating clinically interpretable reports within 2 weeks of sample receipt. The workflow integrates high-quality single-cell data generation and automated charaterization of clinical response determinants, including target expression, integrity, and T-cell functional states. ImmunoMM is a prospective study evaluating implementation of OneMAP within the Hematology Department of CHU Nantes. Reports are delivered to treating hematologists and discussed during molecular tumor boards. Thirteen retrospective samples were analyzed to validate the workflow, and a prospective cohort of 20 patients is ongoing. **Results:** High-quality single-cell profiles were generated from all 13 retrospective samples, with a median of 5,035 tumor cells and 8,550T cells per sample and median detection of 1,480 genes per cell. TNFRSF17 (BCMA) expression was high and homogeneous in anti-BCMA-naïve samples. In contrast, 4 of 6 post-anti-BCMA relapses (4 post-TCE, 2 post-CAR-T) showed marked loss of TNFRSF17 expression, supporting resistance by antigen escape and arguing against further BCMA-targeted treatment. One patient with high GPRC5D expression subsequently achieved a very good partial response to an anti-GPRC5D antibody-drug conjugate, whereas another did not respond to rechallenge with a second anti-BCMA TCE. High sequencing coverage across target genes enabled mutation detection, including a TNFRSF17 R27Q missense mutation in an anti-BCMA-naïve sample. The workflow also reproducibly quantified 14 T-cell functional states, including an exhausted-like CD8 TOX population previously associated with resistance to anti-BCMA TCE. Within the first month of prospective enrollment, three patients were included and reports were delivered with a mean turnaround time of 11.3 days. **Conclusions:**

ImmunoMM is, to our knowledge, the first prospective study evaluating real-time single-cell profiling to support treatment selection in multiple myeloma. Initial results demonstrate the feasibility of generating clinically relevant reports within clinically compatible timelines and support the potential utility of resistance-informed sequencing strategies for T-cell redirecting therapies. Updated prospective clinical and biological results from the 20-patient cohort will be presented at the IMS meeting.

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Real-World (RW) Characteristics, Treatment Patterns, and Outcomes in Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM) in Europe: Results from the HARMONY Big Data Platform

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Introduction: In Europe, the RRMM treatment landscape has evolved with novel immunotherapies, but RW evidence on utilization and outcomes remains limited, and variability in access complicates treatment decisions. Improved understanding of the treatment patterns and outcomes in the TCE population is needed to inform current care. **Methods:** This retrospective study included patients (pts) with RRMM from the HARMONY Alliance Foundation database who had initiated an index line of therapy (LoT), defined as first LoT for a pt after becoming TCE to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody between 2016–2025; subgroup analysis performed for pts initiating index LoT from 2020. **Results:** The overall cohort (N = 500; 3L: 164, 4L: 135, 5L: 98, 6L+: 103) includes pts from Czech Republic (95%), Austria (4%), or Spain (1%); 16 pts already TCE in 2L were excluded. Median age (range) at diagnosis and 3L start was 72 (36–89) and 76 (45–97) years, respectively. Median (range) prior LoT was 3 (2–12) and median (range) follow-up was 9 (0–79) months (mo). At diagnosis, ECOG scores were 0 (22%), 1 (38%), 2 (31%), 3 (9%), and 4 (1%), Revised International Staging System staging was I (16%), II (40%), and III (36%). Overall, 92% (n = 458) were exposed to daratumumab, with 87% first receiving it in 2L and 5% in 1L. Median overall survival (OS) overall and by index LoT was 15.3 mo (3L+) and 19.2 (3L), 15.8 (4L), 15.3 (5L), and 8.6 mo (6L+). Overall median progression-free survival (PFS) and time-to-treatment discontinuation (TTTD) were poor (PFS: 5.5 mo; TTTD: 4.9 mo); time-to-next treatment ranged from 5.1–8.3 mo across LoT and the overall response rate (ORR) at index LoT was 36% (≥complete response [CR]: 3%; very good partial response [VGPR]: 13%; partial response [PR]: 20%; missing: 19%). In a subgroup analysis with pts who initiated index LoT after 2020 (N = 415; 3L: 152; 4L: 121; 5L: 81; 6L+: 61), median (range) prior LoT was 3 (2–9) and median (range) follow-up was 8 (0–48) mo. In the 3L cohort (n = 152), >40 unique regimens were used; top regimens were carfilzomib-dexamethasone (dex) (16%), pomalidomide-dex (14%), and bortezomib-pomalidomide-dex (11%). Across the 2020+ subgroup (N = 415), utilization of BsAbs in index LoT was low: teclistamab (18 [4%]), talquetamab (8 [2%]), elranatamab (2 [< 1%]). Outcomes remained suboptimal for the 2020+ subgroup: median OS overall and by index LoT was 15.6 mo (3L+) and 18.0 (3L), 17.9 (4L), 15.3 (5L), and 8.5 mo (6L+); median PFS overall and by index LoT was 5.6 mo (3L+) and 5.4 (3L), 6.3 (4L), 5.6 (5L), and 3.9 mo (6L+); ORR at index LoT was 35% (≥CR: 3%; VGPR: 13%; PR: 18%; missing: 20%). **Conclusions:** European RW data, primarily from the Czech Republic, show fragmented treatment patterns for 3L+ TCE RRMM. Pts relapse quickly and survival worsens with later LoT. Despite the approval of novel immunotherapies, RW uptake remains limited and outcomes continue to be poor, highlighting the need for more effective and broadly accessible therapies.

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Real-World (RW) Infection-Related Healthcare Resource Utilization (HCRU) and Costs in Patients (pts) with Multiple Myeloma (MM) Receiving T-cell Redirecting Therapies (TCRTs)

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapies and bispecific antibodies (BsAbs) have improved outcomes in MM but are associated with substantial infection risk. RW evidence on infection-related HCRU and costs among pts receiving TCRTs is limited. **Methods:** This retrospective US-based RW study used the COTA MM and PurpleLab linked database through Q3 2025. Adults with MM receiving a first CAR-T infusion or BsAb dose after March 2021 were included; index date was day 1 of treatment (trt). Eligible pts had ≥90 days of continuous medical/pharmacy enrollment pre-index and ≥12 months of follow-up post-index, unless death occurred earlier. Time to first infection-related event was evaluated using cumulative incidence functions, treating death as a competing risk and censoring at next trt or 12 months post-index. Use of intravenous immunoglobulin (IVIG) and other infection prophylaxis (e.g., antimicrobials, antivirals, vaccinations) was described. Outcomes included infection incidence (identified using ICD-10 codes), infection-related hospitalization, other HCRU, and costs. **Results:** Among 264 eligible pts, 52% were male, 72% were White, median (range) age was 68 (39–84) years, and 49% had Medicare coverage; 174 (66%) received CAR-T and 90 (34%) BsAbs. Infection prophylaxis was used in 67% of CAR-T and 49% of BsAb pts, including primary IVIG (initiated before documented infection) in 15% and 7%, and secondary IVIG (initiated after infection) in 5% and 4%, respectively. During follow-up, infection occurred in 53% of CAR-T and 47% of BsAb pts; 7% and 3% had severe infections requiring hospitalization with intensive care unit admission. Primary IVIG recipients had significantly lower cumulative infection incidence within 30/60/90/180 days post-index vs nonrecipients (9%/9%/13%/19% vs 19%/28%/34%/48%; p = 0.03). Among pts with infection, with a median follow-up of 12 months, hospitalization rates were 88% for CAR-T and 95% for BsAbs, median length of stay were 6.5 and 6.8 days, and 53% and 60% had emergency care visits, respectively. Unadjusted median per-patient-per-month all-cause total costs were $24,669 (CAR-T) and $11,705 (BsAbs); median infection-related hospitalization costs were $2,968 and $2,262, respectively. Regardless of infection status, median IVIG prophylaxis costs per use among IVIG recipients were $3,035 (CAR-T) and $2,772 (BsAbs). In evaluable BsAb pts, trt discontinuation was mainly due to toxicity, and 16% had dose reduction/delay or regimen change due to infection-related adverse events. **Conclusions:** Infections remain a significant clinical and economic burden among pts with MM receiving TCRTs in RW practice. This highlights the unmet need for trts that reduce infection-related complications and HCRU, with potential value for pts, payers, and access decision-makers. Further research is warranted to clarify the impact of trt-related infection and adherence to guideline-recommended prophylactic strategies on HCRU and outcomes.

PA-388

Real-World Burden of Infections in Patients with Relapsed or Refractory Multiple Myeloma Treated with Elranatamab in Japan: Findings from the SUMMIT Study

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Introduction: Elranatamab (ELRA) is the first B-cell maturation antigen (BCMA)–targeted bispecific antibody approved in Japan for relapsed/refractory multiple myeloma (RRMM). However, real-world data on infection risk remain limited, particularly in Asian populations. This study described the burden of infections among patients with RRMM receiving ELRA in Japan. **Methods:** This cohort study used de-identified administrative claims data from the Japan Medical Data Vision (MDV) database. Eligible patients were aged ≥18 years, had a diagnosis of MM prior to ELRA initiation, had no evidence of clinical trial participation, and received ≥1 administration of ELRA between March 26, 2024 and July 31, 2025. Patient characteristics were assessed at index date (Day 1) and summarized descriptively. Patients were classified as infection cases if at least one infection diagnosis occurred after ELRA initiation (≥Day 2) and was accompanied by systemic anti-infective therapy. Infection type (bacterial, viral, fungal) was defined based on the class of anti-infective therapy received. Patients could be included in multiple infection type groups, and recurrent infections were not excluded. Outcomes were assessed during the follow-up period and within prespecified time intervals. The proportion of patients with ≥1 infection was reported overall and by type. Information on infection severity grading and microbiological confirmation was not available in the database. **Results:** A total of 425 patients were included, with a median age of 74 years (interquartile range [IQR] 68–78), 52.5% were female, and 37.4% were penta-drug exposed at ELRA initiation. Median follow-up duration was 10.55 months (IQR 9.86–10.87). Overall, 232 patients (54.6%) experienced at least one infection at any time during follow-up. Bacterial infections were most common (48.5%), followed by viral (20.2%) and fungal (11.3%). Infections were observed across prespecified time intervals. Within the first 8 days, 99 patients (23.3%) experienced at least one infection, most commonly bacterial (21.9%), with lower proportions of viral (2.4%) and fungal (3.3%). Over the first 30 days, the proportion increased to 32.5% (138 patients), including 28.5% with bacterial, 6.8% with viral, and 4.7% with fungal infection. **Conclusions:** In this real-world RRMM cohort receiving ELRA in Japan, infection diagnoses were observed in approximately half of patients during follow-up, with bacterial infections being the most common. These findings highlight the need for infection awareness and close monitoring in clinical practice.

PA-389

Real-World Dexamethasone Dose Intensity Patterns in Induction Therapy for Newly Diagnosed Multiple Myeloma in a Mexican Cohort

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Introduction: Dexamethasone has a significant toxicity profile, which is of particular relevance in populations with substantial cardiometabolic comorbidity, nevertheless, it remains an essential component of therapy in newly diagnosed multiple myeloma (NDMM). Most evidence supporting dose reduction comes from predominantly Caucasian cohorts and excludes anti-CD38-containing regimens, leaving a gap for Latin American practice, where type 2 diabetes, hypertension, and obesity affect >14%, >25%, and >36% of adults respectively. We describe real-world patterns of dexamethasone relative dose intensity (RDI) during induction in a Mexican cohort with associated efficacy and safety observations. **Methods:** Single center, retrospective cohort of 57 consecutive adults (≥ 18 years) with NDMM treated between January 2024 and March 2026. RDI was defined as cumulative actual/planned dose × 100 and categorized as high (H-RDI) ≥ 85%, or reduced (R-RDI) < 85%, 50–84% being intermediate and < 50% low. Efficacy outcomes: ≥VGPR (IMWG 2016) and 12-month PFS. Safety followed two pre-specified definitions: broad (any grade ≥3 dexamethasone-related adverse event (AE), including infections) and refined (signature glucocorticoid events, excluding infections). Between-group differences were estimated with 95% CIs (Newcombe method); no non-inferiority claims were made given the retrospective, exploratory design. **Results:** Median age was 58 yrs (39–75); 58% male; ISS III in 65%; high-risk cytogenetics (HRCG) in 30%; type 2 diabetes in 26%; anti-CD38-containing regimens in 40%. Median RDI was 66.7%; only 23% reached ≥85%, while 49% were intermediate and 28% low. ≥VGPR was observed in 33.3% of H-RDI vs 72.7% of R-RDI patients (Δ +39.4%, 95% CI +8.2 to +61.8), following a graded pattern: 33%->64%- >88% (trend p = 0.003). 12-month PFS was 74.0% (H-RDI) vs 76.9% (R-RDI), (difference +2.9%, 95% CI −22.5 to +28.3; log-rank p = 0.36). In an exploratory subset with R-RDI reaching ≥VGPR and evaluated for MRD by flow cytometry, 18 of 20 (90%) were MRD-negative. Broad AEs were similar (23.1% R-RDI vs 31.8% H-RDI), likely reflecting time-dependent confounding from response-adapted physician behavior to a first toxicity event. Hyperglycemia was 69% vs 43%, neuropsychiatric symptoms 8% vs 0%, and signature-event burden 1.31 vs 0.73 events/patient. No deaths were attributable to dexamethasone. **Conclusions:** In this Mexican real-world cohort, dexamethasone exposure was well below the conventional threshold (median RDI 66.7%). De-escalation patterns were feasible, signature toxicities were less frequent with reduced exposure. The observed direction of effect on response likely reflects time-dependent confounding and response-adapted physician behavior, where dose reductions are most likely to happen in patients with deeper responses, rather than a true biologic effect. These exploratory findings are hypothesis-generating and support prospective randomized evaluation of dexamethasone de-escalation in NDMM.

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Real-World Effectiveness of Elranatamab in Patients with Relapsed or Refractory Multiple Myeloma in Japan: Results from the SUMMIT Study

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Introduction: While real-world (RW) evidence on BCMA-targeted bispecific antibodies is emerging from cohorts in the United States and Europe, data from Asian populations remain limited. In Japan, elranatamab (ELRA) was the first approved BCMA bispecific antibody for relapsed/refractory multiple myeloma (RRMM); however, its effectiveness has not yet been fully evaluated. This study assessed RW effectiveness outcomes among patients with RRMM receiving ELRA in Japan. **Methods:** This cohort study used de-identified administrative claims data from the Japan Medical Data Vision (MDV) database, covering a data availability period from March 26, 2024 to January 31, 2026. A patient identification period from March 26, 2024 to July 31, 2025 was applied to ensure a minimum follow-up of 6-months prior to the end of data availability. Eligible patients were adults (≥18 years) who had a diagnosis of MM prior to ELRA initiation, no record of prior clinical trial participation, and received at least one administration of ELRA during the patient identification period. Baseline characteristics were summarized using descriptive statistics. Effectiveness outcomes of real-world overall survival (rwOS), real-world time to next treatment (rwTTNT), and real-world time to treatment discontinuation (rwTTD) were assessed using Kaplan-Meier time-to-event analyses. **Results:** A total of 425 patients were included, with a median age of 74.0 years (interquartile range [IQR] 68.0–78.0), 52.5% female, and a median body weight of 54.8 kg (IQR 47.9–63.1). Prior exposure to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies was high (85.6%, 87.5%, and 89.6%, respectively), and 37.4% were penta-drug exposed at ELRA initiation. The median time from MM diagnosis to ELRA initiation was 58.0 months (IQR 28.5–97.3), and the median follow-up time was around 11 months. Renal failure, bone lesions, and extramedullary disease were present in 28.5%,

43.4%, and 3.4% of patients, respectively; and 33.9% had received prior immunoglobulin replacement therapy. Both median rwOS and rwTTNT were not reached. At 15 months, the rwOS rate was 67.6% (95% CI: 61.6–73.0) and the rwTTNT rate was 58.8% (95% CI: 52.6–64.4). The median rwTTD was 6.44 months (95% CI: 5.16–7.59), indicating that half of patients remained on ELRA beyond 6 months. At 15 months, the rwTTD rate was 25.6% (95% CI: 20.3–31.2), suggesting that about one-quarter of patients continued ELRA at that time. **Conclusions:** These results suggest that ELRA demonstrates clinically meaningful effectiveness in RW practice among Japanese patients with RRMM, with outcomes generally consistent with the clinical trial results. As median rwOS and rwTTNT were not reached, longer follow-up will be needed to fully characterize RW effectiveness.

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Real-World Effectiveness of Thromboprophylaxis Strategies in Newly Diagnosed Multiple Myeloma: An Inverse Probability of Treatment Weighting Study

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Introduction: Patients with newly diagnosed multiple myeloma (NDMM) have a markedly higher VTE risk than the general population, especially within 6 months of treatment initiation. VTE can disrupt therapy and predicts poor prognosis. In real-world practice, thromboprophylaxis selection is non-randomized and influenced by patient characteristics, disease burden, and regimens, potentially introducing selection bias and limiting comparative effectiveness research. The comparative effectiveness of antiplatelet versus anticoagulant prophylaxis in NDMM remains unclear, and Chinese real-world evidence is limited. **Methods:** This retrospective study included 433 NDMM patients at Fuxing Hospital, Capital Medical University (Jan 2017–Nov 2024). Based on initial thromboprophylaxis, patients were assigned to antiplatelet (aspirin/clopidogrel, n = 251), anticoagulation (direct oral anticoagulants, n = 119), or no-prophylaxis (n = 63) groups. Multinomial logistic regression identified factors influencing prophylaxis choice. Propensity scores were estimated using a multinomial logistic model, and inverse probability of treatment weighting (IPTW) balanced baseline covariates. Weighted logistic regression and weighted Cox models assessed associations between prophylaxis strategies and 6-month VTE risk and time-to-event outcomes. **Results:** Before weighting, significant intergroup differences existed in BMI, high-risk cytogenetics, central venous catheterization, anthracycline-based chemotherapy, platelet count, and D-dimer (all $P < 0.05$), indicating baseline imbalance. After IPTW, effective sample sizes were 250.82 (antiplatelet), 115.04 (anticoagulation), and 59.12 (no-prophylaxis). Standardized mean differences (SMDs) reduced substantially (mostly < 0.2), with no significant baseline differences across groups (all $P > 0.05$), confirming good comparability. Overall 6-month VTE incidence was 8.31% (36/433). VTE rates were 6.77% (17/251) for antiplatelet, 7.56% (9/119) for anticoagulation, and 15.87% (10/63) for no-prophylaxis ($P = 0.061$). Multinomial logistic regression showed that higher BMI and platelet count were associated with both prophylactic strategies, while high-risk cytogenetics were significantly associated with anticoagulation choice. After IPTW adjustment, versus no prophylaxis, anticoagulation significantly reduced 6-month VTE risk (OR = 0.25, 95%CI 0.08–0.78, $P = 0.017$; HR = 0.27, 95%CI 0.10–0.74, $P = 0.011$). Antiplatelet prophylaxis showed a risk reduction trend without statistical significance (OR = 0.47, 95%CI 0.20–1.09, $P = 0.074$; HR = 0.48, 95%CI 0.20–1.14, $P = 0.099$). **Conclusions:** In this real-world NDMM cohort, NOAC-based anticoagulant prophylaxis was associated with a significantly lower early VTE risk, whereas antiplatelet prophylaxis did not demonstrate clear protective effectiveness. These findings support individualized, risk-adapted anticoagulation strategies in NDMM, pending further prospective validation.

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Real-World Efficacy and Safety of Daratumumab-Lenalidomide-Dexamethasone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: A Multicentre Italian Study

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Introduction: In the pivotal MAIA trial, daratumumab-lenalidomide-dexamethasone (D-Rd) demonstrated unprecedented clinical

benefit, significantly improving progression-free survival (PFS) and overall survival (OS) in transplant-ineligible (TI) newly diagnosed multiple myeloma (NDMM). Accordingly, EHA-ESMO 2021 guidelines recommended D-Rd as a preferred first-line regimen for this population. **Methods:** We conducted a multicentre retro-prospective observational study including 357 NDMM patients treated across 10 haematology centres in Italy, between January 2021 and December 2025. Transplant ineligibility was defined as age ≥70 and/or the presence of relevant comorbidities. All patients received D-Rd in 28-days cycles according to MAIA schedule, until disease progression or unacceptable toxicity. Patients were stratified by IMWG simplified frailty score and cytogenetic risk assessed by FISH. High-risk (HR) abnormalities included t(4;14), t(14;16), amp (1q21), or del(17p). **Results:** Median age was 75 years (61–86); 17% were ≥80 years and 10% < 70 years. ECOG performance status (PS) ≥2 was present in 15%, 55% were frail. ISS stage II and III were reported in 32% and 26%, respectively. HR cytogenetics were identified in 29%, including 9 double-hit cases. Renal impairment (eGFR < 60 mL/min) was present in 25%, and 4% had amyloidosis. After a median follow-up of 23 months, patients received a median of 18 D-Rd cycles (range 1–65) with a median treatment duration of 18 months. Overall response rate was 97.4%, including ≥ VGPR in 74%. Rates of ≥VGPR were similar in frail and non-frail patients (56% vs 43%, p = 0.33). Median PFS was not reached (NR), with 72% of patients progression-free at 40 months. Patients achieving ≥VGPR had longer PFS (NR vs 23 months; p < 0.001). In univariate analysis, age >75 years, ECOG PS ≥2, frail status, ISS/R-ISS ≥2, or HR cytogenetic, did not significantly affect PFS. Median OS was NR, with an estimated 4-year OS of 81%. Treatment was discontinued in 25% patients, mainly due to progression (53%), adverse events (AEs, 18%), or refractory disease (7%). 34 deaths occurred, mostly due to progression (20%); five were treatment-related, mainly sepsis. The most common AEs were haematological: neutropenia (44%), anaemia (19%), and thrombocytopenia (10%). Infections occurred in 31%, gastrointestinal toxicity in 13%, and renal toxicity in 7%. Grade ≥3 AEs included neutropenia (30%) and infections (10%). Hospitalization was required in 23%, mainly for sepsis and cardiovascular events. Lenalidomide dose reductions/discontinuations occurred in 41% and 29% respectively; while dexamethasone was reduced/discontinued in 17%. Fifty-five patients received second-line therapy, most commonly a proteasome inhibitor-based triplet or doublet, with a PFS2 of 12.1 months. **Conclusions:** This real-world study confirms the effectiveness and feasibility of D-Rd as frontline treatment for TI-NDMM in routine clinical practice, particularly for older or frail patients less suitable for intensive therapies.

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Real-World Efficacy and Safety of Selinexor, Bortezomib, and Dexamethasone (SVd) Utilizing a Novel Dose Ramp-Up Strategy in Lenalidomide-Refractory Multiple Myeloma

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Introduction: The BOSTON study established the efficacy of once-weekly SVd in relapsed/refractory multiple myeloma (RRMM). However, proactive management of adverse events (AEs), particularly thrombocytopenia and nausea, is critical for patient adherence and quality of life. This real-world analysis evaluates the safety and efficacy of an innovative selinexor dose ramp-up strategy in transplant-eligible, lenalidomide-refractory, anti-CD38-naive patients, a challenging-to-treat population and a sequencing gap where optimal regimens are still being defined. **Methods:** This retrospective analysis evaluated 9 transplant-eligible RRMM patients at first progression. To optimize tolerability, patients initiated selinexor at a fitness-based starting dose of 40 mg or 60 mg. Doses were gradually escalated weekly (40-60–80-100 mg). Antiemetic prophylaxis with ondansetron was mandated for all patients. Response evaluations were conducted at 3 months. **Results:** The median age was 67 years, directly parallel to the BOSTON study demographic. Six patients had R-ISS Stage II disease (staging was unavailable for 3). Patients received a median of 15 weeks of therapy (range: 5–40 weeks) at the time of data analysis. The overall response rate (ORR) was 100%, with 4 patients achieving a Complete Response and 4 achieving a Very Good Partial Response. This compares favorably to the 67.9% ORR observed in the lenalidomide-refractory subgroup of the BOSTON study. Safety profiles were markedly improved compared to clinical trial benchmarks. With strict prophylaxis, no patients experienced nausea (compared to 50% in BOSTON). Only one patient experienced >Grade 2 thrombocytopenia, which was successfully managed with a gradual dose reduction to 40 mg; this compares favorably to the 39% incidence of Grade 3/4 thrombocytopenia reported in the BOSTON study. 2 patients utilized SVd as a successful bridge to a second autologous stem cell transplant, discontinuing at 10 weeks for stem cell harvesting without disease progression. Two patients with underlying ischemic heart disease died from a myocardial infarction after therapy was discontinued. One patient was lost to follow-up at week 5. Because no disease progression events were observed during the follow-up period, the median Progression-Free Survival was not reached. **Conclusions:** A selinexor dose ramp-up approach, coupled with routine antiemetic prophylaxis, radically improves the tolerability profile of the SVd regimen, effectively eliminating nausea and minimizing high-grade thrombocytopenia. In a difficult-to-treat, lenalidomide-refractory population, this optimized dosing strategy yielded a 100% ORR (with 4/8 achieving CR), substantially outperforming the 67.9% ORR seen in the BOSTON trial's lenalidomide-refractory cohort. Furthermore, positioning SVd in

anti-CD38-naive patients fills a critical clinical gap, offering a highly effective, tolerable, and innovative sequencing approach for early RRMM, including reliable utility as a bridge to ASCT.

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Real-World Efficacy and Safety Outcomes of Talquetamab: An Updated Analysis in Predominantly Community-based Setting

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Introduction: Relapse/refractory multiple myeloma (RRMM) is a heterogenous hematologic cancer with ongoing unmet clinical needs despite recent treatment advances. In August 2023, talquetamab (TAL), a first-in-class GPRC5D-targeted bispecific antibody, received accelerated approval by the United States (US) FDA for adults with RRMM. The MonumenTAL-1 trial demonstrated clinically meaningful overall response rate (ORR), duration of response (DOR) and overall survival (OS). This analysis presents real-world outcomes in RRMM pts treated with TAL in US community settings. **Methods:** This retrospective, multi-site observational chart review study used data from the Cardinal Health Oncology Provider Extended Network. Adults ≥18 years with confirmed RRMM who initiated TAL (study index) in routine practice between 09 Aug 23 and 14 May 25 and had ≥1 month of follow-up were included. Baseline data were collected in May 2025, with a longitudinal data refresh in December 2025 (reported here); a second data refresh is in progress. Descriptive analyses were conducted for the overall cohort and a subset of pts treated per US Prescribing Information (USPI) criteria. Real-world ORR (rwORR), DOR (rwDOR), progression-free survival (rwPFS), and OS were estimated using the Kaplan–Meier method. Descriptive analysis of safety data is planned. **Results:** A total of 176 pts were included (median age: 68.6 years, 59.7% male, 70.5% White, 72.2% community setting). Longitudinal data were available for 86% (120/139) of eligible pts at the time of the first refresh; 97 pts (55.1%) met USPI criteria. Median follow-up was 9.9 months. Overall, the rwORR was 85.4% (95%CI: 79.0–90.5), median rwDOR was 13.5 months (95%CI: 12.0-NE) and 52.8% achieved very good partial response or better (VGPR+). Twelve-month OS was 81.7% (95%CI: 73.5–87.6) and rwPFS was 72.9% (95%CI: 64.0–79.9). In the USPI cohort, rwORR was 88.9% (80.5–94.5), median rwDOR was 12.0 months (10.8-NE) and 66.7% achieved VGPR+. Twelve-month OS was 91.1% (95%CI: 82.9–95.5) and rwPFS was 78.4% (95%CI: 66.2–86.6). At refresh, mean (SD) weight change was −2.8% (6.3); 70.0% experienced weight loss, 23.3% weight gain, and 6.7% no change. More safety outcomes will be presented at the time of the congress. At the end of follow-up, 63.1% remained on TAL. Disease progression (20.5%) was the most common reason for discontinuation, followed by adverse events (AEs; 5.7%) and patient choice (5.7%). **Conclusions:** In this real world study conducted primarily in US community settings, TAL demonstrated meaningful clinical activity with robust response rates and encouraging survival estimates in the overall population as well as the USPI cohort. Most pts remained on TAL with low rates of AE-related discontinuation. These findings support the effectiveness of TAL in routine clinical practice and highlight the value of continued follow up to further characterize long term outcomes.

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Real-World Evaluation of Prophylactic Anakinra for Toxicity Mitigation in BCMA CAR-T Therapy

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Introduction: BCMA-targeted Chimeric Antigen Receptor T (CAR-T) cell therapy for multiple myeloma is often complicated by cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Anakinra is commonly used for the treatment of these toxicities; however, its role as a prophylactic medication is unclear. This study evaluates the safety and efficacy of anakinra prophylaxis in patients with multiple myeloma receiving BCMA CAR-T therapy in a real-world setting. **Methods:** This single-center retrospective study included multiple myeloma patients who received idecabtagene vicleucel (ide-cel) therapy. Subcutaneous anakinra was initiated on the day of CAR-T infusion at a dose of 100 mg twice daily and continued for at least 10 days or until discharge, with subsequent adjustments to dosage, frequency, and duration guided by the onset and severity of CRS or ICANS. Collected variables included demographics, disease characteristics, anakinra dosing, CRS/ICANS grading, and use of tocilizumab and corticosteroids. Early post-infusion response, longitudinal inflammatory markers (CRP, ferritin, IL-6), and hematologic recovery from day +30 through day +90 were also recorded. **Results:** Twenty-one patients with multiple myeloma who received ide-cel were included. Median age was 63 years (range, 39–74); 10 (48%) were male and 11 (52%) female. Median HCT-CI and ECOG-PS scores were 4 (range, 0–5) and 1 (range, 0–2), respectively. Bridging therapy was utilized in 13 (62%) patients prior to infusion. Median hospital stay was 10 days (range, 6–49). All-grade CRS occurred in 20 (95%) patients, with grade ≥3 in 2 (10%); median duration of CRS was 2 days (range, 1–6). ICANS occurred in 4 (19%) patients, including grade ≥3 in 1 patient (5%), with a median duration of 5.5 days (range, 1–17). Tocilizumab and dexamethasone intervention was required in 6 (29%), and 8 (38%) patients, respectively. At day +30, hematologic recovery included 14 (67%) achieving ANC ≥1.0×10^9/L, 13 (62%)

Hb ≥10 g/dL, and 9 (43%) platelets ≥100 × 10^9/L. The ORR at day +90 was 95% (n = 21): complete remission in 12 (57%), very good partial response in 4 (19%), partial response in 4 (19%), and progressive disease in 1 (5%). Comorbid infection occurred in only 1 (5%) patient. Prophylactic anakinra was administered at a median of 28 total doses per patient (range, 12–102). Based on clinician discretion and evolving CRS or ICANS symptoms, anakinra dosing was escalated in 18 (86%) patients. Nine (43%) patients required greater than the median number of doses to manage toxicities. **Conclusions:** Prophylactic anakinra was well tolerated with a favorable safety profile in multiple myeloma patients receiving BCMA CAR-T therapy. Patients demonstrated manageable rates of severe CRS and ICANS, minimal infection risk, and adequate early cytopenia recovery. Early efficacy was preserved, suggesting anakinra prophylaxis may reduce toxicity without compromising outcomes. Larger prospective validation is needed.

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Real-World Evidence of Clinical Patterns in first and second Relapse Multiple Myeloma Patients: A Spanish Perspective. Design and Preliminary Insights from the REVEAL-MM Study

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Introduction: Multiple myeloma (MM) is a heterogeneous, progressive plasma cell malignancy characterized by recurrent relapses. Management at 1st and 2nd relapse (2L/3L) remains complex with therapeutic decision-making influenced by prior treatment exposure, refractoriness, comorbidities, and functional status. In Spain, the introduction of BCMA targeted therapies from 1st relapse, offer prolonged survival benefit and highlights the need to characterize real-world (RW) patient profiles, treatment pathways, eligibility constraints, and attrition rates in clinical practice. Observational RW studies are essential, although secondary data sources pose methodological challenges that may be mitigated through Artificial Intelligence (AI)-enabled analytics, such as natural language processing (NLP) applied to unstructured clinical records. **Methods:** REVEAL-MM is a multicenter, retrospective, observational study to describe the sociodemographic and clinical characteristics of patients with MM who experienced a 1st and/or 2nd relapse between January 2020 and December 2025 (index date) with clinical history available from 2015 onwards, using electronic health records (EHRs) data from 7 Spanish hospitals. Structured and unstructured EHR data on demographics, disease status, comorbidities, and treatments are extracted. AI-driven NLP techniques are applied to clinical documentation. Data validation ensures consistency and reliability. Analyses are descriptive, focusing on patient characteristics at 2L/3L, treatment patterns, refractoriness, and attrition by transplant status and comorbidity burden. Analyses also assess time to relapse and the proportion of patients at 2L/3L who meet at least one national protocol1 exclusion criterion that makes them not eligible for high complexity BCMA therapies. The study was approved by the Ethics Committee from Hospital Universitario 12 de Octubre, and all data were anonymized prior to analysis. **Results:** A preliminary analysis including data from 6 out of the 7 hospitals, with a reference population of approximately 1.5 million inhabitants, has identified an initial dataset of 3,421 patients with at least one mention of MM in the EHR after first data validation procedure. The median age is 70 years (IQR 60–79); 53.0% of patients are male, and the median follow-up from first mention of MM is 2.3 years, ranging from 1 day to 11.2 years. We will update during the IMS congress the clinical characteristics of the 2L/3L population of these MM patients. **Conclusions:** REVEAL-MM will generate RW evidence on the clinical characteristics and treatment patterns of patients with MM at 2L/3L in Spain to outline the potential opportunity with BCMA novel therapies in improving survival outcomes for patients from 1st relapse. By integrating structured EHR data with AI-driven NLP of unstructured clinical notes, this study supports a more comprehensive characterization of clinical routine patterns.

PA-397

Real-World Experience with Early-Line Ciltacabtagene Autoleucel for Relapsed/Refractory Multiple Myeloma

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Introduction: BCMA-directed chimeric antigen receptor T-cell therapy ciltacabtagene autoleucel (cilta-cel) has demonstrated unprecedented efficacy for patients with relapsed/refractory multiple myeloma (RRMM). It is approved after one prior line of therapy (pLOT) in patients refractory to lenalidomide based on CARTITUDE-4. Here, we explore the use of early-line (1–3 pLOT) cilta-cel in a real-world setting. **Methods:** We retrospectively analyzed all RRMM patients treated at our institution with standard-of-care early-line cilta-cel from April 2024 – August 2025. High-risk cytogenetics were defined as del(17p), t(4;14), t(14;16), and/or 1q21 gain/amplification. Survival was measured by Kaplan-Meier method. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded using ASTCT criteria. **Results:** A total 45 RRMM patients were included. Median age was 67 (45–79), 31% were female, 71% had high-risk cytogenetics, 9% had extramedullary disease, and median pLOT was 3. The majority of patients (93%, 42/45) received bridging therapy of which 7% (3/42) received bispecific antibody-based. Any-grade CRS occurred in 40 patients (89%) (Grade 3 in one patient), and any-grade ICANS occurred in 9 patients (20%). Overall response to bridging therapy defined as partial response or better was 29% (12/42). Non-ICANS neurologic events including parkinsonism and cranial nerve palsies occurred in 0 patients and 10 patients (22%) respectively. Infections, all mild to moderate, occurred in 12 patients (27%) of which 11 were viral, 2 were bacterial, and 1 was fungal. One patient required ICU admission for steroid-induced hyperglycemia. There were two deaths, one related to progression of disease and one related to immune effector cell-associated enterocolitis. Median follow-up was 12 months (3–17 months). The overall response rate was 98% (44/45) with complete response or better rate 76% (34/45). Day-90 clonoSEQ minimal residual disease (MRD) assessment was performed for 35 patients, of which 91% (32/35) were MRD-negative. The 12-month progression-free survival was 85% (95% confidence interval [CI] 68–94) and 12-month overall survival was 95% (CI 81–99). **Conclusions:** Our real-world findings align with the findings in CARTITUDE-4 and support the use of early-line cilta-cel for the treatment of RRMM.

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Real-World Experience with Teclistamab and Talquetamab Combination Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: Combination therapy with teclistamab and talquetamab (tec/tal) is an effective option for patients with relapsed/refractory multiple myeloma (Cohen et al., NEJM 2025). Tec/tal has also demonstrated efficacy in the difficult to treat relapsed/refractory extramedullary disease (EMD) population (Kumar et al., NEJM 2026). Clinical trials have reported that tec/tal is associated with high rates of grade 3+ infection, cytokine release syndrome (CRS) and the well-described on-target, off-tumor GPRC5D associated toxicities. To our knowledge, there have been no published data on the use of this combination therapy in the real-world setting and therefore we now report on our single center experience. **Methods:** We performed a retrospective review of all patients treated at our institution with tec/tal (January 2025 to May 2026) to report on safety and efficacy in this real-world cohort. Patients received teclistamab at a dose of 3 mg/kg and talquetamab at a dose of 0.8 mg/kg every 2 weeks after completion of step-up dosing, per institutional standard. All patients received prophylactic IVIG, a single dose of prophylactic tocilizumab and standardized anti-infective prophylaxis including levofloxacin for a minimum of one month after the initiation of tec/tal. **Results:** We identified 7 relapsed/refractory patients treated with tec/tal. All patients had paraskeletal (n = 3) or extramedullary disease (n = 4). Patients had a median of 5 prior lines of therapy (range 4–7) and most had exposure to a prior BCMA therapy [CAR T-cell therapy (n = 4), bispecific antibody (n = 1)]. All patients were triple-class exposed and refractory to their last prior line of therapy. ECOG performance status (PS) was 2+ in 3 patients. After a median follow-up of 74 days (range 8–295), no cases of documented infection or CRS were observed. On-target off-tumor effects of talquetamab were common [dysgeusia (n = 7), dry skin (n = 2), nail changes (n = 1)]. Two patients have progressed, five patients remain on therapy, and all patients remain alive. Both patients who progressed had prior BCMA exposure (including one to a bispecific). Dosing was de-escalated to once monthly in one patient who remains on treatment. **Conclusions:** In this single-center real-world experience study with tec/tal, no new safety signals were identified among a heavily pretreated cohort of patients despite poor PS and presence of EMD. Surprisingly, when taken in the context of tec/tal clinical trial data, no infectious complications were observed. The lack of infections may reflect improved infectious prophylaxis with IVIG independent of IgG levels and levofloxacin for all patients for at least

one month. It also appears that prophylactic tocilizumab remains effective at preventing CRS in this new combination with no CRS or ICANS events observed. The findings indicate a need for data from a larger cohort of real-world patients to further guide use of tec/tal in relapsed/refractory myeloma.

PA-399

Real-World ISS–R-ISS Discordance, Extramedullary Disease Biology, and Treatment Patterns in Newly Diagnosed Multiple Myeloma: A North Indian Public Sector Cohort

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Introduction: Multiple myeloma (MM) accounts for 10% of haematological malignancies globally; 188,000 new cases in 2022, with a projected 71% rise by 2045. Indian public sector data integrating staging concordance, serum free light chain (SFLC), fluorescence in situ hybridisation (FISH), and treatment patterns remain scarce. **Methods:** We retrospectively analysed 114 newly diagnosed MM patients at Safdarjung Hospital, New Delhi (2017–2024). International Staging System (ISS) and Revised International Staging System (R-ISS) concordance was assessed by weighted Cohen's kappa per International Myeloma Working Group (IMWG) criteria; diagnosis confirmed per IMWG 2014 criteria. Immunofixation electrophoresis (IFE), serum protein electrophoresis (SPEP), SFLC ratio, FISH, bone marrow plasma cell percentage (BMPC%), and extramedullary plasmacytoma (EMP) status were extracted from paper-based records. **Results:** The cohort was 60.5% male, median age 55.5 years (range 27–84); 8% were below 40 years. Anaemia (62.3%), bone lesions (55.3%), hypercalcaemia (20.2%), and renal impairment (20.2%) comprised the CRAB features. ISS staging was available in 83 patients (Stage I 9.6%, II 24.1%, III 66.3%); R-ISS in 68 (I 4.4%, II 73.5%, III 22.1%). Concordance was fair (kappa = 0.268); 68.2% of ISS Stage III reclassified to R-ISS Stage II on cytogenetic-LDH (lactate dehydrogenase) integration. FISH was done in only 54.4%; 45.2% harboured high-risk abnormalities: del 13q (n = 14), gain 1q21 (n = 10), t(4;14) (n = 9), del 17p (n = 4), t(11;14) (n = 3); no difference across ISS stages ($p = 0.174$). EMP was documented in 36.4% (16/44), higher than Western 10–15%, and more prevalent in ISS Stage I/II than Stage III ($p = 0.001$); BMPC% was lower in EMP-positive patients (18% vs 33%; $p < 0.05$), suggesting biologically distinct extramedullary tropism. Median SPEP M-spike was 3.29 g/dL (n = 88); 11 were seronegative. IFE (n = 98) showed IgG dominance (65.3%), light chain only (21.4%), IgA myeloma (11.2%); kappa predominated (58.2%). SFLC ratio was abnormal in 91.4% (n = 81); IFE–SFLC concordance was 89.7%. Of 114 patients, 94 (82.5%) initiated therapy; 89.4% received bortezomib-based regimens: bortezomib-cyclophosphamide-dexamethasone (VCD) 42.6%, bortezomib-lenalidomide-dexamethasone (VRD) 24.5%, VTD 14.9%, VD 7.4%. Among 79 response-evaluable patients, ≥very good partial response (VGPR) was achieved in 46.8%, complete response (CR) 31.6%, VGPR 15.2%, and partial response (PR) in 41.8%. **Conclusions:** ISS–R-ISS concordance was fair (kappa = 0.268); 68.2% of ISS Stage III patients reclassified to R-ISS Stage II - real-world evidence for mandatory FISH in newly diagnosed MM. EMP's inverse ISS association ($p = 0.001$) and lower BMPC% support it as a biologically distinct phenotype. Bortezomib-based induction achieved ≥VGPR in 46.8% in a resource-constrained setting.

PA-400

Real-World Outcomes and Predictors of Bispecific Antibody Therapy Response in a Racially Diverse Multiple Myeloma Cohort

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Introduction: Bispecific antibodies (BsAbs) are transformative in relapsed/refractory multiple myeloma (RRMM); Black patients comprised only 3–6% of pivotal trials. Real-world data on outcomes, PFS predictors, and supportive care in diverse populations are scarce. **Methods:** We retrospectively analyzed 87 RRMM patients (first BsAb course) treated at an academic center (n = 58) and its affiliated community hospital (n = 29). Endpoints included response, PFS, OS, CRS, infection, growth-factor and IVIG use, and sequential (2nd) BsAb activity. Univariable/multivariable Cox proportional hazards and logistic regression were used; race comparisons (White n = 52, Black n = 28, Asian n = 7) used Fisher exact and log-rank tests. **Results:** Median age 69 yr; 32% Black; 42% high-risk cytogenetics; 29% extramedullary disease (EMD); median 4 prior lines of therapy; 84% BCMA-directed, and 16% talquetamab as first bispecific therapy. ORR was 68% (≥VGPR 59%, ≥CR 48%); median PFS was 11.5 mo, OS 33.4 mo. Any CRS 60% (grade ≥2, 13%), ICANS 15%, any infection 39% (grade ≥3, 38%); infection-related mortality (IRM) 11%. Univariable PFS predictors: R-ISS III (HR 3.00, $p = 0.004$), ferritin ≥320 ng/mL (HR 2.74, $p = 0.003$), ECOG ≥2 (HR 2.15, $p = 0.007$), EMD (HR 1.90, $p = 0.028$), hemoglobin per

g/dL (HR 0.85, p = 0.020, protective), and any CRS (HR 0.53, p = 0.025, protective); high-risk cytogenetics trended adverse (HR 2.34, p = 0.051). In Multivariable analysis: EMD (aHR 2.95, p = 0.020) and any CRS (aHR 0.25, p = 0.003, protective) were independently associated with PFS. Response and CRS rates were comparable by race (ORR White/Black/Asian 71/64/57%, p = 0.67; CRS 67/46/57%, p = 0.19). Black patients received more growth-factor support (any 68% vs 31%, p = 0.002; G-CSF 64% vs 21%, p < 0.001; Black race adj OR 4.83, p = 0.002) yet had numerically lower infection rates at any-grade (25% vs 48%, p = 0.057) or grade ≥3 (25% vs 46%, p = 0.092); baseline ANC did not differ. OS did not differ by race (log-rank p = 0.18). Among 17 (20%) receiving a sequential BsAb (71% BCMA→GPRC5D), ORR 59%, median PFS 8.7 mo, OS 17.2 mo; response to the 2nd BsAb was independent of 1st-BsAb response (p = 1.0) and occurred only after class switch. IVIG (n = 64, 74%) was associated with markedly lower IRM (5% vs 30%, p = 0.003) without reducing any-grade or grade ≥3 infection. **Conclusions:** In a racially diverse real-world RRMM cohort, BsAbs achieved efficacy and safety comparable to pivotal-trial benchmarks across races despite higher-risk biology. EMD was the dominant adverse PFS predictor; CRS was a positive independent factor, suggestive of CRS as a marker of on-target T-cell activation. Black patients had markedly higher growth-factor utilization without excess infection or mortality, suggesting that optimized supportive-care strategies may help mitigate disparities in patients receiving BsAbs. IVIG was associated with markedly lower IRM without altering infection incidence, supporting routine use. Sequential BsAb after class switch was active even in 1st-BsAb refractory patients.

PA-401

Real-World Outcomes following Second Line Treatment for Multiple Myeloma in Wales

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Introduction: Myeloma is the third most common haematological malignancy in the UK and is characterised by the uncontrolled expansion of malignant plasma cells in the bone marrow. It remains incurable despite the introduction of novel agents in recent years. There are now numerous licensed therapies available for use in the second line setting which can make treatment selection challenging. We therefore conducted a retrospective review of prescribing practice in Wales to evaluate real-world outcomes at first relapse. **Methods:** We used our chemotherapy prescribing platform to identify all adult patients who received second line treatment for relapsed Myeloma across two health boards in Wales between 2019 and 2024. We collected both demographic and disease-specific data. The primary end point was 1 year progression-free survival (PFS) censored at 12 months after the start of second line therapy. **Results:** Data from 160 patients is included (median age 75 years, male 56.9%, female 43.1%). We categorised patients into six groups according to the second line regimen received: Daratumumab, Bortezomib and Dexamethasone (DVd), Carfilzomib, Lenalidomide and Dexamethasone (KRd), Ixazomib, Lenalidomide and Dexamethasone (IRd), Autologous stem cell transplant (Auto), Lenalidomide and Dexamethasone (Rd) and other Proteasome Inhibitor (PI)-based therapies (Other). The median time from diagnosis to starting second line therapy was 27.2 months and, due to UK prescribing restrictions at the time, no patients were exposed to anti-CD38 monoclonal antibodies or quadruplet regimens as initial treatment. 12-month progression-free survival (12mPFS) was calculated for each group: DVd (n = 70, 70%), KRd (n = 21, 52.4%), IRd (n = 9, 55.6%), Auto (n = 10, 90%), Rd (n = 39, 46.2%), Other (n = 11, 27.3%). 12mPFS was also calculated according to the International Staging System (ISS) for Myeloma: patients with ISS I+II disease (n = 90, 63.3%), patients with ISS III disease (n = 64, 54.7%). Six patients had no documented disease stage. **Conclusions:** In this real-world analysis of prescribing practice in Wales, our data shows that patients treated with DVd at second line achieved a superior 12mPFS, when compared to other triplet therapies. It also demonstrated an excellent 12mPFS for patients receiving an autologous stem cell transplant at second line. The data confirms the superior outcomes seen in patients with ISS I+II disease at diagnosis; genetic data on staging was not available. In 2025, the UK approved the anti-BCMA, antibody drug conjugate Belantamab Mafodotin, in combination with both Bortezomib and Dexamethasone (BVd) and Pomalidomide and Dexamethasone (BPd) for use at second line. The DREAMM-7 and DREAMM-8 clinical trials demonstrated 12mPFS rates of 78% for BVd and 71% for BPd, which are superior to all the regimens included in this analysis except the Auto group. Clinicians now have increasing choice around sequencing of therapies and regular review of real-world outcomes will guide treatment decisions and inform patients.

PA-402

Real-world Outcomes in Smoldering Multiple Myeloma in Europe: Updated results from the SPARK Study

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Introduction: Smoldering multiple myeloma (SMM) is a precursor plasma cell disorder with variable risk of progression to symptomatic multiple myeloma (MM). SMM management generally

consists of active monitoring, in an attempt to diagnose MM and initiate treatment before organ damage occurs. Real-world data on European SMM patient characteristics, progression rates, overall-survival (OS), organ damage incidence, medical visits frequency and treatment patterns by risk category remain limited. The SPARK study aims to provide a comprehensive description of these parameters using different risk models, including Mayo 20-2-20, IMWG 2020 scoring system incorporating cytogenetics (IMWG), and the AQUILA criteria. **Methods:** SPARK is a real-world retrospective chart review study involving hematology centers across Europe. Here we present updated results with extended follow-up, including all available data collected up to the cut-off date of March 2026. **Results:** A total of 411 SMM patients from UK, Germany, Italy, Spain and France were included, of whom 86 (20.9%) were classified as high-risk according to the Mayo 20–2–20 criteria (Mayo HR). In the Mayo HR group, median follow-up was 55.6 months (range 8.4–95.4 months), median age at SMM diagnosis was 67.5 years (range 34–92 years), 37.2% were female, and 81.7% had BMPC >20%. The majority (84.7%) had serum M-protein >2 g/dL, and 66.7% had an involved/uninvolved FLCr >20. Median PFS was 27.1 months (95% CI: 22.3, 41.2), 30.8 months (95% CI: 19.9, 44.2), and 51.8 months (95% CI: 43.9, 69.8) for Mayo HR, IMWG HR and AQUILA HR, respectively. Out of 52 Mayo HR patients who progressed to MM, 33 (63.5%) progressed to MM within 2 years. Out of 52 Mayo HR patients that progressed to MM, 57.7% met CRAB criteria, 32.7% met SLiM, and the rest with unknown progression type. 31 (59.6%) patients had organ damage at MM diagnosis, most commonly bone pain (25.8%), bone fracture (22.6%), anemia symptoms (45.2%) and other (22.6%). Similar patterns were observed in IMWG HR and AQUILA HR. SMM treatment was initiated in 8/411 (1.9%) patients, 2 (25%) were Mayo HR, with regimens including proteasome inhibitors, immunomodulatory drugs, corticosteroids, and monoclonal antibodies. **Conclusions:** In this large real-world European dataset with updated results, despite active monitoring, nearly half of HR SMM patients who progressed to MM had organ damage, suggesting that active monitoring alone might be insufficient for avoiding organ damage in this patient population. These findings reinforce the need for enhanced monitoring strategies and improved risk stratification in order to identify patients that could benefit from early intervention. Full baseline characteristics, visits frequency, time to MM, PFS and OS in HR and non-HR patients according to Mayo 20–2-20, IMWG and AQUILA will be presented in the final presentation.

PA-403

Real-World Outcomes of Anti-CD38-Based Quadruplet Induction Regimens in Newly Diagnosed Multiple Myeloma: A Multinational Latin American Experience

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Introduction: Anti-CD38-based quadruplet regimens (QUADS) have become a new standard of care for transplant-eligible newly diagnosed multiple myeloma (NDMM). There are limited real-word data regarding the use of Anti-CD38 combinations as induction, consolidation and maintenance therapy in Latin America. **Methods:** We conducted an international retrospective multicenter study including transplant-eligible NDMM patients treated with frontline QUADS between 2019 and 2026 across Latin America. Clinical characteristics, response rates, measurable residual disease (MRD), autologous hematopoietic cell transplantation (ASCT), consolidation, maintenance, progression-free survival (PFS), overall survival (OS), and toxicities were analyzed. **Results:** A total of 222 patients were included from Argentina (74%), Mexico (12%), Chile (7%), Colombia (3%), Guatemala (2%) and Uruguay (1%). Median age was 58 years (range 27–78) with 41% aged >60 years. High-risk cytogenetics were present in 33%, R-ISS 3 disease in 28%, renal failure in 24%, and extramedullary disease in 6%. Frontline regimens included Daratumumab combined with bortezomib, lenalidomide and dexamethasone (D-VRd) in 59%; Daratumumab, bortezomib, thalidomide, dexamethasone (D-VTd) in 36% and Isatuximab QUADS in 5%. Median number of induction cycles was 4 (range 1–8). After induction, overall response rate (≥PR) was 96%, while ≥CR was achieved in 33% (95% CI, 26.8–39.7). MRD assessment after induction was available in 83 patients, with 58% achieveing MRD negativity. Stem cell mobilization was feasible, with a median CD34+ cell yield of 4×10^6/kg (range 2–10). However, 1% of

collections failed despite plerixafor use in 55% of patients. ASCT was performed in 88% of patients. Following ASCT, ≥CR improved to 66.3% (95% CI, 59.2–72.9) with MRD negativity documented in 66% of evaluable patients.Consolidation therapy was administered in 70% of patients, resulting in ≥CR rates of 68.8% (95% CI, 60.9–76.0). Maintenance therapy was delivered in 87% of patients, leading to a final ≥CR rate of 75.3% (95 CI, 68.3–81.4), including 47% stringent complete responses. With a median follow-up of 23.6 months (95 CI, 21.7–25.6), 24-month PFS for the overall cohort was 88% (95% CI, 83–94), and the 24-month OS was 96% (95 CI, 92–99). Patients achieving MRD negativity after ASCT demonstrated a superior 24-month PFS compared with MRD positive patients (94% vs 77%; HR, 0.22; 95% CI, 0.07–0.71; p = 0.012). Grade ≥3 toxicities during induction occurred in 18% of patients and were mostly hematological, infectious and peripheral neuropathy. **Conclusions:** In this large real-word Latin America experience, anti-CD38-quadruplet induction demonstrated high response depth, frequent MRD negativity, successful stem cell mobilization, and favorable survival outcomes with manageable toxicity. These findings support the feasibility and effectiveness of quadruplet-based strategies for transplant-eligible NDMM patients in Latin America.

PA-404

Real-World Outcomes of Daratumumab-Based Quadruplet Versus Triplet Regimens in Relapsed/Refractory Multiple Myeloma: A Multicenter Cohort

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Introduction: Daratumumab-based regimens have transformed the treatment landscape of relapsed/refractory multiple myeloma (RRMM). However, real-world data comparing different daratumumab-based combination regimens remain scarce. **Methods:** We retrospectively analyzed 105 RRMM patients treated with DKd (daratumumab, carfilzomib, dexamethasone; n = 27), DKPd (DKd plus pomalidomide; n = 32), or DPd (daratumumab, pomalidomide, dexamethasone; n = 46) between March 2020 and April 2026. The primary endpoints were overall response rate (ORR) and progression-free survival (PFS). Secondary endpoints included overall survival (OS) and safety. Exploratory multivariable Cox regression was performed to assess factors associated with PFS. Responses were assessed according to the IMWG criteria. Adverse events were graded according to CTCAE version 5.0. **Results:** Median age was 59 years (range 32–84) and 55.2% of patients received study treatment at second line. Baseline characteristics were generally comparable across groups, although differences in β2-microglobulin levels were observed. With a median follow-up of 23.7 months, the overall ORR was 80.8%, with ≥VGPR and ≥CR rates of 69.2% and 41.3%, respectively. The DKPd group achieved the highest ORR (87.1% vs 81.5% for DKd and 76.1% for DPd), the highest 2-year PFS rate (64.3% vs 42.4% and 55.5%), and was the only group in which median PFS was not reached, compared with 23.1 months for DKd and 24.7 months for DPd (log-rank P = 0.66). The median OS was not reached in all three groups; 2-year OS rates were 78.4%, 78.7%, and 71.7% for DKd, DKPd, and DPd, respectively (log-rank P = 0.41). In exploratory multivariable analysis, high-risk cytogenetics (HR 4.17, 95% CI 1.19–14.63, P = 0.026) and extramedullary bone disease (HR 4.09, 95% CI 1.29–12.96, P = 0.017) were independently associated with inferior PFS. The most common grade ≥3 hematologic adverse events were neutropenia (60.7%), leukopenia (38.6%), anemia (36.0%), and thrombocytopenia (24.7%). Non-hematologic adverse events included pneumonia (27.0%) and cardiac events (7.9%). The overall safety profile was manageable across three daratumumab-based regimens. **Conclusions:** In this real-world cohort, DKPd was associated with deeper responses and a favorable PFS trend compared with triplet regimens. These findings suggest that quadruplet therapy may be a reasonable option for selected patients with RRMM. However, these findings should be interpreted with caution given the retrospective, non-randomized design, limited sample size, and potential baseline imbalances, and are best considered hypothesis-generating.

PA-405

Real-World Outcomes of Frontline Anti-CD38-Based Regimens in Transplant-Ineligible Newly Diagnosed Multiple Myeloma

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Introduction: Anti-CD38-based triplet and quadruplet regimens have improved outcomes in transplant-ineligible multiple myeloma (TIE-MM), although Latin American real-world evidence remains limited. Given barriers to innovative therapies in low- and middle-income countries (LMICs), regional data are needed to inform clinical practice and treatment access. Objectives: To evaluate the effectiveness, safety, and survival outcomes of frontline anti-CD38-based regimens in TIE-MM patients in Argentina. **Methods:** We conducted a retrospective multicenter study across 16 centers in Argentina. Eligible TIE-MM patients diagnosed according to IMWG

2014 criteria and treated between January 2020 and April 2026 received frontline VRd or anti-CD38-based triplet/quadruplet regimens. Patients with AL amyloidosis, Waldenström macroglobulinemia, POEMS syndrome, or inadequate medical records were excluded. PFS and OS were estimated using the Kaplan–Meier method. Comparisons were performed using log-rank, chi-square, or Fisher's exact tests. **Results:** A total of 142 patients were included. Median age was 76 years (IQR 72–80), 57% were male, and median follow-up was 30.7 months (IQR 15.3–48.7). Most patients had ECOG 0–1 (76%), ISS II–III (62%), and R-ISS II–III disease (58%). High-risk cytogenetics were identified in 6%; FISH was performed in 82% and plasma cell sorting in 35%. Frontline treatment consisted of VRd in 64% and anti-CD38-based regimens in 36%; 18% received quadruplets. ORR was 97%, with 71% achieving ≥VGPR and 41% CR/sCR. No significant differences were observed according to anti-CD38 exposure. However, quadruplet regimens achieved higher ≥VGPR rates than non-quadruplet approaches (92% vs 66%, p = 0.012). MRD assessment was performed in 31% of patients, with 43% achieving MRD negativity. Grade 3–4 adverse events included anemia (5%), neutropenia (6%), thrombocytopenia (7%), peripheral neuropathy (4%), and infections (19%). Anti-CD38-based regimens were not associated with increased severe toxicity or infections. Quadruplet regimens were associated with lower rates of grade 3–4 thrombocytopenia (0% vs 11%, p = 0.014) and peripheral neuropathy (0% vs 7.7%, p = 0.042). Median PFS was 30.5 months in the VRd group and not reached in the anti-CD38 group (p = 0.02). Estimated 24- and 36-month PFS rates were 76.9% and 72.3% versus 66.5% and 44.1%, respectively. In univariate analysis, anti-CD38 exposure was associated with improved PFS (HR 0.47, 95% CI 0.24–0.91; p = 0.027), remaining significant after adjustment for age >75 years, ECOG ≥2, and ISS III (HR 0.42, 95% CI 0.21–0.83; p = 0.013). Median OS was not reached in either group, and no significant OS differences were observed. **Conclusions:** Frontline anti-CD38-based therapy was associated with prolonged PFS without increased severe toxicity. These findings support the incorporation of anti-CD38 regimens in TIE-MM and highlight the need to improve access to innovative therapies in LMICs.

PA-406

Real-World Patient Characteristics and Effectiveness of Daratumumab-Based Regimens in First-Line Management of Multiple Myeloma in France: Results from a Sub-Analysis of French EMMY Study

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Introduction: Multiple myeloma (MM) is a heterogeneous hematologic malignancy for which first-line (L1) treatment strategies have evolved considerably. The introduction of daratumumab, an anti-CD38 monoclonal antibody, has reshaped the L1 landscape, with daratumumab-based combinations now widely used. Real-world evidence is essential to describe implementation outside clinical trials and to contextualize effectiveness in broader populations. The EMMY study, a nationwide French real-world cohort, describes MM treatment patterns. This sub-analysis characterized DVRd (daratumumab, bortezomib, lenalidomide, dexamethasone) and DRd use as L1 treatments and described patient characteristics and outcomes in transplanted and non-transplanted patients. **Methods:** EMMY is a non-interventional, retrospective, multicenter cohort including adults with symptomatic MM initiating a new line of therapy across 70 French centers. Data were extracted annually from medical records up to January 2025, death, or data cut-off. This sub-analysis included patients initiating L1 therapy between September and December 2021–2023. Clinical characteristics included cytogenetics, comorbidities, and frailty. Effectiveness was assessed using progression-free survival (PFS) and overall survival (OS) estimated by Kaplan–Meier methods. **Results:** Overall, 1,291 patients initiated an L1 regimen. Among 325 transplanted patients, 99% received a daratumumab-based regimen. DVRd use increased from 58% in 2021 to 79% in 2023. DVRd-treated patients were relatively young (median age 61 years) and fit; 87% had ECOG 0–1 and 89% ≤1 comorbidity. Cytogenetic testing was performed in 75%, with 43% classified as high risk [t(4;14), del(17p), gain(1q), del(1p)]. Most patients (87.5%) received maintenance therapy. At 24 months, PFS was 91.0% (95% CI 86.2–95.9) and OS 98.4% (95% CI 96.2–100). Among 966 non-transplanted patients, 90% received a daratumumab-based regimen. DRd was most frequently used (stable around 60% from 2021 to 2023), while DVRd increased from 11% to 24%. DRd-treated patients were older than those receiving DVRd (median age 77 vs 67 years) and more frequently frail (approximately two-thirds vs one-third). DVRd was more often used in patients with high-risk cytogenetics (23.7% vs 17.8%). At 24 months, PFS and OS rates were 67.1% and 85.6% with DRd in a real world population with a higher proportion of unfit patients compared to the MAIA trial. Longer follow-up of the data is awaited for DVRd outcomes. **Conclusions:** Daratumumab-based regimens are now central to L1 MM management in France. Among transplanted patients, DVRd rapidly became the predominant regimen, supporting its role as a real-world standard. In non-transplanted patients, DRd remains the backbone, while DVRd is increasingly used in fitter and higher-risk patients. These data highlight the interest of several daratumumab

based regiments in L1 to tailor treatment to patient fitness and disease risk.

PA-407

Real-World Patient Characteristics, General Safety Profile, and Treatment Patterns of Elranatamab (ELRA) use in Relapsed Refractory Multiple Myeloma (RRMM): Interim Results of the AMbrELA Study

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Introduction: ELRA, a BCMA-CD3 bispecific antibody, was approved for RRMM based on the phase 2 MagnetisMM-3 study (MM-3, NCT04649359). ELRA administration includes 2 step-up priming doses followed by a 76 mg weekly (QW) dose until week 24, biweekly (Q2W) when response is achieved until week 48, then monthly (Q4W) if response is maintained. Here, we compare real-world (RW) patient (pt) characteristics between AMbrELA and MM-3 and describe the RW safety and treatment patterns of ELRA. **Methods:** AMbrELA (EUPAS1000000074) is an observational ambispective study of ELRA effectiveness and safety in pts who initiated ELRA in the early access program in France since May 2023. Retrospectively enrolled pts who received ≥1 ELRA dose prior to 31Jul2025 (data cutoff) were selected for this 2nd interim analysis. Adverse events (AEs) occurring before pt inclusion were collected if treatment-related (TR), while all AEs occurring after inclusion were collected regardless of cause. **Results:** A total of 89 pts from 30 centers were included; median follow-up was 13.4 mo (95% CI, 11.5–16.6). Pts from AMbrELA (vs MM-3 BCMA-naive pts) were older (median [range], 72.0 yrs [50–92] vs 68.0 yrs [36–89]) and more likely to have ECOG PS ≥2 (38.5% vs 5.7%) or ISS/R-ISS ≥II (80.4% vs 70.7%). Presence of extramedullary disease (28.2% vs 31.7%), bone marrow plasma cells ≥50% (28.8% vs 21.1%), and prior lines of therapy (median [range], 4 [1–15] vs 5 [2–22]) were similar between cohorts. Triple-class (93.3% vs 100%) or penta-drug (67.4% vs 70.7%) exposure rates were similar but pts in AMbrELA were less likely to have triple-class (37.1% vs 96.7%) or penta-drug (19.1% vs 42.3%) refractoriness; 12.4% vs 0% had prior BCMA-directed therapy. In 65 evaluable pts, 10 had high risk myeloma defined in AMbrELA as having del(17p). In MM-3, 25.2% were high risk [defined as t(4;14), t(14;16) and del(17p)]. Overall, 71.9% of pts had ≥1 AE; 28.1% had ≥1 serious AE. Common AEs (>5%)/TR-AEs were cytokine release syndrome (36.0%/34.8% vs 57.7% in MM-3), asthenia (6.7%/3.4%), pyrexia (6.7%/4.5%), neutropenia (5.6%/2.2%) and injection site reaction (5.6%/5.6%); most were not serious. A total of 23.6% of pts had ≥1 infection (vs 69.9% in MM-3), 9.0% had ≥1 serious infection. Median (range) time to infection onset and resolution was 4.1 mo (0–21) and 0.6 mo (0–3), respectively. Most pts (84.3%) received ELRA QW; 29.2% switched to Q2W and 15.7% to Q4W. Median (range) time from QW to Q2W dosing was 5.3 mo (1–8) and time to Q4W dosing was 6.6 mo (1–16). ELRA was administered in an outpatient setting in 73.0% of pts. **Conclusions:** Overall, pts in AMbrELA were older with a poorer general condition than BCMA-naive pts in MM-3. The RW ELRA safety profile was consistent with that in MM-3, except for lower CRS and infection rates, which may reflect improved management in routine clinical practice in France. ELRA dosing appeared to transition to Q4W more rapidly than recommended. A 3rd interim analysis is planned to update these results (data cutoff 28Feb2026).

PA-408

Real-World Progression-Free Survival Among Non-Transplanted Newly Diagnosed Multiple Myeloma Patients Initiating Frontline DVRd vs VRd

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Introduction: The pivotal CEPHEUS clinical trial demonstrated that the quadruplet regimen daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) offers superior efficacy with a tolerable safety profile compared with the triplet VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). However, comparative real-world evidence on these treatments in this population is lacking, especially for older patients. This study evaluated progression-free survival (PFS) among non-transplanted patients with NDMM initiating DVRd or VRd as frontline (1L) treatment in routine clinical practice in the US. **Methods:** This retrospective observational study used the Flatiron Health Research database. Patients aged ≥18 years with NDMM who did not receive a hematopoietic stem cell transplant prior to or during 1Land initiated DVRd or VRd regimen as 1L between May 7, 2018 and February 28, 2026 were included. The index date was the date of 1L initiation. Frailty was assessed using the Intergroup Francophone of Myeloma (IFM) simplified frailty score. PFS was defined as the time from the index date to disease progression or death. Patients receiving DVRd or VRd were matched 1:1 using propensity scores based on demographic

and clinical characteristics. A Cox proportional hazards model, adjusting for variables that remained imbalanced post-match, was used to compare PFS between the matched cohorts. Results were reported as an adjusted hazard ratio (HR) with 95% confidence interval (CI). **Results:** A total of 929 patients initiating DVRd and 1,950 patients initiating VRd met the inclusion/exclusion criteria. At index date, DVRd patients were younger (mean age [range], 66 [19–85] vs 69 [32–85] years), had higher rates of high cytogenetic risk (40% vs 33%), were more often treated in academic settings (22% vs 11%), and a lower proportion were frail (29% vs 35%) than VRd patients. After matching, each cohort included 919 patients, and baseline characteristics were balanced except for age group and year of index. The median follow-up was 18 months in the DVRd cohort and 40 months in the VRd cohort. Disease progression or death occurred in 13% of DVRd and 30% of VRd patients (log-rank $P < 0.0001$). Median PFS was not reached in the DVRd cohort and was 51 months in the VRd cohort. After adjusting for confounders that remained imbalanced post-match, DVRd was associated with a 41% lower risk of disease progression or death compared with VRd (HR: 0.59; 95% CI: 0.45–0.78; $P = 0.0002$). Similar results were observed among a subgroup of patients aged ≥70 at index (HR: 0.47; 95% CI: 0.32–0.69; $P = 0.0001$). **Conclusions:** In this real-world study of non-transplanted patients with NDMM, DVRd was associated with a significantly lower risk of disease progression or death than VRd, including among patients aged ≥70 years. These real-world results are consistent with the findings from the CEPHEUS trial and demonstrate a consistent benefit of the DVRd quadruplet regimen compared with VRd.

PA-409

Real-World Survival Outcomes and Treatment Patterns Among Frail Older Adults with Multiple Myeloma: A United States Veterans Affairs Cohort Study from 2000 to 2023

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Introduction: Multiple myeloma (MM) affects older adults with a median age of diagnosis of 69 years. Many patients are frail, with multiple comorbidities that influence treatment selection and tolerability. Studies suggest that frail patients are less likely to receive intensive therapy. We characterized treatment patterns and outcomes among patients aged ≥75 years with MM within the United States Veterans Health Administration (VHA). **Methods:** Adults aged ≥75 years with newly diagnosed MM (NDMM) receiving care at the VHA were identified using ICD-10 codes seen at the VHA for 3 separate visits. Frailty status was determined using VHA Frailty Index categorized as frail or robust/pre-frail (frail: 0.21–0.4, robust/pre-frail: 0.0–0.20). Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to evaluate overall survival (OS) and treatment sequencing outcomes. **Results:** Among 4,613 patients aged ≥75 years with NDMM, 59.7% were classified as robust/pre-frail and 40.3% as frail. Mean age at diagnosis was 80.4 years and patients identified as 63.7% White, 17.4% Black and 4.9% Hispanic. Most resided in urban areas (67.7%) and reported annual incomes below $30,000 (68.5%). ISS Stage III disease was more common among frail vs robust/pre-frail patients (28.6% vs 14.7%). Frail patients demonstrated greater comorbidity burden, including congestive heart failure (24.8% vs 4.8%), chronic pulmonary disease (29.0% vs 10.1%), and renal disease (38.2% vs 12.7%) (all $p < 0.001$). Frail patients were also less likely to receive subsequent lines of therapy for MM, with 56.2% vs 39.2% receiving only one line of therapy. Median OS was shorter among frail patients compared to robust/pre-frail patients (127.2 vs 260.6 months; $p < 0.001$). On multivariable analysis, frailty independently predicted shorter time to next treatment (TTNT) (HR 1.27, 95% CI 1.10–1.45; $p < 0.001$), independent of age, ISS Stage, and VHA priority status. ISS Stage III disease was associated with inferior TTNT compared with ISS Stage I disease (HR 1.40, 95% CI 1.14–1.74; $p = 0.002$). Other notable associations to lower survival included older age, ISS stage III (vs Stage I), lower income, lower priority status, rural (vs urban), chronic pulmonary disease, and congestive heart failure. The impact of individual lines of treatment regimens will be further explored for this cohort. **Conclusions:** In this VHA retrospective cohort, frailty among adults aged ≥75 years with NDMM was associated with greater comorbidity burden, less intensive induction therapy, fewer subsequent lines of therapy, and worse OS. Frailty remained an independent predictor of mortality after adjusting for sociodemographic and clinical factors, supporting the importance of frailty assessment in treatment planning and risk stratification for older adults with NDMM.

PA-410

Real-World Teclistamab in Heavily Pretreated Relapsed/Refractory Myeloma: Deep Responses, Infections, and Extramedullary Escape

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Introduction: Real-world teclistamab data from resource-constrained settings are limited, especially regarding infections, supportive care, and extramedullary/functionally high-risk relapsed/refractory multiple myeloma (RRMM). We analysed efficacy, survival, CRS, ICANS, infections, IVIG, and tocilizumab use in a single-centre cohort. **Methods:** We ambispectively analysed 15 RRMM patients treated with teclistamab. Baseline disease, prior therapy, extramedullary disease (EMD), response, progression, survival, CRS, ICANS,

infections, IVIG, vaccination, and tocilizumab data were reviewed. Best documented response was recorded. PFS was calculated from teclistamab initiation to progression/death, and OS to death; patients without events were censored at last follow-up. Follow-up was estimated by reverse Kaplan-Meier method. **Results:** Median age was 68 years (range, 37–72); 10 patients were female. Relapse R-ISS was II in 8 and III in 7 patients. Median prior therapy lines were 6; all patients were exposed to daratumumab, bortezomib, and lenalidomide. Prior carfilzomib and pomalidomide exposure were present in 10 (66.7%) and 11 (73.3%) patients. Prior autologous transplant was documented in 8 patients. EMD was documented in at least 5 patients (33.3%). Best documented ORR was 86.7% (13/15), with VGPR or better in 80.0%, CR or better in 60.0%, and MRD-negative response in 26.7%. At last follow-up, 10 patients (66.7%) were alive without documented progression; 5 (33.3%) had progression or death, including 2 deaths. Progression events comprised 2 relapses after response and 3 early refractory/progressive cases, including EMD progression despite initial serologic response. Median observed follow-up was 5.8 months; reverse Kaplan-Meier median follow-up was 8.0 months. Median PFS and OS were not reached; estimated 6-month PFS and OS were 61.7% and 82.5%. CRS occurred in 10 patients (66.7%), predominantly grade 1–2; one clinically significant grade 3 CRS-like hypotensive episode during step-up rechallenge was described and subsequently rechallenged successfully. Grade 3 ICANS occurred in 1 patient and resolved with dexamethasone and anakinra. Routine prophylactic tocilizumab was used in 14 patients. IVIG was used in all patients before and during teclistamab, generally 400 mg/kg monthly. Despite this, infections occurred in 9 patients (60.0%), including fungal infections, CMV reactivation/viremia, Gram-negative sepsis, recurrent urinary tract infection, and anal abscess. **Conclusions:** Teclistamab produced deep responses in heavily pretreated RRMM despite universal prior anti-CD38, proteasome inhibitor, and immunomodulatory drug exposure. However, early progression, EMD escape, and infections remained key outcome determinants despite proactive IVIG and tocilizumab-based supportive care. These findings support structured infection-prevention pathways and close monitoring for aggressive/EMD relapse during BCMA bispecific therapy.

PA-411

Real-World Treatment Patterns and Survival Outcomes in Relapsed/Refractory Multiple Myeloma (RRMM) in a MajesTEC-3 Study–Like Population From the US Optum Claims Database

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Introduction: Many patients (pts) with RRMM do not proceed to a subsequent line of therapy (LOT) at progression. Among those who do, outcomes deteriorate with each successive relapse, underscoring the importance of using the most effective therapy at each relapse. Novel BCMA-targeted therapies, including the teclistamab-daratumumab (Tec-Dara) combination recently approved based on results of the MajesTEC-3 study, may help improve outcomes in earlier lines. As most pts receive frontline proteasome inhibitors (PIs) and lenalidomide (Len) and/or anti-CD38 therapy, we characterized real-world treatment patterns and outcomes in an RRMM population similar to that of MajesTEC-3 to aid in contextualizing findings from this study. **Methods:** Data were derived from the US Optum commercial and Medicare claims database between January 2016 and May 2025. Eligible pts met the MajesTEC-3 inclusion criteria (RRMM with 1–3 prior LOT, including a PI and Len [Len refractory if only 1 prior LOT]; no prior anti-B-cell maturation antigen exposure; could be anti-CD38 exposed but not refractory) and had an index date (initiation of 2L+) in January 2021 or later. Time-to-event analyses were estimated using the Kaplan-Meier method. **Results:** A total of 1453 pts met all inclusion criteria (1 prior LOT, 36.1%; 2 prior LOTs, 53.7%; 3 prior LOTs, 10.2%). Most pts (84.7%) were aged >65 years; 51.1% were female; 12.9% received prior Dara; 0.6% received prior isatuximab; 80.7% and 83.5% were refractory to PIs and Len, respectively. Median time from index date to end of follow-up was 40.3 mo. Overall, 57.2% of pts received triplet regimens. The most common triplet regimen was Dara/pomalidomide/dexamethasone (14.1%), a comparator in the MajesTEC-3 study. Median (95% confidence interval [CI]) time to next treatment (TTNT) from the first index LOT in the total population was 15.9 mo (14.0–18.1). Median (95% CI) TTNT was numerically shorter with increasing LOT, at 16.8 mo (14.8–20.5), 14.9 mo (13.3–18.4), and 11.4 mo (9.7–19.8) in pts with 1, 2, and 3 prior LOTs, respectively (P = 0.32). There was a shorter median (95% CI) TTNT in pts who were Len refractory (15.0 mo [13.4–17.4]) versus those who were not (22.7 mo [15.5–32.8]; P = 0.0048). Median (95% CI) overall survival (OS) from the first index LOT in the total population was 40.3 mo (37.1–46.6). Median (95% CI) OS was shorter with increasing LOT and was not estimable (NE; 40.2-NE), 38.9 mo (34.8–46.8), and 34.3 mo (29.0–46.6) in pts with 1, 2, and 3 prior LOTs, respectively (P = 0.048). There was a shorter median (95% CI) OS in pts who were Len refractory (39.7 mo [35.6–43.0]) versus those who were not (NE [35.1-NE]; P = 0.013). **Conclusions:** In this real-world analysis, poorer outcomes were associated with refractoriness to Len and increasing prior LOTs. These findings highlight the importance of earlier use of highly effective treatment options, such as the Tec-Dara combination, to improve patient outcomes.

PA-412

Recurrent Anterior Uveitis Associated With Teclistamab in Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab, a BCMAxCD3 bispecific antibody, has demonstrated significant efficacy in relapsed/refractory multiple myeloma (RRMM). The most commonly reported adverse events include cytokine release syndrome, infections, and cytopenias. Ocular inflammatory toxicities remain poorly characterized, with very limited data available in the literature. **Methods:** We report the clinical course of an 80-year-old woman with heavily pretreated IgG lambda RRMM who developed recurrent anterior uveitis during teclistamab treatment. Clinical, ophthalmologic, and laboratory findings were retrospectively reviewed, including infectious and viral studies performed on blood samples and aqueous humor. **Results:** The patient had previously received multiple treatment lines, including VTd, lenalidomide-dexamethasone, daratumumab-based therapy, and KPd, which was discontinued after ocular thrombotic complications. Ophthalmologic history was notable for left central retinal vein occlusion, neovascular glaucoma, hypertensive uveitis secondary to intravitreal aflibercept, and severe visual impairment in the left eye. No previous inflammatory involvement had been documented in the right eye before teclistamab exposure.Due to biochemical progression and CAR-T refusal, fifth-line therapy with teclistamab was initiated. During treatment, the patient developed a first episode of acute anterior uveitis in the right eye, requiring temporary teclistamab interruption and treatment with topical and systemic corticosteroids, achieving clinical improvement. Following drug rechallenge, a second episode of anterior uveitis occurred, leading to definitive treatment discontinuation.Ophthalmologic examination demonstrated preserved visual acuity in the right eye, positive anterior chamber Tyndall effect, absence of posterior synechiae, and no significant vitreous inflammation. Extensive diagnostic work-up excluded infectious causes and viral reactivation through serological testing and aqueous humor analysis. Symptoms resolved with oral prednisone taper, topical prednisolone, and atropine. **Conclusions:** We describe a rare case of recurrent anterior uveitis temporally associated with teclistamab exposure in RRMM. The recurrence after rechallenge and exclusion of infectious or viral etiologies support a possible immune-mediated mechanism. This report highlights the importance of multidisciplinary management and close ophthalmologic monitoring in patients receiving BCMA-directed bispecific antibodies.

PA-413

Renal Histomorphology - How Often Initiates Monoclonal Work Up Including Monoclonal Gammopathy of Renal Significance

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Introduction: Kidney disease is a frequent complication of monoclonal gammopathies that manifests with a wide range of renal lesions. Many times renal symptoms and further investigations lead to diagnosis of myeloma. Many of these cases with renal involvement fulfil the criteria for monoclonal gammopathy of unknown significance (MGUS) but not overt myeloma or any other monoclonal lymphoid proliferation, are classified as monoclonal gammopathy of renal significance (MGRS). **Methods:** Objective: To document the spectrum and prevalence of monotypic disorders including MGRS and analyse how often monoclonal work up initiated after monoclonal renal histomorphology. Eighteen years (from January 2007 to June 2026) renal biopsy reports of the patients were reviewed in the Department of Histopathology. Clinical details of the patients were reviewed from the departments of central registry, Nephrology and Clinical Haematology and Medical Oncology departments. All monotypic renal biopsies were retrieved and their monoclonal work-up analysed to categorise into MM, MGRS or monoclonal haematolymphoid disease. **Results:** There were 5.7% (423) monotypic renal biopsies out of 21092 renal biopsies and 39% had renal symptoms as first manifestation. 59.1% were diagnosed as MM and 40.1% qualified for MGRS. 89% had MM already diagnosed at the time of biopsy whereas 11% were diagnosed after renal biopsy. Haematolymphoid proliferation was seen in 3. Male to female ratio was 2.3:1 and the average age of presentation was 53.5 years. Spectrum of lesions diagnosed were cast nephropathy (n = 218), amyloidosis (n = 7), PGNMID (n = 21), MIDD (n = 34) and proximal tubulopathy (n = 37), monoclonal membranous (n = 7), C3 glomerulopathy (n = 7), thrombotic microangiopathy (n = 7), cryoglobulemic glomerulonephritis (n = 7), crystal storing histiocytosis (n = 3), plasma cell/lymphoid infiltration (n = 3), immunotactoid (n = 3). **Conclusions:** Almost 40% monoclonal renal deposition disease do not fulfil the criteria of myeloma and were categorised MGRS. Haematolymphoid proliferation was seen in 3. Renal manifestation is their first presentation; hence vigilant immunofluorescence interpretation is the key factor. The pathologic spectrum of

monotypic renal diseases in this setting is wide and a kidney biopsy is required to determine the exact nature of the disease.

PA-414

Repurposing Polyether Ionophores to Target Stem-like Compartments and Microenvironmental Resistance in Multiple Myeloma

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Introduction: Multiple myeloma (MM) remains incurable owing to drug-tolerant, stem-like clones harbored in the bone marrow niche. We hypothesized that the polyether ionophores salinomycin (SAL) and monensin (MON), known to kill cancer stem-like cells in solid tumors, would target the Hoechst-low side-population (SP) compartment of MM. **Methods:** SAL and MON were profiled across fifteen MM cell lines, primary CD138+ plasma cells from 13 patients and PBMCs from six healthy donors using MTT and CTG assays. Five MM cell lines were subjected to JC-1 (mitochondrial membrane potential), Annexin V/PI apoptosis, cell-cycle and time-resolved immunoblotting assays. Activity was tested in HS-5 stromal co-culture and within the SP compartment, which was further interrogated by bulk RNA-sequencing in SP cells (DESeq2; GSEA KEGG/GO). Translational relevance was assessed by Chou-Talalay combination indices with standard MM agents and by in vivo efficacy in NSG mice bearing subcutaneous RPMI-S xenografts. **Results:** SAL and MON induced dose- and time-dependent cytotoxicity (MON more potent; SAL with a modest therapeutic window over PBMCs) in MM cell lines and in ex vivo patient samples. Mechanistic dissection of SAL and MON revealed mitochondrial depolarization, apoptosis, and G0/G1 cell cycle arrest as key contributors to cytotoxicity. Time-resolved immunoblotting revealed an early (6 h) collapse of PI3K/AKT/mTOR/4E-BP1, MAPK and NF-κB signaling with stress activation (p-JNK, p-Hsp-27, γH2AX), evolving by 24 h into Chk1-driven DNA-damage response, Cyclin B1/A2 loss, p21/p27 induction and extinction of IRF-4, SIRT1 and c-Myc. Both compounds retained activity in HS-5 stromal co-culture and selectively depleted the Hoechst-low SP fraction. SP transcriptomics identified 1,178 SAL- and 921 MON-regulated genes with highly concordant signatures, including the strongest down-regulation of mitochondrially-encoded OXPHOS components (MT-ND/MT-CO/MT-ATP; log2FC down to −6.3). GSEA confirmed coordinated repression of oxidative phosphorylation (NES≈-3.0), ribosome biogenesis, spliceosome, proteasome, DNA replication and cell cycle, with induction of the integrated stress response (DDIT3, CHAC1, GDF15), ER-stress intrinsic apoptosis (BBC3, PMAIP1) and autophagy/lysosome programs (SQSTM1, MAP1LC3B). Both compounds synergized (Chou-Talalay CI< 0.9) with bortezomib, carfilzomib, lenalidomide, pomalidomide, doxorubicin, dexamethasone and melphalan, and significantly reduced subcutaneous RPMI-S xenograft growth in NSG mice without overt toxicity. **Conclusions:** SAL and MON are mechanistically convergent, stroma-resistant and cancer stem-like cell-directed agents that dismantle the bioenergetic, translational and survival machinery of the MM SP compartment, synergize with standard MM therapies and show in vivo efficacy without overt toxicity, supporting their further development for MM combination strategies. This study was supported by the NextGenerationEU project No.09I03-03-V04-00451 (JJ).

PA-415

Resetting the Aberrant Methylation Landscape and DNA Damage Response in Multiple Myeloma Through MAT2A Targeting Reveals Novel Combination Strategies

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Introduction: Emerging evidence highlights a critical role for epigenetic defects, including aberrant DNA and histone methylation, in driving disease progression and relapse of the plasma cell malignancy multiple myeloma (MM). However, the mechanisms underlying these epigenetic defects remain largely unknow. Previously, we showed that silencing of methionine adenosyltransferase 2A (MAT2A) impairs myeloma survival by inhibiting mTOR-mediated protein synthesis. As MAT2A is the main producer of the universal methyldonor s-adenosylmethionine (SAM), we here investigated the effects of MAT2A depletion on the methylation landscape and downstream signaling pathways. **Methods:** MAT2A knockdown (KD) in OPM2 and AMO-1 cell lines was achieved using doxycycline inducible lentiviral shRNA vectors targeting MAT2A. KD efficiency was determined on mRNA and protein level using qRT-PCR and Western blot (WB). The effect on cell viability, cell cycle progression and apoptosis was measured by a CellTiter Glo assay, AnnexinV/7AAD and BrdU stainings. The impact of MAT2A silencing on DNA methylation and histone methylation was evaluated using Enzymatic Methyl sequencing (EM-seq), Chromatin ImmunoPrecipitation sequencing (ChIPseq) and WB, while the impact on the MM transcriptome was determined using RNA sequencing (RNA-seq). **Results:** In line with our previous findings, stable MAT2A KD in MM cells using shRNA confirmed the tumor promoting role of MAT2A in MM, as evidenced by a

significant reduction in MM cell viability and growth and a strong increase in apoptosis. On a mechanistic level, MAT2A-depleted cells showed a clear decrease in global DNA methylation levels. Gene set enrichment of the differentially methylated regions revealed significant enrichment of genes involved in p53 pathway, KRAS signaling down and apoptosis. Furthermore, we also observed significant changes in global histone methylation levels, with a strong decrease in the repressive histone marks H3K27me3, H3K9me2 and H4K20me2/3 and the active mark H3K36me3 along with their respective histone methyltransferases. ChIPseq is currently performed to identify the locus specific methylation changes. Concomitant RNA-seq upon MAT2A KD identified 449 genes upregulated and 493 genes downregulated, with genes/pathways affected mainly involved in interferon responses, MYC targets V1, G2M checkpoint and mTORC1 signalling. Additionally, gene ontology enrichment analysis revealed that MAT2A depletion mostly affects pathways involved in ATP-dependent binding, replication and protein interaction activities. Lastly, critical vulnerabilities were identified in DNA damage response pathways, leading to synergistic anti-myeloma activity of the novel MAT2A inhibitor AG-270 in combination with either the DNA damaging agent melphalan or the PRMT5 inhibitor EPZ015938. **Conclusions:** In conclusion, targeting MAT2A in MM cells reverts aberrant methylation and impairs pro-tumoral signalling offering promising avenues for more effective combination therapies.

PA-416

Resolution of Clonal Cytopenia of Undetermined Significance Following Autologous Stem Cell Boost in a Patient with Multiple Myeloma: A Case Report

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Introduction: Clonal cytopenia of undetermined significance (CCUS) is characterized by persistent unexplained cytopenia(s) in the presence of somatic mutations associated with myeloid neoplasms, without meeting morphologic criteria for myelodysplastic syndrome or other hematologic malignancy. CCUS confers a significantly increased risk of progression to myeloid neoplasms, particularly in patients with multiple mutations, higher variant allele frequency, or high-risk gene alterations. CCUS is also associated with inferior overall survival compared with non-clonal cytopenias. Currently, there are no established disease-modifying therapies for CCUS and management is based on surveillance and supportive care. To our knowledge, there are no published reports describing the use of autologous stem cell boost for management of CCUS. While stem cell boost has been reported in the setting of post-transplant or immunotherapy-associated cytopenias, its impact on clonal precursor hematopoietic conditions has not been described. **Methods:** Retrospectively reviewed the clinical course, pathology, and cytogenetics of a patient with MM who developed severe cytopenias after ASCT and maintenance therapy and was treated with an stem cell boost without conditioning. **Results:** This case report examines a 71 year old man with kappa light chain multiple myeloma (MM). He received bortezomib, lenalidomide, and dexamethasone induction and autologous stem cell transplant consolidation with melphalan prep followed by stem cell rescue utilizing 6.32×10^6 CD34+ cells/kg. An additional 6.32×10^6 CD34+ cells/kg were stored at that time. The patient achieved a stringent complete response after which he received 20 months of lenalidomide maintenance prior to treatment disruption for unexplained cytopenias including hemoglobin (Hgb) 6.9 g/dL and platelets (Plt) 3 K/mcL. He remained transfusion dependent despite supportive care including epoetin alfa and romiplostim. A bone marrow biopsy showed that of 20 metaphases, 18 had an unbalanced 3:18 translocation resulting in a 3q duplication and an 18q deletion. He underwent stem cell boost infusion using his stored cells without conditioning treatment. His counts fully recovered within 6 months (Hgb 12.1 and Plt 210) and repeat bone marrow biopsy demonstrated normal hematopoiesis without clonal abnormality. He remains in stringent complete response without any maintenance for his MM. **Conclusions:** This case suggests that autologous stem cell boost may represent a potential treatment option for select patients with CCUS and refractory cytopenias, a population for whom no established disease-modifying therapies currently exist. These findings support consideration of early collection and storage of additional autologous stem cells when available. Stem cell boost may provide a valuable salvage strategy in certain clinical settings. Further studies are needed to define patient selection, durability of response, and long-term outcomes.

PA-417

Response to Bispecifics in Relapsed-Refractory Multiple Myeloma (RRMM) Patients with Severe Renal Insufficiency: Case Series

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Introduction: While multiple myeloma is not curable, therapies such as bispecific antibodies have increased time to disease progression. Teclistamab (Tec) and talquetamab (Tal) are approved for relapsed-refractory multiple myeloma (RRMM); however, patients with pre-treatment creatinine clearance (CrCl) less than 40 mL/min were excluded. Real-world data is needed to evaluate efficacy and

safety of Tec and Tal in RRMM patients with renal insufficiency. **Methods:** A retrospective, single-center analysis of patients initiated on Tec or Tal between October 2022 to February 2026 with pre-treatment CrCl less than 40 mL/min at treatment initiation. **Results:** Nine patients with RRMM and pre-treatment CrCl less than 40 mL/min were treated with Tec and/or Tal. Median age at treatment initiation was 75 years (range 67 to 84 years) with a median of six prior lines of therapy (range three to ten) and mean pre-treatment CrCl was 21 mL/min. Five patients received Tec only, one received Tal only, two received both agents separately, and one received Tec plus daratumumab. All patients received uniform antimicrobial prophylaxis and supportive care in accordance with the institutional standard. Additionally, all patients received tocilizumab 8 mg/kg (capped at 800 mg) once prior to step-up dose 1 for cytokine release syndrome (CRS) prophylaxis in accordance with the institutional standard. All patients responded to treatment with four patients achieving complete response, three achieving very good partial responses, and two achieving partial response. The median time to first response was one month and median duration of response was 6.5 months. Best CrCl on treatment increased a mean of 31 mL/min from pre-treatment CrCl. Four patients progressed after a mean of 11.2 cycles, while six remain on therapy. No CRS or major infections were observed, and one patient experienced grade 2 ICANS which resolved within 48 hours. **Conclusions:** Tec and Tal were well tolerated in RRMM patients with CrCl < 40 mL/min. Patients with renal insufficiency should not be excluded from getting BsAbs.

PA-418

Rethinking Routine IVIG Use With Talquetamab in Relapsed/Refractory Multiple Myeloma

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Introduction: Talquetamab (TAL), a GPRC5D-directed bispecific antibody (bsAb) is effective in relapsed/refractory multiple myeloma (RRMM) and has reported lower rates of severe infection than BCMA-directed bsAbs, although hypogammaglobulinemia remains common. Intravenous immunoglobulin (IVIG) is associated with reduced rates of severe infections with BCMA-directed bsABs, but its role in patient receiving TAL remains unclear. We evaluated IVIG use, infection outcomes, and infection risk in TAL-treated RRMM. **Methods:** We conducted a retrospective multicenter analysis of adults with RRMM treated with TAL. IVIG exposure was evaluated before TAL or within one month of initiation and at any time during treatment. Infectious events were captured from TAL initiation through last follow-up and categorized by timing, recurrence, pathogen, and hospitalization. Cause-specific Cox models evaluated associations with first infection and infection related hospitalization. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier methods. **Results:** A total of 126 patients were included. Median age was 66 years, and patients had received a median of 6 prior lines of therapy; 61% had prior BMCA-directed therapy and 80% had prior transplant. IVIG was administered prior to TAL initiation in 23% of patients, within 1 month of TAL initiation in 34%, and at any point in treatment 48%. Median follow up was at 16 months. Cumulative incidence of first infection was 39% at 3 months, 45% at 6 months, and 47% at 12 months. Among 101 infectious events, 54 (53%) required hospitalization and 11 (11%) required ICU admission. Bacterial, viral, fungal infections accounted for 49%, 47%, and 4.2% of events, respectively. Recurrent infections accounted for 42 events with 24 (57%) requiring hospitalization. IVIG prior to TAL initiation was not associated with a reduced risk of first infection (HR 1.10, 95% CI 0.62–1.97; p = 0.7). IVIG within 1 month was not associated with reduced any-grade infection (HR 1.09, 95% CI 0.54–2.22; p = 0.8), but showed a trend toward fewer hospitalization-associated infections after month 1 (HR 0.42, 95% CI 0.14–1.31; p = 0.11). Prior BCMA-directed therapy was not associated with first infection risk (HR 1.17, 95% CI 0.68–2.01; p = 0.6). Median PFS and OS were 11 and 25 months, respectively. **Conclusions:** In this multicenter real-world cohort, infections during TAL therapy were common were often early, recurrent, and frequently required hospitalization. Early IVIG was not associated with reduced first infection risk, but the trend toward fewer later hospitalization-associated infections suggests potential utility in selected higher-risk patients rather than as a routine prophylaxis for all. Prior BCMA exposure did not increase first infection risk. These findings support a risk-adapted approach to IVIG in TAL treated RRMM to balance infection mitigation, hospitalization risk, with supportive care burden.

PA-419

Revealing the Potential Mechanism for Extracellular Matrix Remodeling via Mechanical Stimulation in Myeloma Bone Disease

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Introduction: As a hallmark feature of multiple myeloma (MM), myeloma bone disease (MBD), which occurs in up to 80% of patients with MM, is characterized by disruption of bone remodeling, impaired osteogenesis and increased osteoclast activity, leading to osteolytic lesions and skeletal-related events (SREs). However, current treatment strategies using bone-modifying agents like bisphosphonates or denosumab only suppress bone resorption without stimulating sufficient bone repair through bone remodeling. Previously, we have shown that biophysical stimuli preserve bone structure and reduce tumor growth and dissemination in a murine MM model, in which the molecular mechanism underlying remodeling of the bone microenvironment remains largely unknown. **Methods:** MOPC315.BM cells or PBS were intratibially injected into seven-week-old female BALB/c mice followed by a single loading session (216 cycles, 4 Hz) after tumor onset. Osteocyte RNA from tibial cortical bone was extracted for transcriptome profiling and bioinformatic gene set enrichment analysis of the differentially expressed genes. Additionally, changes in gene expression levels were also examined in human MM cell line INA-6 co-cultured with human mesenchymal stroma cells (hMSC) in vitro. **Results:** In osteocytes from MM-injected mouse tibiae, 2,598 genes were downregulated compared to PBS-injected control. Among them, 92 genes were shown to be rescued through mechanical loading. Gene ontology and gene set enrichment analysis revealed that these counter-regulated genes are clustered in terms associated with extracellular matrix (ECM) related components and the NABA matrisome gene list. Similarly, we identified genes including adhesion factors, ECM protein and matrix metalloproteinases to be upregulated in MSC-adherent INA-6 cells. Taken together, our findings indicate substantial regulation of ECM remolding occurs in the myeloma bone microenvironment and can be modulated through biophysical stimulation. Further correlation analysis with survival data in human MM cells and precursor conditions are evaluated with the LfM-Heidelberg cohort. We identified 60 adhesion-related genes that are significantly associated with overall survival and identified 19 potential prognostic gene markers such as VEGFA and CCL2, whose expression increases across disease stages (MGUS, AMM, MM, MMR, HMCL) and could be involved in bone remodeling in MM. **Conclusions:** We demonstrate that bone marrow-resident MM cells induce ECM alterations in the tumor microenvironment, and that biophysical stimuli could counteract these changes. Moreover, the analysis of the cancer genome atlas indicates that the tumor cell-derived ECM signature can strongly distinguish among myeloma cell types, suggesting that changes in ECM composition of the tumor microenvironment might be relevant for the prediction of disease stage and patient prognosis.

PA-420

Reversed Albumin/Globulin Ratio on Routine Liver Function Testing as a Low-Cost Screen for Monoclonal Gammopathy: Concordance with Electrophoresis and Diagnostic Yield in a 90-Day Laboratory Cohort

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Introduction: Reversal of the albumin/globulin (A/G) ratio (A/G < 1) is a routinely reported, no-cost by-product of the liver function test (LFT) panel and a classical pointer to monoclonal gammopathy. Whether this automated signal reliably reflects true electrophoretic reversal, and what diagnostic yield it carries, is poorly defined. **Methods:** We analyzed every LFT performed in a hospital biochemistry laboratory over 90 days (16 Dec 2025–14 Mar 2026). All A/G-reversal samples were logged prospectively and reflexed to serum protein electrophoresis (SPEP); suspicious SPEP was confirmed by serum immunofixation (SIFE). A/G was recomputed from albumin/globulin. Concordance between LFT-derived and SPEP-derived A/G reversal was assessed by Cohen's kappa and McNemar's test; predictors of SPEP positivity by logistic regression. **Results:** Of 6,227 LFTs (mean 82/day), 840 (13.5%) showed A/G reversal (cohort n = 904). SPEP was positive in 58/904 (6.4%); 85% of patterns were polyclonal or inflammatory. LFT and SPEP A/G reversal were strongly discordant (agreement 41.7%; kappa = 0.01; McNemar $p < 0.001$): routine biochemistry over-called reversal (mean A/G 0.73 vs 1.03 by SPEP), reclassifying 530/900 LFT-reversed patients as non-reversed, while missing only 2/372 true reversals. SIFE in 40 patients confirmed 12 monoclonal proteins (IgG-predominant 9/12; lambda 8/12). SPEP positivity was independently associated with male sex (aOR 2.0) and lower albumin (aOR 0.32/g/dL); monoclonality with older age (median 64.5 vs 45 years) and higher BUN, creatinine and bilirubin. Overall yield was one monoclonal gammopathy per 75 reversals (approximately one per 519 LFTs); A/G discriminated SPEP positivity poorly (AUC 0.64). **Conclusions:** A/G reversal on automated LFT is a highly sensitive but very low-specificity, zero-cost flag that correlates poorly with electrophoretic reversal. Used indiscriminately, it generates substantial low-value testing, but selectively reflecting older patients with hypoalbuminemia to SPEP/SIFE materially improves the detection of monoclonal gammopathy.

PA-421

Revised Dynamic Frailty-Tailored Therapy (DynaFiT-v2) in Elderly Patients with Newly Diagnosed Multiple Myeloma: A Prospective Multicenter Study

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Introduction: Early treatment discontinuation (TD) due to frailty remains a major challenge in the management of elderly patients with newly diagnosed multiple myeloma (NDMM). Our previous study has shown the feasibility and benefit of bortezomib, lenalidomide, and dexamethasone (VRd)-based dynamic frailty-tailored therapy (DynaFiT) in this population. Based on its safety profile, the anti-CD38 monoclonal antibody daratumumab plus VRd (D-VRd) has been recommended as first-line therapy for elderly patients with NDMM. Accordingly, we revised the DynaFiT by integrating daratumumab (designated DynaFiT-v2). The study aims to evaluate the efficacy and safety of the D-VRd-based DynaFiT-v2 in NDMM patients aged ≥ 65 years. **Methods:** This is a prospective multicenter study (NCT06099912). After enrollment, participants received eight cycles of D-VRd for induction, with the doses of bortezomib, lenalidomide, and dexamethasone adjusted according to longitudinal changes in the frailty category (defined by IMWG-FI) at each cycle. The primary endpoint was overall response rate (ORR) during induction. Other key endpoints included TD, adverse events (AEs), minimal residual disease (MRD), PFS, and OS. **Results:** At the time of analysis, 132 patients were enrolled, including 54 (41%) fit, 19 (14%) intermediate fit, and 59 (45%) frail as defined at baseline. Of 118 patients who had geriatric assessments for at least twice, 46 (39%) experienced changes at least once in the frailty category: improvement in 30/53 (57%, including 25% fit and 32% intermediate fit) of frail and 6/17 (35%) of intermediate fit patients, but deterioration in 10/48 (21%) of fit patients. 51 patients had completed all eight cycles of induction and proceeded to maintenance. During induction, 23/132 (17%) patients experienced TD, including 8/54 (15%) fit, 2/19 (11%) intermediate fit patients, and 13/59 (22%) frail patients, with 3/54 (6%), 1/19 (5%), and 7/59 (12%) within the first four cycles, mainly because of non-hematologic toxicity (mostly infections). The competing risk of AE-associated TD was higher in frail than non-frail (fit and intermediate fit) patients (P = 0.08). The ORR was 94.8% (61.5% CR or sCR; 15.4% VGPR; 17.9% PR) 100% (43.7%, 37.5%, 18.8%), and 93.2% (40.9%, 22.7%, 29.5%) for fit, intermediate-fit, and frail patients, respectively. Of 78 patients who received at least four cycles of induction, 52.9%, 63.6%, and 51.5% of fit, intermediate-fit, and frail patients achieved undetectable MRD. Cumulative grade ≥3 non-hematologic and hematologic toxicities were reported in 32 (24%) and 48 (36%) patients, with infection (14%) as the most common grade ≥3 non-hematologic AEs. Median PFS of frail and non-frail patients was 26.5 months and not reached (P = 0.059); median OS was 26.5 months vs. not reached (P = 0.017). **Conclusions:** DynaFiT-v2 improves the fitness status and reduces TD, augmenting therapeutic efficacy and safety in elderly patients, particularly frail patients.

PA-422

Revisiting Biclonal Gammopathies in the Era of High-Resolution Mass Spectrometry with EXENT®

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Introduction: Biclonal gammopathies (BG) are estimated to represent approximately 5% of clonal gammopathies; however, their true prevalence may be underestimated due to limited analytical resolution of conventional diagnostic techniques such as serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE). Scientific data comparing the detection of BG versus monoclonal gammopathies (MG) using advanced analytical platforms remain limited. Although previous studies suggest that BG do not significantly differ from MG in terms of progression or survival, BG have been reported to be more frequently associated with lymphoproliferative disorders. Improved detection may therefore be relevant for disease characterization and follow-up. **Methods:** EXENT analysis was applied to a cohort of 119 patients evaluated for monoclonal gammopathies. Results obtained using EXENT were compared with routine SPE and IFE findings. Cases with discrepant interpretations regarding monoclonal versus biclonal patterns were identified and reviewed. **Results:** In four cases (3.4%), conventional SPE and IFE misclassified biclonal gammopathies as monoclonal due to insufficient resolution. In two patients, SPE and IFE identified a monoclonal IgGλ component, while EXENT clearly demonstrated a biclonal IgGλ pattern. In two additional patients, conventional methods showed a monoclonal IgGκ profile, whereas EXENT revealed distinct biclonal IgGκ components. These findings are consistent with previously published data, including a cohort of 271 patients in which EXENT identified a second M-protein >0.2 g/L in 13.3% of cases, suggesting that biclonal gammopathies may occur more frequently than previously recognized. Literature data indicate that while the presence of a second monoclonal component does not appear to significantly impact survival or progression compared to MG, BG are more often associated with lymphoproliferative diseases. Furthermore, the emergence of a second monoclonal component during MGUS follow-up has been linked to malignant transformation. **Conclusions:** EXENT improves the detection of biclonal gammopathies compared with conventional electrophoretic techniques, revealing potential underdiagnosis in routine clinical practice. Given the limited size of existing studies and the likelihood of

underestimated prevalence, larger prospective studies are needed to better define the clinical and prognostic significance of biclonal gammopathies.

PA-423

Risk Stratification, Treatment Patterns, and Survival Outcomes in Newly Diagnosed Multiple Myeloma Patients: A Real-World Analysis from the Chinese Myeloma Committee

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Introduction: Treatment patterns for newly diagnosed multiple myeloma (NDMM) in China have changed substantially with broader access to proteasome inhibitor–based triplets and increasing use of autologous stem cell transplantation (ASCT). The recently proposed 2025 IMS/IMWG Consensus Genomic Staging (CGS) also requires validation in large Asian real-world cohorts. We aimed to characterize contemporary treatment patterns, outcomes, and CGS-defined risk in Chinese patients with NDMM. **Methods:** We performed a multicenter retrospective study of 1,384 consecutive patients with NDMM from 10 Chinese Myeloma Committee–affiliated centers. Peking University People's Hospital (PUIH) provided a longitudinal cohort of consecutive patients with NDMM diagnosed between January 2019 and December 2023. The nine collaborating centers contributed to a cross-sectional cohort of consecutive patients diagnosed during 2021. Baseline characteristics, cytogenetics, staging, treatment, and outcomes were collected. Risk was assessed using ISS, R-ISS, R2-ISS, and the 2025 IMS/IMWG CGS. Progression-free survival (PFS) was analyzed in a two-center subcohort of 629 patients, and overall survival (OS) was analyzed in the full cohort. Survival status was verified through the National Mortality Surveillance System to minimize loss-to-follow-up bias. **Results:** The median age was 62 years, and 20.9% of patients had extramedullary disease. RVD was the predominant induction regimen, used in 51.8% of patients, while 98.0% received proteasome inhibitor–containing therapy. Among patients aged ≤65 years, 40.0% underwent upfront ASCT. In the PFS subcohort, median PFS was 44.2 months after a median follow-up of 45.7 months. In the overall cohort, median OS was not reached after a median follow-up of 46.6 months, with an estimated 4-year OS rate of 66.4%. Upfront ASCT was independently associated with superior PFS and OS, and daratumumab exposure during induction was independently associated with improved PFS. According to the 2025 CGS, 26.2% of patients were high risk; 3.8% had two or more CGS high-risk features and showed particularly poor outcomes. **Conclusions:** This national multicenter real-world study provides a contemporary benchmark for NDMM care in China. The 2025 IMS/IMWG CGS was validated in an Asian cohort and identified patients with multiple high-risk features as a distinct subgroup with major unmet need.

PA-424

Risk-Directed Front-Line Therapy for Newly Diagnosed Multiple Myeloma (NDMM) incorporating selinexor - The RIDDLE-MX Trial AMaRC 21-04

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Introduction: Multiple myeloma is a clinically and biologically heterogenous disease with diverse survival outcomes following front-

line (1L) therapy. Whilst available prognostic models – ISS, R-ISS, R2-ISS and more recently, IMS/IMWG Consensus Genomic Staging (CGS) model identify those with inferior survival, there has been limited opportunity to systematically explore novel strategies in those with high-risk (HR) disease. **Methods:** RIDDLE-MX (ACTRN12622001366741) is an Australian Myeloma Research Consortium (AMaRC) SKY92 MMProfiler risk-directed, multi-site study exploring novel quadruplet induction with 4, 35-day cycles of 1.3 mg/m2 bortezomib (V) SC weekly, 25 mg lenalidomide (R) PO D1-21, 40 mg dexamethasone(d) PO weekly and 40 mg weekly selinexor (X) PO weekly in HR NDMM prior to high-dose therapy (HD) + ASCT, 2 cycles X-VRd consolidation and maintenance comprising × 40 mg weekly, R 10 mg daily (X-R) to disease progression (PD). SKY92 standard-risk (SR) patients receive 4xVRd induction, HD-ASCT, 2xVRd consolidation prior to Euroflow response-adaptation to X-R vs R maintenance, MRD positive vs negative, respectively. Primary objective is to establish after 12 months, safety, MRD-negativity pre-ASCT, end of consolidation, end of cycle 6 and 12 maintenance and PFS of X-VRd in HRMM. We present the preliminary analysis of the HR group. **Results:** At full-recruitment, 01APR2026, 48 HR were registered, 68.8% males, median age 63.5 years (range 43.3–73.7), 27.1% R-ISS III at diagnosis; 34 had successful FISH (without TP53 mutation testing): 35.2%, 47.1%, 14.7%, 2.9% had 0, 1, 2, 3 HR cytogenetic abnormalities, respectively; 8/34 (23.5%) meeting CGS high-risk criteria. At analysis, 27 patients remained on study treatment with 2, 11 and 14 pts were undergoing ASCT, consolidation and maintenance, respectively; 21/48 pts off study: 11 PD, 1 non-myeloma related death due to COVID, 5 pts due to AEs, 2 pts withdrew consent due to logistical barriers, 1 withdrew due to transplant ineligibility and 1 failed stem cell collection. The ORR (≥PR) was 95.8% (46/48, 95%CI:85.8–99.5), 37.5% CR, 33.3% VGPR, 25% PR; 36/48 underwent at least 1 MRD assessment with 6 patients achieving MRD(-) CR, 4/6 demonstrating MRD(-) at ≥ 2 consecutive timepoints. Preliminary estimate of median PFS is 28.4 mos (95%CI:17.1-NA mos) at a median follow-up of 14.9 mos, with a 12-mo PFS rate of 77.0% (95%CI: 64.3–87.0%). All patients reported at least one AE: 81.3% were ≥ grd 3, with neutropenia, constipation, nausea, peripheral neuropathy and diarrhea commonly reported. **Conclusions:** RIDDLE-MX explored SKY92 MMprofiler risk-directed X-VRd induction, ASCT, consolidation and X-R maintenance in HR NDMM patients. Centralised SKY92 testing successfully facilitated risk-directed therapy at sites throughout Australia, providing rapid identification of HR pts. Whilst ORR and preliminary estimation of PFS are promising, rates of sustained MRD negativity were low in this HR NDMM population.

PA-425

Role and Mechanism of Multiple Myeloma Cells in Regulating Macrophage Polarization and the Antitumor Effect via ENO1

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Introduction: Multiple myeloma (MM) is an incurable hematologic malignancy. Abnormalities in tumor cell energy metabolism and immune environment play important roles in MM development. The aim of this study was to investigate the role and mechanism of alpha-enolase (ENO1) in the regulation of cell proliferation and energy metabolism in MM, and to analyze the role and mechanism of ENO1 in the regulation of macrophage polarization and the anti-tumor effect. **Methods:** Bioinformatics combined with clinical samples to analyze the expression of ENO1 in MM cells and the correlation between ENO1 and the clinical prognosis of patients, flow cytometry and zymography to detect the role of ENO1 on the proliferation and energy metabolism of MM cells; Constructing a co-culture system of MM cells and macrophages, flow-cytometry to detect the polarization and killing function of macrophages, and western-blot to detect the expression of macrophage polarization-related proteins; MM nude mouse subcutaneous tumor model to verify the effect of ENO1 on macrophage proliferation and the anti-tumor effects. **Results:** Tumor cells from MM patients highly expressed ENO1 and correlated with poor prognosis of MM patients; after inhibiting the ENO1, the proliferation level of MM cells was reduced, and the apoptosis level was increased, and the cell cycle was blocked; then we found that after inhibiting the ENO1, p-Akt level was reduced and restored by supplementation of ENO1. M2-type macrophage was increased, and killing and phagocytosis of macrophage was decreased after co-culture of MM cells and macrophages, which was improved after ENO1 inhibition; exogenous L-lactic acid and microvesicles derived from MM cells with high expression of ENO1 similarly promoted macrophage M2 polarization and decreased macrophage function; after supplementation of ENO1, macrophages showed increased levels of p-AKT, p-GSK3-β, β-catenin, and PGC1α protein, increased levels of cellular OCR, and decreased levels of ECAR. In the MM nude mouse model, the volume of tumor mound was significantly reduced and the number of M1-type macrophages was increased in the group of infused macrophages combined with the ENO1 inhibitor. **Conclusions:** High expression of ENO1 may promote MM cell proliferation through PI3K/AKT pathway, ENO1 inhibitor could inhibit MM cell tumorigenesis while promoting macrophage polarization to M1 and increasing the killing ability of MM cells, targeting ENO1 is a novel and effective potential target for the treatment of MM.

PA-426

Role and Mechanism of Pim-2 Kinase Inhibitors-Induced Immunogenic Cell Death in Multiple Myeloma

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Introduction: Immune dysfunction is an important part of pathogenesis in multiple myeloma, and restoring anti-myeloma immunity has become a key research direction. The goal of this study was to determine whether and how Pim-2 kinases inhibitors induce immunogenic cell death in multiple myeloma. **Methods:** By using bioinformatics, reanalyze scRNA seq data from the Gene Expression Omnibus (GEO) database to explore the expression of Pim-2 gene, endoplasmic reticulum stress, and DAMP related genes in MM patients. In vitro, SMI-16a were applied to MM cell lines (RPMI-8226, OPM-2, U266) for 24 hours, followed by DCFH-DA staining. Flow cytometry (FCM) was used to detect intracellular reactive oxygen species (ROS) levels and the expression of Calreticulin (CALR) on the surface of MM cells. Western blot (WB) was used to detect the expression of DAMPs (HMGB1, HSP70) in the supernatant. Co-culture DCs, pan-T lymphocytes,NK cells and MM cell lines treated with PBS, SMI-16a, IL-15 superagonist fusion protein, and SMI-16a+ IL-15 superagonist fusion protein. **Results:** Pim-2 kinase inhibitors up-regulate IRE1 phosphorylation, promote XBP1 and CHOP transcription,thereby mediating endoplasmic reticulum stress in MM cells. ER-stress and increased ROS levels can promote the expression of damage related molecular patterns and promote immunogenic cell death in MM cells. Pim-2 kinase inhibitors-treated MM cell lines can up-regulate the expression of activation molecules on the surface of DCs from MM patients, promote T lymphocyte differentiation from Naïve T cells to effector memory T cells, and promote the expression of T lymphocyte functional molecules. In addition, combination of IL-15 superagonist fusion protein and SMI-16a can improve the expression of CD107a, NKG2D, Granzyme B and perforin in NK cells. **Conclusions:** Pim-2 kinases regulates anti-myeloma immunity and provide efficient therapy for applying Pim-2 kinases inhibitors in MM treatment.

PA-427

Role of Autologous Stem Cell Transplantation in Transplant-Eligible Dialysis-Dependent Multiple Myeloma

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Introduction: The role of autologous stem cell transplantation (ASCT) in transplant-eligible patients with dialysis-dependent multiple myeloma (DDMM) remains poorly defined. We compared the outcomes of ASCT versus non-ASCT approaches in patients with newly diagnosed DDMM. **Methods:** In this multicenter retrospective study, 117 patients with newly diagnosed DDMM who remained dialysis-dependent throughout induction therapy were included. In the ASCT group, patients also remained dialysis-dependent at the time of transplantation. Patients treated with outdated conventional induction regimens or those who became dialysis-independent during induction were excluded. Progression-free survival (PFS), overall survival (OS), response rates, and safety outcomes were compared between patients who underwent ASCT and those who did not. **Results:** Post-induction overall response rates and rates of very good partial response or better (≥VGPR) were similar between the two groups. In the ASCT group, responses deepened substantially after transplantation: among 53 paired-evaluable patients, the ≥CR rate increased from 18.9% before ASCT to 60.4% after ASCT, the ≥VGPR rate from 52.8% to 83.0%, and 67.9% experienced response deepening. ASCT was associated with significantly longer PFS than non-ASCT therapy (median, 39.4 vs. 12.1 months; $P < 0.001$), and a significant OS benefit was also observed (median, 71.4 vs. 33.5 months; $P = 0.018$). Both PFS and OS benefits were maintained in a propensity score–matched sensitivity analysis (PFS $P < 0.001$, OS $P = 0.017$). The PFS benefit of ASCT was consistent across prespecified subgroups, including patients receiving triplet or quadruplet induction. Early post-transplant mortality was 5.5%. Durable dialysis discontinuation beyond one year was observed in 16.4% of patients in the ASCT group and 12.9% in the non-ASCT group ($p = 0.611$). **Conclusions:** In transplant-eligible patients with DDMM, ASCT was feasible and associated with deeper responses and longer PFS, with a favorable trend toward improved OS after adjustment. These findings support ASCT as a potential consolidation strategy for carefully selected patients with DDMM.

PA-428

Role of BCMA Modulation in the Effect of Belantamab Mafodotin in Multiple Myeloma

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Introduction: B-cell maturation antigen (BCMA) is the target of the antibody–drug conjugate (ADC) Belantamab mafodotin (BLMF) and its expression has been linked to disease progression towards an active multiple myeloma (MM). As ADC efficacy critically depends on target antigen density, its modulation may influence anti-BCMA strategies. **Methods:** BCMA expression was analyzed by flow cytometry (FC) in bone marrow plasma cells from MGUS (n = 12), sMM (n = 6), NDMM (n = 29), and RRMM (n = 14) patients. BCMA expression in MM cell lines was determined by FC, western blot and qPCR. MM1S, RPMI8226 and H929 were treated with anti-myeloma agents and ATRA, and BCMA levels were quantified. BLMF binding and internalization were assessed by confocal microscopy and FC. Cell viability and drug interactions were analyzed by MTT and SynergyFinder. Apoptosis was evaluated by Annexin V/PI staining and caspase/PARP cleavage. Two resistance models were evaluated. MM1S, RPMI8226 and OPM2 were cultured in the presence of mesenchymal stromal cells (MSCs) from MM patients. Response to BLMF was determined by BrdU incorporation. Three BLMF-resistant MM cell lines were developed (MRB, RRB and GRB), from MM1S, RPMI8226 and MM1SGFP, respectively, by dose escalation culture. Response to BLMF was determined by MTT and BCMA expression was evaluated. Genomic analysis was carried out by gene expression profile (GEP) and optical genome mapping (OGM), and their tumorigenic capability in vivo by subcutaneous plasmacytoma in SCID mice. **Results:** BCMA expression was significantly higher in NDMM compared to MGUS and RRMM patients (median intensity MGUS 21853, $p < 0.01$; sMM 47456; NDMM 52538; RRMM 29287, $p < 0.05$). ATRA significantly increased BCMA (fold change MM1S 1.6; RPMI8226 1.4; H929 2.3; $p < 0.05$), confirmed at mRNA and protein levels, supporting transcriptional regulation, and enhanced BLMF binding and internalization. The combination showed synergism (synergy scores MM1S 14, RPMI8226 24, H929 17) and increased apoptosis compared to BLMF alone. Coculture of MM cells with MSCs significantly decreased BCMA expression (fold change MM1S 0.7; RPMI8226: 0.5; OPM2: 0.7; $p < 0.01$), as well as mRNA and protein levels, thus rescuing these cells from BLMF cytotoxicity. While IC50 at 72 hours for MM1S, RPMI8226 and MM1SGFP was < 1 μg/ml, resistant cell lines didn't respond to doses of up to 50 μg/ml. MRB and GRB completely lost BCMA expression, while RRB maintained some BCMA expression. GRB showed higher tumor growth and reduced mice survival than its sensitive counterpart in vivo. MRB revealed a homozygotic loss of the BCMA gene (VAF 0.98) by OGM and enrichment in NFκB signaling pathways by GEP. **Conclusions:** We here show how modulating BCMA influences BLMF effect. Increasing BCMA expression in MM plasma cells potentiates BLMF effect through an increased binding and internalization. On the other hand, the presence of the microenvironment and continuous exposure to BLMF significantly downregulate BCMA expression, limiting BLMF efficacy.

PA-429

Safety and Efficacy of Flat-Dose Intravenous Immunoglobulin Prophylaxis in Patients with Relapsed/Refractory Multiple Myeloma Receiving Ciltacabtagene Autoleucel

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Introduction: Ciltacabtagene autoleucel (CiltaCel) use in patients (pts) with previously treated multiple myeloma has been associated with cytopenias, hypogammaglobulinemia, and increased infection risk, underscoring the need for optimal primary infection prophylaxis (ppx). Intravenous immunoglobulin (IVIG) is guideline recommended post chimeric antigen receptor (CAR) T-cell treatment, typically dosed at 0.4 g/kg, given at provider discretion. However, the optimal IVIG dosing post-CAR T-cell therapy remains undefined, and the impact of lower IVIG dosing strategies unknown. **Methods:** The first 10 pts treated with CiltaCel at the Vanderbilt University Medical Center were given IVIG ppx via flat-dose: 10 g starting, increased as needed in 10 g increments until full weight-based dosing was reached, based on IgG levels < 400 mg/dL. Infection rates, severity/grades were followed and analyzed. In patients with IgG myeloma, IgG levels were corrected for monoclonal spike. **Results:** Pts were followed for a median (range) of 10 (7–20) months, and received a median of 3 (2–5) prior lines of therapy. All pts were triple-class refractory (20% and 10% penta-class and XPO-1 inhibitor refractory, respectively). A total of 21 infectious events were documented in 10 pts, and all but 1 pt experienced at least one infection, while 7 experienced > 2. There were 7 bacterial infections in 5 pts (1 G4, and 6 G2), 13 viral infections in 9 pts (1 G3, 2 G2 and 10 G1), and 1 G1 fungal infection. Overall, 19 (90%) of infections were mild (handled outpatient) and 1 (5%) each were moderate (hospitalization) and severe (intensive care unit level care). The pt with a G4 infection was not hypogammaglobulinemic at the time of the event, and was not on IVIG ppx; they were ultimately placed on flat-dose IVIG ppx post-hospital discharge. Of all infections, 2 (10%) were associated with G3 and 4 (19%) with G1 lymphopenia. No grade 4 cytopenias were reported. All hematologic adverse events (AEs) observed at the time of infections were G1–2, except for 2 G3 lymphopenias. The median time to first infection and IVIG dose post CiltaCel was 126 (4–291) days and 39 (19–159) days, respectively. Median IgG levels at CiltaCel infusion were 601.5 (108–2487), at first infection 410 (123–1156), and at second infection 257 (35–671). Time to IgG nadir after CiltaCel was 164 (6–374) days, to first IVIG infusion 39 (19–159) days, and to first infection 126 (4–291) days. **Conclusions:** In a limited cohort of CiltaCel treated patients, flat-dose IVIG infection ppx points to an acceptable safety profile,

with the vast majority of infections being low grade, managed in the outpatient setting. We highlight the potential role of flat-dose IVIG use in primary infection ppx compared to weight-based dosing, which can significantly improve stewardship of a critical health-care resource with limited global availability, toward more cost-conscious utilization. Larger, multi-institutional prospective cohort analysis is needed for confirmation of these promising results.

PA-430

Safety and Efficacy of Talquetamab in Multiple Myeloma Patients with Renal Insufficiency

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Introduction: Bispecific T cell-engaging antibodies (BsAbs) are the standard treatment for patients with relapsed or refractory multiple myeloma (RRMM). Talquetamab (talq) is the first G protein-coupled receptor C5D × CD3 BsAb approved for RRMM patients after at least four lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Renal insufficiency (RI) is a common complication of multiple myeloma, affecting up to 40% of patients, and is driven by disease-related kidney injury, monoclonal light chain-mediated damage, and treatment-associated nephrotoxicity. It is difficult to assess the safety and efficacy of talq in RRMM patients with RI, as these patients have been excluded from clinical trials of talq. For example, the pivotal phase 1/2 MonumenTAL-1 study of talq required a creatinine clearance of at least 40 mL/min. Our study evaluates the outcomes of talq in RRMM patients with RI. **Methods:** We conducted a retrospective chart review of 132 patients with RRMM treated with talq across nine tertiary care centers in the United States between January 2023 and December 2025. Patients without evaluable responses were excluded (n = 3). RI was defined as creatinine clearance (CrCl) < 40 mL/min. Overall response rate (ORR) was assessed per IMWG criteria. **Results:** Among the 129 patients included in the analysis, 14 (10.9%) had RI at the time of talq initiation, including one patient requiring dialysis. On average, patients with RI had a longer median duration of hospitalization for ramp-up (12 vs 8 days, $p < 0.01$) and higher rates of RISS-II (50.0% vs 46.8%) or RISS-III disease (50.0% vs 25.5%) ($p = 0.05$) than patients without RI. The ORR was 65% in the total cohort. A very good partial response or better (≥VGPR) was seen in 53% of the population and a complete response or better (≥CR) in 35%. The odds ratio (OR) of achieving ≥VGPR was not significantly affected by RI (OR 0.89, CI 0.29–2.69, $p = 0.83$), high-risk cytogenetics (OR 1.17, CI 0.57–2.38, $p = 0.67$), or R-ISS stage II/III (OR 0.73/1.48, CI 0.28/0.51–1.89/4.32, $p = 0.33$). Additionally, dose delays (OR 1.07, CI = 0.50–2.32, $p = 0.86$) or dose interruptions (OR 2.83, CI = 0.86–9.36, $p = 0.09$) were not significantly associated with achieving a ≥VGPR. RI was not found to be significantly associated with adverse events ($p > 0.05$), including CRS, ICANS, infection, gastrointestinal toxicity, dysgeusia, dry mouth, weight loss >10%, or skin and nail-related changes. **Conclusions:** RI did not affect the response to talq in our cohort but was associated with a longer duration of hospitalization to complete ramp-up. RI was also not associated with more adverse events of talq compared to RRMM patients without RI. Larger studies are needed to evaluate the efficacy of BsAbs in RRMM patients with RI; however, RI itself should not be an exclusion to enrollment in these studies.

PA-431

Safety and Feasibility of Outpatient Bispecific Antibodies Step-Up Doses Administration for the Treatment of Relapsed/Refractory Multiple Myeloma: A Real-World Multicenter Study

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Introduction: The increasing use of bispecific antibodies (bsAbs) for relapsed/refractory multiple myeloma (RRMM) has led to a growing interest in outpatient (outpt) step-up dosing (SUD), however guidelines are lacking. **Methods:** We designed a real-world (RW) multicentric study to evaluate feasibility, safety, and protocols in use for outpt bsAb SUD in RRMM. **Results:** Overall, 86 patients (pts) received outpt bsAb SUD (30 teclistamab, 16 elranatamab, 40

talquetamab) in 18 Italian centers (ctr), with a median follow up of 7 (range 1–35) months (m). Outpt represented 32% of the global bsAbs-treated population (n = 265) across all ctr. Ctr organization included an Intensive Care Unit and neurology on site in all cases (100%), an Emergency Department in 17 (94%), and a Day Hospital operating for ≥8 hours/day as well as a 24/7 hematologist on call in 16 (89%). All ctr required the presence of a caregiver and residence within 60 minutes as criteria for pts selection. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome prevention strategies (CRS/ICANS-PS) consisted in per label premedication for all pts; in addition, 26 (30%) received prophylactic tocilizumab (PT), 33 (38%) dexamethasone post medication and 6 (7%) both. Overall, median age was 71 years (range 34–85) and median number of prior lines 4 (range 2–8); 68 pts (79%) were triple class refractory, 27 (29%) were exposed to T cell redirecting therapies, 57 (66%) presented with CRAB criteria, 17 (20%) with extramedullary disease, 64 (74%) had a Charlson comorbidity index >2, while 15 (17%) an ECOG >2. No baseline differences were recorded between pts receiving additional PS or not, save for a higher incidence of CRAB in the former ($p < 0.001$). CRS occurred in 32 (37%) pts, all grade (G) 1 save 1 G2; median time of onset was 7 days (d) (range 1–30) and duration 2 d (range 1–10); 22 (26%) pts were treated with T and/or steroids. 1 G2 ICANS case was recorded, with onset at d 30 and resolution after 1 d of steroids. During SUD, 26 (31%) pts experienced complications, defined as: additional visits (20 pts [23%], median 1, range 1–3), dose delays (17 pts [20%], median 4 d, range 1–86), and/or need of hospitalization (7 pts [8%]; median 9 d, range 2–33). PT was associated with lower incidence of CRS ($p = 0.01$), SUD delays ($p = 0.03$) and hospitalization ($p = 0.02$), and with higher probability of SUD completion with no complications ($p = 0.02$). Throughout treatment, infections occurred in 49 (57%) pts (15% ≥G3) with no difference between different PS. Overall response rate was 76%, and complete response rate 34%. Median progression-free survival (PFS) was 12 m, and 12 m overall survival rate 82%. PT (HR 0.23, $p = 0.01$) and absence of complications during SUD (HR 0.47, $p = 0.04$) were associated with longer PFS. **Conclusions:** Our RW results support outpt bsAb SUD as a safe and viable option with the use of structured protocols, with PT emerging as the most effective strategy to reduce CRS and facilitate SUD completion in this setting.

PA-432

Safety and Reliability of Isatuximab Subcutaneous On-Body Injector: Results Across the Phase 3 IRAKLIA, Phase 2 IZALCO, and Phase 1b TCD15484 Trials

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Introduction: Subcutaneous (SC) drug-delivery options have become more widely available in multiple myeloma (MM), benefiting both patients and healthcare providers. SC delivery of isatuximab (Isa), an anti-CD38 monoclonal antibody, has been investigated across clinical trials via a novel hands-free on-body injector (OBI). Isa SC OBI features a small, retractable needle, establishing the first device-enabled delivery of an oncological treatment. The Phase 3 IRAKLIA, Phase 2 IZALCO, and Phase 1b TCD15484 trials consistently demonstrated similar efficacy and safety of Isa SC OBI vs Isa intravenous (IV) in patients (pts) with relapsed/refractory MM (RRMM). Here, we present a pooled analysis exploring safety and reliability of Isa SC OBI in pts with RRMM. **Methods:** Pts with RRMM in IRAKLIA (N = 263) and the Phase 1b expansion cohort (N = 22) received 1400 mg Isa SC OBI plus pomalidomide and dexamethasone (d). In IZALCO, RRMM pts (N = 64) received 1400 mg Isa SC OBI + carfilzomib (K)-d. The pooled analysis included data from all 3 trials with 349 total pts. Pts were monitored for 4 hrs (IRAKLIA) or 1 to 2 hrs (IZALCO) following first administration and for 1 hr for the following cycle (C) 1 administrations to assess local tolerability. Preinfusion medications included montelukast (C1), steroids, acetaminophen, and H1 antihistamines. Pts without systemic infusion-related reactions (IRRs) after 4 consecutive administrations of Isa SC OBI had subsequent premedication reassessed at the investigators' discretion. Safety and device performance explored in this pooled analysis of company sponsored studies were assessed in the Isa SC OBI cohorts by the duration of injection, IRRs, local injection-site reactions (ISRs), and injection/device success, which were defined similarly across all trials. **Results:** 349 pts had a median age of 66.0 years and median weight of 73.7 kg. The median duration of Isa SC OBI injections was 12.0 minutes with 6426 total injections administered. IRRs across trials occurred in 4/349 (1.15%) patients. IRRs were mostly grade 1 (5/6426, 0.08%) with 1 grade 3 (0.02%) and none leading to discontinuation. Overall, 1063/6426 (16.5%) injections were given without premedication and led to no IRRs. ISRs occurred in 34/6426 (0.53%) injections in 21/349 (6.02%) patients. Most ISRs were grade 1 (33/6426, 0.51%), with 1 grade 2 (1/6426, 0.02%) and generally occurred on the day of injection. 99.9% (6419/6426) of injections in 98% (342/349) of patients were successful (completed without interruption) across all trials. **Conclusions:** These findings

support overall low rates of IRRs and ISRs across trials, with >6000 (99.9%) Isa SC OBI injections successfully delivered. Isa SC OBI shows reproducible safety and reliability in IRAKLIA, IZALCO and Phase 1b trials, supporting it as a novel administration option for pts with MM and its potential for future exploration in at-home administration.

PA-433

Safety Profile and Impact of Body Weight on Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: Patients with triple-class-exposed relapsed/refractory multiple myeloma (RRMM) have faced dismal clinical outcomes. Elranatamab (ELRA), a BCMA-targeted bispecific antibody, was recently approved for this population. While the pivotal MagnetisMM-3 trial demonstrated favorable efficacy and a manageable safety profile, patients from Asia accounted for only 9.8% of the study population. Consequently, real-world data specifically among Japanese patients are warranted. **Methods:** We conducted a retrospective analysis of RRMM patients treated with ELRA between May 2024 and March 2026. **Results:** Eighteen patients were analyzed. Median age was 74.5 years (range, 42–89), with a median body weight (BW) of 54.3 kg (37.9–83.1). Median number of prior lines of therapy was 3 (2–13). Median ELRA cycles were 4 (1–22). Nine patients discontinued treatment (median 2 cycles [1–7]), 4 due to progression and 5 due to adverse events (AEs). Non-hematologic AEs included transaminase elevation (n = 14), cytomegalovirus (CMV) reactivation (n = 14), cytokine release syndrome (CRS; n = 13), hypogammaglobulinemia (n = 11), infection (n = 9), and rash (n = 6). Grade ≥ 3 hematologic AEs were neutropenia (n = 9), thrombocytopenia (n = 5), and anemia (n = 4). To evaluate the impact of ELRA's fixed-dose regimen, the relationship between BW and AE profiles was analyzed. While the incidences of CRS and infections were independent of BW, rash tended to occur more frequently in patients with lower BW (< 55 kg). All CRS events were limited to cycle 1 (grade 1, n = 10; grade 2, n = 3), with a median onset of 2 days after the most recent dose. Management included dexamethasone (n = 5), tocilizumab (n = 2), or both (n = 6). CRS was accompanied by transaminase elevation in 10 patients (including one grade 4 event) and rash in 3 patients; all resolved with CRS treatment. With a median follow-up of 8 months, among the 17 efficacy evaluable patients, the ORR was 76.5%, and the 6-month progression-free survival and overall survival rates were 67.8% (95% CI, 38.1–85.5) and 87.8% (95% CI, 59.5–96.8). Response rates tended to be lower in high-risk subgroups, particularly those with ≥3 prior lines of therapy, triple-class refractoriness, penta-drug exposure, soft-tissue plasmacytoma, and high-risk cytogenetic abnormalities. **Conclusions:** While the incidences of CRS and infections were BW-independent, the higher incidence of rash in patients with lower BW suggests that this subgroup requires careful monitoring for dermatologic toxicity. Notably, the co-occurrence of transaminase elevation and rash with CRS reflects a manageable systemic inflammatory response rather than isolated organ toxicity. Furthermore, given the high baseline CMV seroprevalence in Japan, caution is warranted regarding the risk of CMV reactivation during ELRA treatment. Finally, lower response rates in patients with high-risk biology highlight the need for further optimization of treatment timing and strategies for these subgroups.

PA-434

Second Primary Malignancies After Autologous Transplantation for Multiple Myeloma in the Modern Treatment Era: Incidence, Risk Factors, and Prognostic Impact Using a Competing-Risk Approach

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Introduction: Second primary malignancies (SPMs) are increasingly recognized as late complications in patients with multiple myeloma (MM) undergoing autologous hematopoietic stem cell transplantation (auto-HSCT), yet their contemporary incidence, clinical spectrum, risk factors, and prognostic impact remain incompletely defined. **Methods:** We conducted a retrospective single-center study of 2,420 patients with MM who underwent upfront auto-HSCT following induction therapy that included at least one modern agent (bortezomib, lenalidomide, thalidomide, or carfilzomib). SPM incidence was analyzed using Fine–Gray competing-risk models, and predictors were evaluated in multivariable analyses. The impact of SPM occurrence on overall survival (OS) was assessed using Cox regression with SPM modeled as a time-dependent covariate. Non-melanoma skin cancers (NMSCs) were excluded from cumulative incidence and survival analyses because of their limited expected impact on OS. **Results:** With a median follow-up of 74.2 months (95% CI 70.8–76.7), 245 patients (10.1%) developed 281 SPMs, including 25 patients with more than one malignancy. The median latency from auto-HSCT to SPM diagnosis was 48.5 months (interquartile range 29.6–69.5). Among recorded SPMs, myeloid neoplasms were the most frequent, predominantly myelodysplastic syndrome (MDS, 54 cases; 19.2%) and acute myeloid leukemia (AML, 9 cases; 3.2%). NMSCs were also common, including

squamous cell carcinoma (SCC, 38 cases; 13.5%) and basal cell carcinoma (BCC, 28 cases; 10.0%), whereas melanoma accounted for 15 cases (5.3%). Among solid tumors, genitourinary and thoracic malignancies predominated, including prostate cancer (17 cases; 6.0%), renal carcinoma (14; 5.0%), bladder cancer (12; 4.3%), lung cancer (12; 4.3%), and breast cancer (10; 3.6%). In the competing-risk analysis, the cumulative incidence of SPMs reached 6.0% at 5 years, 10.6% at 10 years, and 13.6% at 15 years, whereas the competing risk of death without prior SPM was substantially higher (23.6%, 47.2%, and 58.9%, respectively). In multivariable Fine–Gray analysis, increasing age at auto-HSCT (subdistribution hazard ratio [sHR] per year 1.04, 95% confidence interval [CI] 1.02–1.06; $p < 0.0001$), male sex (sHR 1.67, 95% CI 1.21–2.29; $p = 0.0018$), and post-transplant lenalidomide maintenance (sHR 1.45, 95% CI 1.02–2.05; $p = 0.0370$) were independently associated with higher SPM risk. In multivariable time-dependent Cox regression, SPM occurrence was independently associated with inferior OS (HR 2.58, 95% CI 2.06–3.24; $p < 0.0001$). **Conclusions:** SPMs represent a relatively common late complication after auto-HSCT and independently confer a substantial adverse impact on long-term survival. Although competing mortality from MM remains higher, these findings highlight the importance of long-term surveillance and survivorship-focused risk assessment in MM patients undergoing auto-HSCT.

PA-436

Selinexor Treatment Upregulates BCMA and Increases Belamaf Sensitivity in BCMA-Low Cell Line Models

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Introduction: Selinexor (Seli), an exportin 1 inhibitor, is approved in combination with bortezomib and dexamethasone for relapsed/refractory multiple myeloma (MM). Beyond direct antitumor efficacy, Seli has immunomodulatory effects and may increase BCMA expression for improved BCMA-directed immunotherapy. Since previous studies relied on flow cytometry, we used super-resolution microscopy and qPCR to quantify BCMA receptor density and evaluate whether Seli pretreatment improves response to BCMA-targeted therapy in vitro. **Methods:** OPM2 and AMO1 MM cell lines were treated with non-toxic concentrations (10,50 nM) of Seli. BCMA surface density was quantified by direct stochastic optical reconstruction microscopy (dSTORM), and gene expression was assessed by qPCR. Functional effects were evaluated using belantamab mafodotin (Belamaf) after 5 days of Seli pretreatment. Monoallelic and biallelic BCMA CRISPR/Cas9 knockout models were generated and BCMA expression characterized by dSTORM. **Results:** dSTORM measurements demonstrated a dose- and time-dependent increase in BCMA receptor density in both OPM2 (high BCMA) and AMO1 (low BCMA) cells. In OPM2 cells, BCMA density increased 1.6-fold after 2 days and 4.2-fold after 5 days of Seli treatment. AMO1 cells showed 1.6- and 1.9-fold increases at the respective time points. qPCR confirmed elevated BCMA transcript levels in OPM2 and AMO1 cells of 1.2- and 1.8-fold at day 2, and 1.5-fold in both lines at day 5. Prior to Belamaf exposure, Seli-pretreated cells retained significantly higher BCMA receptor densities than DMSO controls (AMO1: 0.7 vs 0.4, $p = 0.006$; OPM2: 2.7 vs 1.6 receptors/μm^2, $p = 0.04$). Functionally, Seli-pretreated AMO1 cells showed increased Belamaf sensitivity, with reduced viability after 4 days compared with controls (27% vs 51%, $p = 0.004$), whereas OPM2 cells showed no significant difference (17% vs 26%, $p = 0.06$). dSTORM characterization of BCMA CRISPR/Cas9 knockout models confirmed graded reductions in receptor density in mono-allelic (0.90) and complete loss in biallelic knockout cells (0.02 receptors/μm^2), providing an ideal model system to further define the mechanistic contribution of BCMA expression levels. **Conclusions:** Our findings demonstrate that Seli induces a robust upregulation of BCMA receptor density in MM cell models, as quantified by dSTORM and supported by increased BCMA gene expression. This enhanced surface expression was associated with increased sensitivity to Belamaf in AMO1 cells, suggesting that Seli may be especially effective as a sensitizing agent in BCMA-low contexts.

PA-437

Selinexor, Mezigdomide, and Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Relapsing/Ineligible for T-Cell–Redirecting Therapy (TCRT): STOMP Phase 1 Preliminary Results

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Introduction: Maintaining anti-tumor activity between TCRT while promoting a tumor microenvironment facilitating T-cell recovery is an unmet need. Selinexor (S), an oral exportin 1 inhibitor, and mezigdomide (M), a novel, potent cereblon E3 ubiquitin ligase modulator (investigational in RRMM), have shown T-cell preservation/stimulatory activity. We present preliminary results from Arm 12 of the Phase 1b/2 STOMP trial (NCT02343042), investigating SMd in pts with RRMM who failed or were ineligible for TCRT. **Methods:** Arm 12 followed a 3+3 design evaluating 3 dose levels: cohort 1 received S 40 mg/M 0.6 mg/d 40 mg; cohort 2 S 60 mg/M 0.6 mg/d 40 mg; and cohort 3 S 60 mg/M 1.0 mg/d 40 mg. Prophylaxis for

nausea (dual anti-emetics, at least first 2 months) and thromboembolism (all cycles) were required. Objectives: determine MTD and RP2D and assess safety and efficacy of SMd. **Results:** Thirteen pts were enrolled: 3 in cohort 1, 3 in cohort 2, 7 in cohort 3. Overall, 69.2% were male, with median age 66 years and median of 5 prior lines of therapy; all pts were triple-class exposed. Three pts relapsed after TCRT (3 cilta-cel; 2 talquetamab; 1 IGM-2644) and 4 after belantamab mafodotin, with 3 pts refractory to B-cell maturation antigen–targeted therapy. As of July 8, 2025, there were no DLTs in cohorts 1 and 2 and 2 in cohort 3. Despite preexistence, 1 pt experienced Grade (G) 2 constipation and proctitis considered possibly related and withdrew consent prior to cycle 1 completion, qualifying as DLT. Another pt experienced G4 neutropenia on C1D15 not resolved within 7 days of medication hold; G4 neutropenia recovered by C2D15 after 2 filgrastim doses and pt continued with S reduced to 40 mg and M 0.6 mg. Two pts in cohort 3 were not evaluable for DLT, but continued therapy based on clinical benefit (included in analyses). Most common treatment-emergent adverse events (TEAEs) were neutropenia (69.2%), thrombocytopenia (69.2%), constipation (46.2%), and leukopenia (46.2%). Most common G3/4 TEAEs were neutropenia (38.5%), thrombocytopenia (15.4%), and leukopenia (15.4%). As of July 25, 2025, 10 pts had ≥1 response assessment; disease control (≥SD) was reported in all 10 pts. Overall response rate was 40%; VGPR 4 pts (2 pts in cohort 2). Treatment with SMd led to an increase in proliferating (Ki-67+), activated (HLA-DR+), and effector memory (CD45RA-/CCR7-) T cells, with a decrease in TIGIT+ T cells by C2D15. **Conclusions:** For the SMd all-oral combination, TEAEs were consistent with AE profiles for S and M, and no new safety signals were detected. The DLT of G4 neutropenia was manageable with filgrastim and dose reduction. Across all dose levels SMd showed efficacy in pts with heavily pretreated RRMM in whom TCRT had failed or who could not receive TCRT. Initial analysis of primary pt samples demonstrated presence of proliferating cytotoxic T-cells, and a decrease in markers of exhaustion. Results support continued investigation of SMd in pts with RRMM.

PA-438

Sequential BCMA/FCRL5-Based Multi-Target CAR-T Reveals an Expansion-Efficacy Paradox in Ultra-High-Risk RRMM with EMD/sPCL

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Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) progressing after BCMA-directed cellular therapies face dismal survival outcomes, especially those complicated by extensive extramedullary disease (EMD) and secondary plasma cell leukemia (sPCL). FCRL5 (FcRH5) has emerged as a highly promising novel target. We hypothesized that sequentially infusing a novel bispecific BCMA/FCRL5 CAR-T alongside other multiplex CAR-T cells (CD19&BCMA, CD20, or GPRC5D) could mitigate antigen escape in this heavily pretreated, end-stage population. **Methods:** This retrospective case series evaluated three ultra-high-risk RRMM patients (median age 53; all males). All patients had prior ASCT and ≥1 prior CAR-T therapy failures, presenting with refractory EMD (n = 3) and sPCL (n = 2). Individualized sequential CAR-T regimens were administered: Pt 1 (Extensive EMD, relapsed post-BCMA & GPRC5D CAR-Ts): Sequential CD19&BCMA and BCMA&FCRL5 CAR-T cells. Pt 2 (sPCL + bulky EMD, relapsed post-BCMA CAR-T): Sequential BCMA&FCRL5 and GPRC5D CAR-T cells, followed by autologous stem cell rescue for cytopenia. Pt 3 (sPCL, relapsed post-CAR-T): Sequential CD20 and BCMA&FCRL5 CAR-T cells. In vivo cellular kinetics (flow cytometry/qPCR), safety, and clinical outcomes were evaluated. **Results:** Despite profound baseline immune exhaustion, remarkably robust in vivo co-expansion of sequentially infused CAR-T cells was universally achieved. In Pt 1, dual CAR-T cells expanded significantly (Peak Day 7 CD19&BCMA: 8.99%; Peak Day 6 BCMA&FCRL5: 9.21% of peripheral lymphocytes). The patient achieved symptomatic relief and stable disease with Grade 0 CRS/ICANS. In Pt 2, staggering cellular kinetics were recorded (Peak Day 6 GPRC5D-CART: 40.3% of lymphocytes; Peak Day 15 BCMA&FCRL5-CART: 12.6%). Paradoxically, despite this explosive expansion, the massive EMD progressed rapidly, complicated by severe infections. In Pt 3, both CARs expanded steadily (Peak Day 13 CD20-CART: 3.17%; Peak Day 12 BCMA&FCRL5-CART: 7.61%). However, intense systemic inflammation triggered severe secondary hemophagocytic lymphohistiocytosis (HLH, ferritin >8235 ng/mL), ultimately leading to rapid disease progression. **Conclusions:** Sequential multi-target CAR-T therapy incorporating a novel BCMA/FCRL5 construct successfully overcomes T-cell exhaustion to achieve robust in vivo expansion, even in pan-refractory RRMM patients. However, we identified a striking "expansion-efficacy paradox": exceptional cellular expansion does not inherently translate into durable tumor control in bulky EMD or sPCL. Instead, efficacy is overshadowed by extreme microenvironmental physical barriers, rapid tumor kinetics, and fatal hyperinflammation like HLH. Multiplex CAR-T therapies warrant investigation in earlier treatment lines before definitive barriers are established.

PA-439

Serial EMD Antigen Mapping Guides Sequential CAR-T Targeting in Relapsed/Refractory Multiple Myeloma

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Introduction: Extramedullary multiple myeloma (EMD-MM) has aggressive biology and poor outcomes. Antigen escape after

BCMA- or GPRC5D-directed immunotherapy may drive relapse, but sequential CAR-T selection often relies on archival marrow data rather than current lesion biology. We conducted to test whether serial EMD profiling could identify actionable antigen evolution for target-adaptive CAR-T sequencing. **Methods:** Eight R/R MM patients with biopsy-confirmed EMD and planned cellular immunotherapy underwent repeat EMD biopsies at protocol-defined disease/treatment timepoints (2–4 biopsies/patient). IHC assessed BCMA, GPRC5D, CD38, CD138, CD19, and CD70. Available samples underwent flow cytometry, multiplex IHC for CD3/CD8/PD-1, and targeted NGS of immune-target/escape genes. Results were integrated with clinical context to prioritize or exclude sequential CAR-T targets. This is a planned interim descriptive analysis. **Results:** EMD sites included soft-tissue, chest-wall, pelvic/iliac, breast/chest-region, and combined marrow/soft-tissue disease. Median age was 58 years (range, 46–71); 5 patients were female. Serial profiling revealed multiple actionable target states. One post-BCMA CAR-T EMD biopsy showed GPRC5D copy-number loss (1.14 copies) with near-absent protein, supporting de-prioritization of GPRC5D therapy. Two patients showed marked GPRC5D downregulation after BCMA-directed immunotherapy (40% to 5% and 50% to undetectable), whereas one showed de novo GPRC5D gain (0% to 50%) after BCMA CAR-T failure, enabling GPRC5D-directed sequencing. BCMA expression was heterogeneous, with complete BCMA loss in one EMD lesion and preserved high expression (80%–90%) in others. A BCMA-dim lesion showed aberrant focal CD19 co-expression (approximately 70%), supporting CD19 incorporation into the next target strategy. CD70 expression of 70%–80% was detected in bilateral EMD lesions in one patient, suggesting an investigational alternative target. Available microenvironment profiling showed sparse T-cell infiltration (CD 3 + 0.92%–15.76%; CD 8 + 0.09%–0.51%) and low PD-1/CD3 co-localization (< 6%), consistent with immune-excluded lesions. Antigen-informed sequences included BCMA to GPRC5D, modified BCMA to BCMA/GPRC5D, CS1 to GPRC5D, BCMA/FCRL5 to GPRC5D, and BCMA to GPRC5D to CD19. **Conclusions:** In this IIT cohort, serial EMD tissue profiling was feasible and uncovered clinically relevant, bidirectional antigen evolution not reliably inferred from archival marrow data alone. GPRC5D copy-number loss, post-treatment GPRC5D modulation, lesion-level BCMA loss, CD19 co-expression, and CD70 positivity provided a rationale for individualized CAR-T target selection or avoidance. These data support real-time lesion-based antigen remapping as a translational strategy for sequencing cellular therapy in immune-refractory EMD-MM.

PA-440

Severe Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) During Talquetamab Treatment in Relapsed/Refractory Multiple Myeloma: A Case Report

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Introduction: Bispecific antibodies have significantly improved outcomes in relapsed/refractory multiple myeloma (MMRR). Although cytokine release syndrome is frequently reported, immune effector cell-associated neurotoxicity syndrome (ICANS) remains uncommon, particularly with GPRC5D-directed therapies such as talquetamab. **Methods:** We describe a single-center case report of a patient with MMRR who developed severe neurological toxicity during talquetamab treatment. Clinical, laboratory, imaging, treatment, and outcome data were retrospectively reviewed from medical records. The patient was followed at a private tertiary referral center for hematologic malignancies in Recife, Pernambuco, Brazil. **Results:** A 77-year-old woman was diagnosed with IgG/kappa multiple myeloma in November 2022 after presenting with extensive bone disease, multiple fractures, and plasmacytomas. First-line treatment with DVMP achieved VGPR, followed by bone progression after 13 cycles. Second-line KRD achieved a partial response lasting five months before disease progression. The patient subsequently became triple-class exposed and refractory. Third-line teclistamab resulted in primary refractory disease, with progression characterized by increased lytic lesions, cortical bone disruption, bulky soft tissue plasmacytomas, and extensive skeletal involvement. Due to aggressive progression and high tumor burden, fourth-line DCEP was administered without satisfactory response. Talquetamab monotherapy was initiated as fifth-line treatment. Six hours after the first step-up dose (0.01 mg/kg), the patient developed grade 2 cytokine release syndrome (CRS) characterized by hypotension without vasopressor requirement and hypoxemia. She received tocilizumab (8 mg/kg) and dexamethasone (10 mg every 6 hours, with complete CRS resolution within 12 hours. However, 48 hours after talquetamab administration, while still receiving dexamethasone, she developed aphasia, and decreased level of consciousness, consistent with grade 2 ICANS. Computed tomography and magnetic resonance imaging of the central nervous system excluded alternative neurological etiologies. High-dose methylprednisolone (1 g/day for 3 days) was initiated, resulting in complete neurological recovery. Talquetamab was resumed, and subsequent doses were administered without recurrence of CRS or ICANS. **Conclusions:** This case highlights a rare but potentially severe neurological complication associated with talquetamab. Early recognition and timely management of ICANS are

crucial to minimize neurological complications, improve patient outcomes, and allow safe continuation of therapy, particularly in heavily pretreated elderly patients with complex clinical presentations.

PA-441

Severe Neuropathy Following Unintentional Ixazomib Overdose in Multiple Myeloma: A Case Report and Review of the Literature

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Introduction: As the use of oral anti-myeloma agents increases, medication errors have emerged as an important safety concern. Ixazomib overdose is rare, and its clinical manifestations remain poorly characterized. We describe a patient who developed severe neurotoxicity after ixazomib overdose and review all published cases. **Methods:** n/a. **Results:** An 85-year-old man with relapsed multiple myeloma was started on ixazomib, lenalidomide, and dexamethasone (IRd). Due to a medication dispensing error, he ingested three 3-mg capsules of ixazomib (total dose 9 mg) instead of the prescribed weekly dose. The overdose was recognized approximately 3 hours later, precluding gastric lavage. The patient developed grade 2 diarrhea and grade 3 thrombocytopenia, both of which resolved with supportive care. Beginning on day 10, he experienced recurrent syncope associated with orthostatic hypotension. A head-up tilt test supported severe autonomic neuropathy. Additional toxicities included painful grade 3 peripheral neuropathy, dysphagia, gastroparesis requiring parenteral nutrition, urinary retention requiring catheterization, and marked functional decline. Most autonomic manifestations improved over 6 months; however, grade 3 peripheral neuropathy persisted until death. Although treatment was discontinued after day 1 because of severe toxicity, the patient achieved a partial response that was maintained for 13 months. He died 20 months later after disease progression. Review of the literature identified three additional overdose cases. Two patients ingested the entire weekly dose (12 mg) in a single day and developed severe toxicity; one recovered after gastric lavage and supportive care, whereas the other died from aspiration-associated acute respiratory distress syndrome. Another patient who ingested 3 mg daily for three consecutive days (total dose 9 mg) developed severe gastrointestinal toxicity but recovered. Across all cases, overdose resulted from medication errors and was associated with gastrointestinal toxicity, cytopenias, cardiovascular instability, and neurologic complications. Our patient represents the most prominent case of prolonged autonomic and peripheral neurotoxicity reported to date. **Conclusions:** Ixazomib overdose can result in substantial morbidity and mortality. Our case is the first reported case of severe, prolonged autonomic neuropathy following ixazomib overdose. Across all reported cases, the most severe toxicities occurred in patients who ingested the entire dose on a single day rather than over multiple days. Given the dose-proportional pharmacokinetics of ixazomib, elevated peak plasma concentrations may contribute to severe neurotoxicity, although direct evidence remains limited. No specific antidote is available, and management is primarily supportive; gastric decontamination may be considered if overdose is recognized within 1–2 hours of ingestion. Prevention remains essential through education, clear dosing instructions, and intuitive packaging to minimize medication errors.

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Shifting Landscapes in Triple-Class Exposed Multiple Myeloma in Latin America (LATAM): Real-World Outcomes with Bispecific Antibodies versus Standard of Care

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Introduction: Patients with triple-class exposed relapsed/refractory multiple myeloma (TCE-RRMM) historically have poor outcomes with standard salvage therapies. Bispecific antibodies (BsAbs) have transformed the therapeutic landscape; however, comparative real-world data from LATAM remain limited. **Methods:** This retrospective multicenter study included pts with TCE-RRMM treated across LATAM centers between January 2021 and December 2025. Pts receiving BsAbs (teclistamab, talquetamab, or elranatamab) were compared with those treated with standard-of-care (SoC)-based salvage regimens. Belantamab mafodotin-treated pts were excluded from the primary comparative analysis due to limited sample size and retained for descriptive purposes only. SoC regimens were grouped as carfilzomib-based, pomalidomide-based, carfilzomib plus pomalidomide-based, chemotherapy-based, and other regimens. Baseline variables included age, prior lines of therapy (LOT), refractory status, ISS stage, extramedullary disease (EMD), prior autologous stem cell transplantation (ASCT), and high-risk cytogenetics. Primary endpoints were overall response rate (ORR),

progression-free survival (PFS), and overall survival (OS). Survival analyses were performed using Kaplan-Meier (KM) methodology and Cox proportional hazards models. **Results:** A total of 349 pts from LATAM were included: Argentina (n = 167), Mexico (n = 138), Chile (n = 14), Colombia (n = 11), Peru (n = 7), Paraguay (n = 7), and Uruguay (n = 5). Baseline characteristics were generally balanced between cohorts regarding age and prior LOT, with a median of 2.6 prior LOT. However, pts receiving BsAbs exhibited significantly higher rates of advanced refractory disease, including quadruple- and penta-refractory MM (p = 0.001), as well as higher EMD prevalence (p = 0.009). Treatment era distribution differed significantly between cohorts (p = 0.001). Median follow-up estimated by reverse KM was 15.2 mo. Among 341 evaluable pts, BsAbs were associated with significantly higher ORR compared with SoC (78.5% vs 58.8%; p = 0.001), higher ≥VGPR rates (63.3% vs 40.1%; p < 0.001), and higher CR/sCR rates (57.0% vs 21.0%; p < 0.001). Median PFS was 18.9 mo with BsAbs versus 7.7 mo with SoC (log-rank p < 0.001), while median OS was 26.0 versus 22.8 mo, respectively (log-rank p = 0.011). In multivariable Cox regression analysis adjusted for clinically relevant baseline factors, BsAbs remained independently associated with improved PFS (HR 0.45, 95% CI 0.30–0.68; p < 0.001) and OS (HR 0.54; p = 0.032). Disease progression remained the leading cause of death across both cohorts. **Conclusions:** In this large real-world LATAM cohort of TCE-RRMM pts, BsAbs were associated with significantly improved response rates and survival outcomes compared with SoC, despite a population enriched with higher refractory burden and EMD prevalence. These findings support the effectiveness of BsAbs in routine clinical practice across LATAM and reinforce the importance of expanding access to novel immunotherapeutic strategies in the region.

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Short-Term Spinal Bracing for Long-Term Benefit? The BACBONE Randomised Trial in Newly Diagnosed Multiple Myeloma

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Introduction: Myeloma bone disease (MBD) affects ~70% of patients with newly diagnosed multiple myeloma (NDMM), with the spine the most commonly involved site. 38% of patients report back pain and 27% present with vertebral compression fractures. Fracure risk is highest early in therapy; fractures worsen deformity and pain and subsequent partial healing renders deformity and disability permanent. Some centres have introduced spinal bracing, but no robust evidence supports this practice. Furthermore, bracing could depress QoL and function or cause sarcopenia and current patient selection is unproven and inquitous. The NIHR-funded BACBONE study, a Myeloma UK Trials Research and Innovation at Leeds (MyeTRIAL) Partnership project, with King's College Hospital London, will evaluate whether short-term rigid bracing improves long-term outcomes in NDMM. **Methods:** BACBONE is a phase III, multicentre, randomised controlled trial with an embedded internal pilot and cost-effectiveness evaluation. 260 NDMM patients with painful spinal MBD will be randomised 1:1 at 34 UK sites to rigid custom-made thoraco-lumbar sacral orthosis (TLSO; 12 weeks daytime wear) + education vs education alone. Two-stage consent has been implemented to widen accessibility. Stage 1 permits review of standard-of-care imaging and medical records wherever treatd. Eligibility will be confirmed by central multidisciplinary team (spinal surgery, radiology, haematology, orthotics) within 72 h. Stage 2 consent is at the trial site for randomisation. Trial visits are minimised. Usual MM care proceeds at the patient's local centre. Permissive eligibility criteria will maximise inculsivity: ECOG 3–4 & severe renal impairment are eligible. The primary endpoint is reduction in disability at 12 months (Oswestry Disability Index improvement ≥8 points). Secondary outcomes include pain, spinal deformity and QoL. A Study Within A Project will explore patient experiences of living with myeloma-related spinal disease and bracing. Subgroup analyses and translational work will refine fracture risk prediction and allow targeting of the intervention in standard of care. Orthotics training delivered by the study team will enable national roll-out if the interventtion is effective. **Results:** Site feasibility work has confirmed marked disparity in access to rigd spinal bracing ranging from widespread use to no access. The study is now in set-up, supporting orthotics provision to all sites. The internal pilot will evaluate feasibility, including recruitment rates, intervention delivery, adherence, and acceptability, with predefined progression criteria. **Conclusions:** BACBONE will provide the first definitive evidence on the clinical and cost-effectiveness of early rigid spinal bracing in NDMM. The trial will collect health-economic and logistic information to support commissioning and national implementation if the intervention is effective, and cost savings and service streamlining if not.

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Single Cell RNA-Seq-Based 5-Axis Transcriptomic Phenotyping Integrated with Cytogenetic Risk Scores in Multiple Myeloma: Chr1q Gain Is the Dominant Independent Predictor of Overall Survival

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Introduction: Risk stratification in multiple myeloma (MM) relies on cytogenetics and serum-based staging, while transcriptomic phenotype axes — including apoptotic dependency, pathway activity, and immune escape — have been studied only in isolation. No study has simultaneously quantified these axes as scRNA-seq-informed scores and evaluated their prognostic weight against cytogenetic variables in a single multivariable framework. **Methods:** We analyzed 859 newly diagnosed MM patients from the CoMMpass dataset (IA18) with paired baseline bulk RNA-seq and overall survival (OS) data (200 events). Five transcriptomic phenotype scores were derived from scRNA-seq-informed gene signatures: MCL1/BCL2 apoptotic ratio, Plasma Cell Identity, MAPK activity, NF-κB activity, and HLA class I (immune escape). Cytogenetic transcriptomic scores were constructed for Chr1q gain, Chr1p loss, TP53 loss, del13q, t(4;14), and t(11;14) as continuous z-scores. Multivariable Cox proportional hazards regression was performed adjusting simultaneously for all five phenotype axes and cytogenetic scores. Proportional hazards assumptions were verified by Schoenfeld residual testing (global $p > 0.44$ across all models). **Results:** In a multivariable model adjusting for all five phenotype axes and Chr1q/Chr1p scores simultaneously, Chr1q transcriptomic gain was the sole variable achieving statistical significance (HR 1.87, 95% CI 1.54–2.27, $p < 0.001$; C-statistic 0.679). HLA class I score was the only second independent predictor (HR 0.83, 95% CI 0.70–0.98, $p = 0.026$), consistent with immune escape as an independent survival determinant. All five phenotype axes that reached univariate significance — Plasma Cell Identity, MAPK, and NF-κB (all $p < 0.05$ on univariate) — were fully attenuated after Chr1q adjustment, indicating that their prognostic signal is confounded by Chr1q gain. In a fully expanded model further adjusting for TP53 loss, del13q, t(4;14), and t(11;14), Chr1q gain remained the dominant signal (HR 1.77, 95% CI 1.44–2.18, $p < 0.001$), with t(4;14) reaching borderline significance (HR 1.16, $p = 0.050$) and all other cytogenetic variables non-significant. Collapsing Chr1q and Chr1p into a single composite score reduced model discrimination (C-statistic 0.608), confirming that directionally opposing variables cannot be summed without signal cancellation. **Conclusions:** Among all transcriptomic phenotype and cytogenetic variables tested, Chr1q transcriptomic gain score is the dominant, independent prognostic determinant in NDMM, superseding five biologically distinct phenotype axes in direct multivariable competition. HLA class I downregulation emerges as a second independent marker of immune escape. These findings support Chr1q transcriptomic scoring as a priority variable for next-generation MM risk models and suggest that current phenotype axes may function as Chr1q-dependent downstream surrogates.

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Single Center, Real World Data Exploring the Impact of Extramedullary Disease and CHIP on the Risk of Non-ICANS Neurotoxicity

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Introduction: Non-ICANS neurotoxicity refers to neurotoxicity following chimeric antigen receptor T-cell (CAR T-cell) therapy distinct from immune effector cell–associated neurotoxicity syndrome (ICANS). In BCMA directed CAR T-cells, increased CAR T-cell expansion, often reflected by an elevated absolute lymphocyte count (ALC), may be associated with an increased risk of non-ICANS neurotoxicity. This study aimed to evaluate additional factors associated with non-ICANS neurotoxicity. **Methods:** We conducted a single center, retrospective study of adults with multiple myeloma (MM) who received commercial CAR T-cell therapy from June 2021 to December 2025 at UCLA. Data collected included baseline demographics, disease characteristics, and outcomes measures. High ALC was ≥3 x103/μL measured within the 14 days post-CAR-T. High tumor burden was defined as M-protein ≥3 g/dL or bone marrow plasma cell ≥60% prior to lymphodepletion. **Results:** Of 123 patients treated with CAR T-cell therapy (cilta-cel n = 101, ide-cel n = 22), 17 (13.8%) patients developed non-ICANS neurotoxicity. Baseline demographics were comparable between patients with and without non-ICANS neurotoxicity (with vs. without), including median age (65 vs. 64), ECOG 0–1 (81.3% vs. 92%), prior autologous stem cell transplant (52.9% vs. 74.5%) as well as bridging therapy (76.5% vs. 78.3%). Among patients with non-ICANS neurotoxicity, the most common presentation was cranial nerve palsy (52.9%), followed by radiculoneuropathy/peripheral motor neuropathy (17.6%), movement and neurocognitive toxicity (11.8%), and other (5.9%). Consistent with previous reports, patients with ALC ≥3 x103/μL were significantly more likely to develop non-ICANS neurotoxicity compared to those patients with ALC < 3 x103/μL (58.8% vs 24.5%; $p = 0.0078$). In a multivariable regression analysis, high ALC remained significantly associated with non-ICANS neurotoxicity after adjustment for extramedullary disease (EMD) (OR 7.47, 95% CI 2.15–26.02; $p = 0.002$). Further, EMD was independently associated with non-ICANS neurotoxicity after adjustment for peak ALC (OR 5.02, 95% CI 1.32–19.16; $p = 0.018$). CHIP mutations were more common in patients with non-ICANS neurotoxicity (50.0% vs. 36.0%, $p = 0.41$), as was high tumor burden (23.1% vs. 12.2%, $p = 0.379$), but lacked statistical significance. While dexamethasone use within 30 days was more common among patients with non-ICANS neurotoxicity (82.4% vs 33.0%; $p < 0.001$), infection rates did not differ significantly (35.3% vs. 22.6%, $p = 0.36$). **Conclusions:** In this real-world retrospective study of patients with MM, EMD was independently associated with non-ICANS neurotoxicity after adjustment for peak ALC. While

CHIP mutations were more frequently observed in non-ICANS neurotoxicity, it did not reach statistical significance. The association between EMD and non-ICANS neurotoxicity underscores the potential importance of effective disease control with bridging therapy prior to CAR T-cell infusion.

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Single Sample Prediction of Multiple Myeloma High-Risk Genomic Events Using Bulk and Single-Cell Gene Expression

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Introduction: Genomic events like copy number alterations and translocations contribute to high-risk disease in multiple myeloma and are associated with changes in gene expression (Skerget, et al., 2024). IMWG-IMS Consensus Genomic Staging (Avet-Loiseau, et al., 2025) Criteria 1–3 refer to high-risk genomic events, including t(4;14), t(14;16), t(14;20), 1q+, del(1p32), del(17p13), and TP53 mutation. Event status may be missing for some patients in research or clinical settings, so complementary methods to determine risk status are needed. Single sample predictors (SSPs) can use gene expression to predict genomic events. SSPs like k Top Scoring Pairs (kTSP) and Random Forest (RF) generate sets of rules based on the relative values of features, like Gene A > Gene B. Combining rules gives a prediction score for each sample. SSPs robustly handle data from outside sources, data processed using different methods, or data generated on distinct platforms, without reference to the original data. We built SSPs to predict high-risk genomic events using gene expression data from CoMMpass (NCT01454297), a prospective, longitudinal observational study that followed 1143 newly diagnosed myeloma patients starting in 2011. The MMRF Immune Atlas (IA) profiled 337 CoMMpass patients using 10X 3′ single-cell RNA (Pilcher, et al., 2026). **Methods:** We trained and tested high-risk genomic event prediction models using bulk RNA-seq of CD138+ plasma cells from CoMMpass (n = 670). Ground truth for high-risk events like t(4;14) and 1q+ was determined using DNA sequencing data. We evaluated the performance of kTSP and RF models for each high-risk genomic event across 10 training/testing splits (80%/20%) using Cohen's kappa to account for class imbalance. We then retrained our top performing models on non-IA bulk samples only for application to IA plasma single cells and sample-level pseudobulk. **Results:** Overall, kTSP models outperformed RF models. Two unweighted kTSP models showed excellent performance: t(4;14) with median kappa = 0.96 and t(14;16) = 0.92. Three models showed good performance: del(17p13) = 0.76, 1q+ = 0.76, and del(1p32) = 0.70. Models for TP53 mutation and t(14;20) showed subpar performance with kappa < 0.6.For the retrained, non-IA bulk model applied to IA scRNA plasma cells (n samples = 233, n cells = 227 K), t(4;14) and t(14;16) model performance remained high. In pseudobulk, the t(4;14) model had kappa = 0.94 and t(14;16) = 0.65. For individual cells, the t(4;14) model predicted an event in a median of 88.4% of cells in samples with t(4;14), while 96.4% of cells had no event predicted in samples without t(4;14). The t(14;16) model showed 91.1% positive concordance and 97.8% negative concordance. **Conclusions:** SSPs predict myeloma high-risk genomic events including t(4;14), t(14;16), t(14;20), 1q+, del(1p32), and del(17p13) using gene expression. Gene expression models add value to existing or missing genomic data and promise utility for scRNA subclonal analysis.

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Single-Cell Genomic Profiling of Multiple Myeloma Identifies Parallel Evolution of High-Risk Markers and Subclonal Selection During Patient-Derived Xenograft Growth

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Introduction: Multiple myeloma (MM) is shaped by significant genomic heterogeneity. While primary genomic events are clonal and inherited by all subsequent clones, secondary copy-number alterations (CNAs), structural variants (SVs), and mutations can arise in subsets of cells, generating subclones with distinct evolutionary potential. These populations may drive progression and therapeutic escape but are difficult to resolve by bulk sequencing alone. **Methods:** CD138+ cells isolated from the bone marrow of six relapsed patients with MM or plasma cell leukemia were sequenced using Direct Library Preparation plus single-cell whole-genome sequencing (DLP+ scWGS). Matched cells were engrafted into SCID-rab mice (n = 12). Paired patient and PDX samples also underwent bulk WGS. CN profiles were identified from scWGS using HMMcopy segments mapped onto 250 kb genomic bins. Similarity between single cell CN profiles was measured using Pearson correlation, and hierarchical clustering grouped cells with shared copy-number alterations. For WGS, mutations, CNAs, and SVs were identified by Strelka, AscatNGS, and Manta, respectively. **Results:** DLP+ scWGS resolved substantial CNA heterogeneity within single-site marrow biopsies that was not apparent from bulk WGS alone, identifying a mean of six

copy number defined subclones per patient. Importantly, we found that PDX engraftment could be traced to expansion of pre-existing subclones for each patient. In one t(11;14) case, bulk WGS identified biallelic CDKN2C inactivation. However, scWGS resolved two distinct CDKN2C inactivated subclones which engrafted in separate PDX mice. One PDX arose from the dominant patient subclone (44% of cells) with biallelic CDKN2C deletion. A second PDX expanded from a rare subclone comprising only 0.5% of cells with deletion of one CDKN2C allele and a R15fs mutation in the remaining allele (VAF = 0.03). In a t(4;14) case, bulk WGS identified biallelic deletion of TP53. scWGS was able to resolve two distinct subclones with biallelic TP53 inactivation, each of which engrafted in separate PDX mice. Both PDX arose from minor subclones making up 10.6% and 7.6% of the population, respectively. The first clone harbored deletion 17p plus focal deletion of TP53, while the second clone featured focal biallelic TP53 deletion. **Conclusions:** Of the 6 patients analyzed, 4 patients contained multiple genomically distinct high-risk subclones, indicating that even in late-stage disease multiple high-risk genetic features can exist in parallel which may shed light on mechanisms of relapse. These findings show that high-risk abnormalities are a convergent feature of genetically distinct subclones but also carry additional private changes which can be selected. Integrating DLP+ scWGS with the SCID-rab PDX model revealed disease-relevant clonal heterogeneity in patients and identified multiple distinct pre-existing high-risk subclones which can be rare and capable of dominant expansion in vivo.

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Single-Cell Landscape of the Bone Marrow Stromal Ecosystem Reveals Disease-Associated Subclusters Driving Progression in Multiple Myeloma

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Introduction: The bone marrow microenvironment drives multiple myeloma (MM) pathogenesis. While immune and malignant cells are well-characterized, the non-hematopoietic stroma remains poorly defined. This study maps the MM stromal niche at single-cell resolution to uncover how specific stromal subpopulations dynamically expand, reprogram, and dictate patient survival. **Methods:** We performed single-cell RNA sequencing on bone marrow biopsies from 7 treatment-naïve multiple myeloma patients and 2 healthy donors were processed. After computational quality control, 58,911 cells were analyzed. The stromal compartment was sub-clustered into mesenchymal (MSCs), endothelial (ECs), osteoblast (OBs), and mural cells. Trajectories and regulons were mapped using Monocle2 and SCENIC. Gene signatures were validated in independent bulk RNA-seq cohorts for survival analysis. **Results:** The global bone marrow ecosystem exhibited structured remodeling in MM, characterized by macrophage expansion and a significant shift in stromal architecture. High-resolution sub-clustering resolved three specific pathogenic stromal subsets that selectively expanded in MM, correlated with tumor genomic instability, and predicted poor survival. First, MSC3 represents a terminally reprogrammed, highly inflammatory mesenchymal state governed by stress-responsive regulons (ARID5B, KLF9, BATF3) that strongly predicted worse overall survival (OS). Second, CapEC2 represents a specialized, hyperactive capillary endothelial phenotype overexpressing activation markers (SELE, CCL2, ICAM1) driven by an aberrant tumor-induced differentiation branch that correlated with inferior OS. Third, OB2 represents a stress-responsive osteoblast population defined by a loss of bone-forming signatures (COL1A1, SPARC) and marked upregulation of heat shock proteins (HSPA6); normal OB differentiation was forcefully redirected toward this non-osteogenic fate, predicting poor survival. Interactome analysis revealed a tripartite alliance where MSC3 acts as an apex regulator, inducing the dysfunctional OB2 state via THBS1-CD36 and driving capillary endothelial remodeling. In turn, the corrupted stroma provided tumor-homing and physical anchoring signals to malignant plasma cells via CCL2-CCR2 and SPP1-integrin axes. Simultaneously, the stroma paralyzed local immune surveillance by reprogramming macrophages and plasmacytoid dendritic cells through SPP1-integrin and APP-CD74 tolerogenic pathways. **Conclusions:** MM progression relies on a tripartite stromal-immune-malignant alliance. The expansion of pathogenic MSC3, CapEC2, and OB2 subclusters promotes tumor anchoring, fuels inflammation, and constructs an immunosuppressive barrier. The identified ligand-receptor interactions (CCL2-CCR2, APP-CD74) are promising targets to disrupt the tumor sanctuary and overcome resistance.

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Single-Cell Metabolic Profiling Links Elevated Antioxidant Metabolism to Measurable Residual Disease in Multiple Myeloma

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Introduction: Measurable residual disease (MRD) following high dose melphalan (HDM) conditioning and autologous stem cell transplant (ASCT) is the strongest predictor of early relapse in multiple myeloma (MM). Metabolic reprogramming of malignant plasma cells and immune subsets are emerging as key determinants of MRD; however, the metabolic programs that separate MRD+ from MRD- patients remain poorly understood. As an alkylating agent, HDM induces oxidative stress and DNA damage that selects for malignant plasma cells with altered metabolism, while impairing immune recovery. Certain germline variants may prime for distinct metabolic fates and immune reconstitution post-ASCT. We posit that MRD reflects dual pressures: metabolically adapted MM clones and

germline variation in HDM response. **Methods:** We integrated three scRNA-seq datasets comprising CD138+ cells from 54 individuals including healthy donors (n = 9), MGUS (n = 14), SMM (n = 19), NDMM (n = 13) alongside paired CD138- bone marrow aspirates from 28 MM patients (progressors n = 13 vs. non-progressors n = 15; MRD-positive n = 17 vs. MRD-negative n = 11) collected pre- and post-ASCT. Germline and somatic variant discovery in single-cell transcriptomes was performed using Monopogen, with variants mapped to pharmacologically relevant loci. Metabolic activity was inferred from pseudobulked B- and T-cell populations using METAflux. **Results:** Germline variant discovery in single-cell plasma cell transcriptomes identified 1,296 ancestry-informative variants across 18 pharmacologically relevant genes, enriched in African (AFR) compared to European (NFE) populations (AF > 8%). Variants clustered in energy metabolism, drug metabolism, and cell survival pathways. Loss-of-function variants were identified in 14 genes, implicating germline architecture in HDM response and immune target expression. Notably, ancestry-informative germline variants were detected across precursor disease stages, suggesting early establishment of pharmacogenomic risk before MM diagnosis. METAflux analysis of pseudobulked B-cell populations, including plasma cells, revealed that antioxidant metabolism was correlated with MRD positivity (OR:1.50, 95% CI 1.05–2.16), while disease progression was associated with increased glycolytic flux (OR:1.44, 95% CI 1.02–2.05). In the T-cell compartment, progression was strongly linked to oxidative phosphorylation (OR:2.46, 95% CI:1.44–4.20), while the pentose phosphate pathway trended toward a significant association with MRD positivity (OR:1.53, 95% CI 0.94–2.51). **Conclusions:** This study identifies cell-type specific metabolic alterations distinguishing MRD-positive from MRD-negative patients post-ASCT. Enrichment of antioxidant metabolism in malignant plasma cells coupled with germline variants in pharmacologically relevant loci demonstrates dual vulnerabilities: metabolic reprogramming and germline risks. Together, these findings emphasize germline-aware metabolic dependencies as therapeutic targets to eliminate MRD and improve transplant outcomes.

PA-450

Single-Cell Phylogenetic Dynamics During Immunotherapy and at Minimal Residual Disease Timepoints in Multiple Myeloma

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Introduction: Despite deep and durable responses achieved with modern immunotherapies in multiple myeloma (MM), many patients ultimately relapse, making characterization of the persistent minimal residual disease (MRD) cells that drive relapse of particular interest. To identify these cells, we used longitudinal single-cell whole-genome sequencing (scWGS) to characterize tumor cells, including rare MRD cells, from patients treated with quadruplet therapy (Daratumumab, Lenalidomide, Bortezomib, Dexamethasone; DRVd), anti-BCMA-directed T-cell-redirecting therapy (Teclistamab), or anti-BCMA CAR-T cell therapy (Cilta-cel). **Methods:** We isolated 152 single cells from five patients, including HR-SMM patients treated with DRVd (n = 3) or Teclistamab (n = 1), and one RRMM patient treated with Cilta-cel. Samples were collected at baseline, MRD, and progression timepoints from bone marrow (BM) or peripheral blood (PB). Tumor plasma cells were enriched using magnetic CD138 selection followed by 9-color FACS. Baseline bulk WGS was performed for all patients. DNA amplification was performed using ResolveDNA (Bioskryb Genomics), followed by scWGS at ~10 × coverage per cell. After quality control, 114 single cells were retained for downstream analysis. Phylogenetic trees were reconstructed using Sequoia, and mutational signatures were inferred using a Bayesian hierarchical Dirichlet process. **Results:** Across patients, scWGS phylogenetic analyses demonstrated that persistent cells originated from genomically mature late tumor clones rather than ancestral stem-like populations. Persistent subclones acquired additional genomic alterations during therapy, including alterations affecting therapeutic targets. One DRVd-treated patient acquired del(16q) during therapy despite MRD negativity and became MRD-positive shortly thereafter. Another DRVd-treated patient harbored MRD cells with monoallelic del(4p) encompassing CD38, which persisted at relapse. In a Teclistamab-treated patient, a residual tumor cell detected during MRD negativity carried chromosome 16 loss involving the TNFRSF17 (BCMA) locus. A patient treated with Teclistamab showed apparent biallelic TP53 inactivation by bulk WGS at progression; however, scWGS resolved this into independent TP53-mutant and del(17p) subclones that were already detectable at baseline and evolved separately under therapy. Mutational signature analysis demonstrated enrichment of SBS9-mediated somatic hypermutation and SBS1 clock-like signatures within the shared tumor trunk across all cases, suggesting that persistent MRD cells derive from late plasma cell clones. **Conclusions:** Longitudinal scWGS reveals that persistent tumor cells during immunotherapy and at MRD timepoints arise from genomically mature residual clones that continue to evolve under therapeutic pressure. scWGS enables detection of resistant subclones and target-antigen alterations below the sensitivity of bulk sequencing, providing insight into mechanisms of resistance and relapse evolution in MM.

PA-452

Single-Cell Transcriptomic Subtyping of Multiple Myeloma Identifies a Proliferative Tumor Subtype Associated with Treatment Resistance and Correlated with Aberrant Immune Patterns

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Introduction: Multiple myeloma (MM) is an incurable hematological malignancy characterized by heterogeneous disease genetics. Tumor transcriptomic patterns have been proposed to delineate biologically distinct subtypes associated with unique genomic vulnerabilities or adverse outcomes, although this remains underexplored in a single-cell context. Here, we use longitudinal single-cell RNA sequencing (scRNA-seq) of MM tumor cells to identify robust disease subtypes and characterize their biology and associations with clinical variables and bulk RNA sequencing (RNA-seq) features. **Methods:** We used ~20 K CD138+ scRNA-seq data collected from 41 relapsed MM patients, treated with daratumumab, carfilzomib, lenalidomide, and dexamethasone, at baseline, cycle 4, and cycle 10. Unsupervised Leiden clustering was performed on embeddings across a range of resolutions, with final resolution selected by optimal Silhouette score. CytoTRACE2 inferred developmental potential across subtypes and timepoints, and CopyKat predicted copy number abnormalities. Subtype-specific gene markers were aggregated into gene signatures and used to score CD138+ bulk RNA-seq tumor samples from the MMRF-CoMMpass trial, which were used in Cox proportional hazards models for clinical outcomes alongside paired CD138- scRNA-seq profiles from the MMRF Immune Atlas. **Results:** Eight transcriptionally distinct subtypes were identified. The Proliferative (Pr) subtype exhibited an aggressive phenotype, characterized by high cell cycle activity and significantly less differentiated tumor states than all other subtypes across all timepoints. The Pr subtype was significantly more frequent among non-responders at all timepoints and showed a higher prevalence of aneuploidy. A 200-gene Pr subtype signature was projected onto the CoMMpass cohort using single-sample gene set enrichment analysis, and these scores were then associated with logit-transformed immune microenvironment composition and overall survival using Cox proportional hazards models. Higher Pr scores were associated with increased immature neutrophils and monocytes, as well as HLA-presenting effector CD8+ T cells, and with reduced pan-B cell, erythroblast, and both helper CD4+ and memory CD8+ T cells. **Conclusions:** We performed machine learning analysis of single-cell profiles from relapsed MM patients to discover robust subtypes, identifying 8 distinct disease subtypes including a Pr subtype, marked by elevated differentiation potential and proliferative gene signatures, and enrichment among non-responders across all treatment timepoints. These findings were validated in an independent MM patient cohort, where a gene signature of the Pr subtype was associated with an immunologically distinct tumor immune microenvironment. These findings support single-cell subtyping as a strategy for risk stratification in MM and nominate the Pr subtype as a putative resistance-associated biomarker for treatment with daratumumab-based therapy.

PA-454

Single-Cell Transcriptomics Reveals Distinct Invasive Clones and Primary Immune Evasion Ecosystems in Primary Plasma Cell Leukemia Compared to Multiple Myeloma

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Introduction: Primary plasma cell leukemia (pPCL) is a rare, highly aggressive malignancy characterized by de novo leukemic dissemination, biologically distinct from bone marrow-localized multiple myeloma (MM). The unique clonal properties and immune ecosystems driving the primary extramedullary invasiveness of pPCL remain poorly defined. This study systematically compares the distinct tumor microenvironments of pPCL and MM at single-cell resolution to uncover mechanisms of primary systemic dissemination. **Methods:** Single-cell RNA sequencing was performed on bone marrow (BM) and peripheral blood mononuclear cell (PBMC) samples from patients with MM(n = 4) and pPCL(n = 6). Unsupervised clustering, differential gene expression, and ligand-receptor interaction network analyses were utilized to map malignant clonal heterogeneity, immune subset functional polarization, and cell-cell communication. **Results:** pPCL and MM are driven by fundamentally distinct malignant clones and immune ecosystems. pPCL is characterized by intrinsically invasive malignant clones overexpressing RND3 and CNTN1, conferring trans-endothelial migratory capacity, alongside extreme patient-specific clonal heterogeneity. In contrast, MM is dominated by localized resident clones. The myeloid compartments are divergently polarized: MM maintains a chronic pro-inflammatory state via classic S100A8/A12+ monocytes. Conversely, pPCL establishes a primary immunosuppressive environment by recruiting a disease-specific VMO1+/LYPD2+ monocyte subset and triggering emergency myelopoiesis. Lymphoid responses reflect this divergence; MM elicits a robust CD8+ effector memory T cell response, whereas pPCL demonstrates primary antigen presentation failure and a profound depletion of effector T cells. Crucially, interactome analysis uncovers a profound signaling takeover in pPCL; unlike MM where resident clones maintain broad homeostatic interactions, the invasive pPCL clones actively hijack the communication network. These invasive clones exhibit drastically enhanced, targeted signaling specifically directed at the monocytic compartment and hematopoietic stem/progenitor cells (HSPCs). This malignant-to-myeloid targeted crosstalk provides the

mechanistic basis for the polarization of the suppressive monocytic niche and the subsequent collapse of systemic immune surveillance. **Conclusions:** pPCL is characterized by intrinsically invasive malignant clones that construct a primary, highly suppressive immune ecosystem, fundamentally differing from the inflammatory microenvironment of MM. The targeted communication from invasive clones to the myeloid compartment dictates this primary immune evasion. Disrupting this specific tumor-stromal crosstalk presents a promising strategy to treat systemic dissemination in advanced plasma cell dyscrasias.

PA-455

Skeletal-Related Events and Treatment-Associated Toxicities with Bone-Directed Therapy Use in Transplant-Eligible Newly Diagnosed Multiple Myeloma

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Introduction: Osteolytic bone lesions occur in up to 80% of patients with multiple myeloma (MM). These are often complicated by skeletal-related events (SREs), which are associated with reduced quality of life, increased mortality, and increased healthcare costs. The use of bone-directed therapies to reduce skeletal complications varies, and the real-world data regarding their utilization patterns, associated toxicities, and incidence of SREs during therapy in the MM patients remain limited. This study aims to evaluate the real-world incidence of SREs during bone-directed therapy and associated treatment-related toxicities in patients with MM. **Methods:** We conducted a retrospective single-center study of adult patients with symptomatic MM who underwent autologous stem cell transplantation (ASCT) at our academic medical center between January 1, 2008, and June 30, 2024. Clinical data were extracted using REDCap. Primary outcomes included the development of skeletal-related events following bone-directed therapy use. Secondary outcomes included treatment-associated toxicities, including osteonecrosis of the jaw (ONJ), renal toxicity, and hypocalcemia, graded according to CTCAE v5.0 criteria. Standard definitions for SREs and ONJ were utilized. **Results:** A total of 481 patients were included. Baseline lytic lesions were identified in 315 patients (65.5%), while extramedullary disease was present in 113 patients (23.5%). Prior to transplant, 222 patients (46.2%) received bone-directed therapy, including zoledronic acid in 165 patients (74.3%) and denosumab in 57 patients (25.7%). Following transplant, 267 patients (55.5%) received bone-directed therapy overall. After initiation of induction therapy, skeletal-related events occurred in 36 patients (7.5%). The most common SRE was development of new osteolytic lesions in 31 patients (86.1% of SREs), followed by vertebral or non-vertebral fractures in 6 patients (16.7%), spinal cord compression in 2 patients (5.6%), and radiation or surgery to bone lesions in 3 patients (8.3%). Treatment-associated toxicities included ONJ in 22 patients (4.6%), with 54.5% of cases occurring after transplant, and all affected patients had received both pre- and post-transplant bone-directed therapy. Clinically significant grade 2–3 hypocalcemia occurred in 0.8% of patients, while grade 2 acute kidney injury attributed to bone-directed therapy occurred in 1.7% of patients. **Conclusions:** In patients with MM undergoing ASCT, SREs were uncommon following anti-myeloma and bone-directed therapy, although new osteolytic lesions remained the predominant skeletal complication. Treatment-related toxicities were infrequent, while ONJ remained an important adverse event with prolonged therapy. Further studies are needed to optimize the duration of bone-directed therapy and balance skeletal protection with toxicity risk.

PA-456

Slow-Cycling and Cycling Persister Cells in Multiple Myeloma Share Adaptive Apoptotic Priming as a Common Resistance Mechanism

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Introduction: While current therapies in multiple myeloma (MM) lead to remarkable outcomes, the emergence of resistance remains an obstacle to curing MM patients. Existing studies have predominantly focused on genetic heterogeneity as a driver of therapy resistance, whereas recent evidence suggests that a non-genetic persister state is equally important; however, such studies are lacking in MM. **Methods:** To investigate persister emergence, we utilized the doxycycline (dox) inducible Histone-2B-mCherry (H2B-mCherry) from the watermelon library to measure cell proliferation. We investigated whether therapies lead to slow cycling persister cells by measuring H2B-mCherry retention and cell cycle distribution after dox washout. KMS-11 cells were treated with lenalidomide (LEN), MCL1 inhibitor S63845 (S63), the DNA alkylating agent melphalan (MPN) and proteasome inhibitor bortezomib (BTZ). OCI-MY5 cells were treated with the BCL2 inhibitor venetoclax (VEN), MPN, S63 and BTZ. Next, we determined apoptotic priming by BH3 profiling. We investigated how stromal microenvironment affects persister development by treating with or without 20% stromal cell-conditioned media (CM). Lastly, we tested persister cells for cross persistence to other MM drugs. **Results:** H2B-mCherry retention identified slow-cycling persisters in both cell lines with BTZ and MPN. In contrast, persister cells after treatment with BH3 mimetics or LEN were not slow cycling. We found high G1 arrest in BTZ persisters and G2/M arrest in MPN-derived persisters, with no significant cell cycle changes in others compared to DMSO. CM slowed down the proliferation of vehicle, and drug treated cells and had some protective effects, but persister emergence was not significantly changed. Since BH3 mimetics didn't cause slow-cycling persisters, we next examined if the treatment selects cells

with reduced apoptotic priming, rather than relying on slow-cycling for persistence. Our longitudinal BH3 profiling demonstrated reduced apoptotic priming in both slow-cycling (BTZ and MPN) and cycling (S63, VEN and LEN) persister cells, highlighting that persister cells adapt through changes in apoptotic priming irrespective of proliferation changes. Interestingly, while there was a decrease in overall priming, VEN persisters had increased MCL1 priming and S63 persisters displayed increased response to the BAD peptide (BCL-2 and BCL-XL priming) suggesting that persistence results from both quantitative and qualitative changes in priming. Drug screening on persisters showed retained sensitivity to BTZ and BH3 mimetics, except OCI-MY5 MPN persisters lost sensitivity to S63, KMS11 MPN persisters to LEN, and KMS11 S63 persisters to LEN. **Conclusions:** Together, these data demonstrate that drug-tolerant persister cells exist and are phenotypically heterogeneous in MM. It remains to be determined if these persister cells are an acquired state or are pre-existing within tumors.

PA-457

Spatial Multi-Omics of Multiple Myeloma Uncovers Niche-Dependent Signaling Supporting Treatment Resistance and Immune Suppression

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Introduction: Multiple myeloma (MM) progression and treatment resistance are strongly influenced by interactions between malignant and non-malignant cells in the bone marrow (BM) microenvironment. However, existing spatial sequencing approaches have been limited in their ability to resolve interactions underlying MM survival signaling, cell adhesion-mediated drug resistance, and immune dysfunction. To characterize these processes, we developed an integrated spatial transcriptomics (ST) framework to improve spatial resolution, transcriptomic depth, and biological interpretation. **Methods:** We performed Visium HD ST on 21 MM BM biopsies and developed an empirical Bayesian framework to identify niche-specific transcriptional programs. Spatial findings were orthogonally validated using Xenium ST data. Spatially derived programs were mapped onto 258 scRNA-seq profiles to extend transcriptomic characterization. **Results:** Application of our empirical Bayesian framework to 21 clinically collected BM biopsies confidently assigned 198,717 spatial bins to major malignant and immune (e.g. T, NK) cell populations and resolved recurrent neighborhoods, including MM- and immune-rich niches. To define pathologic signaling programs, we compared ligand expression across neighborhoods. Plasma cells in MM-dense niches expressed increased non-canonical Wnt (ncWnt) ligands, including WNT5B (Log2Fold Change [L2FC] = 0.95, adjusted p [adj.p] = 1.78 × 10–27). Spatial proximity analyses found downstream ncWnt signaling was strongest near ligand-expressing MM cells, with ligand enrichment and spatial dependence validated in Xenium data. Projection of spatial programs onto MM scRNA-seq profiles revealed preferential activation of the Ca2+/NFAT branch of ncWnt signaling (L2FC = 4.10, adj.p = 1.78 × 10–163), driving increased expression of genes linked to MM survival (DEPTOR, L2FC = 1.66, adj.p = 1.49 × 10–206) and CAM-DR (CDH2 L2FC = 1.83, adj.p = 1.05 × 10–28). Elevated WNT5B was additionally associated with earlier disease progression (HR = 1.39, p = 1.0 × 10–5), plausibly associating spatial signaling with TR and early disease progression. Immune cells within plasma-rich niches exhibited reduced cytotoxicity and increased exhaustion-associated phenotypes. T cells had increased LAG3 (L2FC = 1.18, adj.p = 3.44 × 10–19) and enrichment of FOXP3 activity. Integration of immune and MM spatial markers yielded a 15-gene model associated with accelerated progression in independent discovery (HR = 2.003, p = 4.4 × 10–5) and validation cohorts (HR = 1.484, p = 0.0262). **Conclusions:** Integrated spatial multi-omics combining Visium HD, Xenium, and scRNA-seq enables high-resolution characterization of niche-specific transcriptional programs in MM. Our approach revealed MM-rich niches characterized by ncWnt signaling, TR-associated transcriptional states, and T-cell suppression. These spatial signaling networks represent potential therapeutic vulnerabilities and demonstrate the prognostic relevance of niche-resolved transcriptional profiling in MM.

PA-458

Spatial Transcriptomics and Proteomics Determinants of Resistance to T Cell Engagers in Extramedullary Multiple Myeloma

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Introduction: Extramedullary disease (EMD) in multiple myeloma (MM) is associated with therapeutic resistance and poor outcomes. The spatial organization of the tumor microenvironment (TME) and mechanisms of immune evasion in EMD remain poorly understood, representing a critical unmet need. **Methods:** High-resolution spatial profiling of 29 EMD samples from 24 patients treated with CAR-T or BiTE was performed across anatomical sites (skin, lymph node, paramedullary, visceral organs). 10x Genomics Xenium spatial transcriptomics (5 K panel plus a 100-gene custom

myeloma set) and spatial 17-marker proteomic profiling were applied. **Results:** Malignant plasma cells dominated biopsies (60–90% of cells). Target antigens BCMA and GPRC5D demonstrated marked inter- and intratumoral heterogeneity. BCMA was detected in 70–95% of plasma cells in 21 patients. Conversely, GPRC5D expression was highly variable: 5 patients showed high expression (≥85%), 6 low-intermediate (10–45%), and 13 rare (< 5%). Profiling identified macrophages (4.1%), T cells (2.7%), dendritic cells (0.35%), NK cells (0.01%), and B cells (0.06%). $CD8^+$ T cells predominated (CD4:CD8 ratio 1:25), with a 1:1 ratio of exhausted ($PD\text{-}1^+TIM\text{-}3^+LAG\text{-}3^+$) to activated/proliferative $CD8^+$ T cells. Notably, around 30% of macrophages belonged to immunosuppressive $CD163^+$ and $SPP1^+$ subsets. Treatment response showed a striking divergence in $CD8^+$ T cell biology between responders and non-responders. In responders, $CD8^+$ T cells had an average 3.5-fold expansion in density across all EMD tissues and enhanced spatial localization near tumor cells within skin, lymph node, and paramedullary lesions. Effective tumor infiltration was driven by significantly elevated CXCR3 expression, implying successful therapy reactivates a chemokine-guided homing program directing cytotoxic T cells to tumor sites. Conversely, non-responders harbored focal immunosuppressive niches where $CD8^+$ T cells were spatially trapped near macrophages. Critically, $CD8^+$ T cells within 10, 20, and 50 µm of these $SPP1^+$ or $CD163^+$ macrophages showed significantly reduced expression of effector molecules GZMB, IFNG, and CXCR3, suggesting macrophage co-localization actively suppresses T cell function. Notably, an organized tertiary lymphoid structure was uniquely identified in a single responder's pre-treatment skin lesion, representing an isolated instance of a highly structured baseline microenvironment. **Conclusions:** Spatial multi-omic profiling reveals heterogeneous expression of BCMA and GPRC5D complicates therapeutic targeting in EMD. Pairing spatial transcriptomics with proteomics, we translated transcriptomic signatures into spatially resolved protein expression and cellular interactions. Deficient $CD8^+$ T-cell density, poor tumor proximity, CXCR3 trafficking defects, and macrophage-associated suppression collectively drive resistance. Our results highlight macrophage-modulating agents and enhancing T-cell trafficking as promising avenues to overcome resistance.

PA-459

Spatially Resolved Transcriptomics Delineates "Immunocores" and Clonal Resistance Architecture in Extramedullary Multiple Myeloma

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Introduction: Extramedullary multiple myeloma (EMM) is an aggressive manifestation associated with poor prognosis and immunotherapy resistance. Because EMM lesions harbor distinct, site-specific microenvironmental architectures rather than uniform systemic extensions of bone marrow disease, characterizing their spatial and clonal heterogeneity across the immunotherapy trajectory is crucial to uncovering resistance mechanisms. **Methods:** We performed multi-platform spatial transcriptomic profiling on a total of thirteen extramedullary plasmacytoma samples spanning three clinical contexts: at diagnosis, post-CAR T-cell therapy relapse, and post-bispecific T-cell engager (BiTE) relapse. The NanoString CosMx cohort comprised five samples from heavily pre-treated patients from anatomically diverse sites (neck mass, liver, thigh, neck lymph node, epidural), profiled using the CosMx SMI 6 K panel. The 10X Genomics Xenium cohort included eight additional samples: four at diagnosis (two paired bone marrow samples and two EMD sites, thorax and thigh) and four at relapse (skull, lymph node, pancreas, thigh), profiled using both the Xenium 480 and Xenium 5 K panels. High-quality fields of view (FOVs) were selected for downstream analysis across all platforms, which included cell type deconvolution, plasma cell characterization, copy number variant (CNV) inference, and spatial neighborhood analysis. **Results:** Across all platforms, EMD lesions exhibited pronounced site-specific cytoarchitectural diversity with distinct tumor microenvironment (TME) compositions. Plasma cells were resolved into three transcriptionally distinct clusters (PC_1, PC_2, PC_3) conserved across EMD sites. PC_1 was defined by a proliferative gene signature (TK1, TUBB, TOP2A), and its expression was independently associated with worse progression-free survival in the 337 NDMM patients (Pilcher et al., 2026). CD8 T cells closely related to PC_1 had significantly higher cytotoxicity and exhaustion scores when compared to the CD8 T cells closely related to the other two clusters. Spatial neighborhood and cell-to-cell distance analyses identified distinct "immunocores" that physically sequester effector T cells, while demonstrating an evolutionary shift from myeloid-enriched protective niches at diagnosis to highly evasive, immune-excluded structures following immunotherapy relapse. **Conclusions:** Multi-platform spatial transcriptomics reveals EMM is a constellation of site-specific niches rather than uniform systemic disease. A prognostically adverse proliferative cluster (PC_1: TK1/TUBB/TOP2A), physical T-cell sequestration within tumor-defined "immunocores," and an evolutionary shift from myeloid protective shields at diagnosis to complex, evasive neighborhoods at relapse collectively delineate a spatial roadmap of immunotherapy resistance. These architectural discoveries provide a compelling rationale for spatially informed biomarkers and targeted combinatorial strategies to disrupt the localized niches sustaining resistant clones.

PA-460

Spatio-Temporal Architecture of the Bone Marrow Niche in Relapsed/Refractory Multiple Myeloma Upon T-Cell-Engager Therapies

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Introduction: T-cell-engagers (TCE) therapies targeting BCMA and GPRC5D have transformed relapsed/refractory multiple myeloma (RRMM) management. However, their longitudinal dinamycs on the bone marrow (BM) ecosystem remain poorly characterized. Here, we combined single-cell multiomics and high-resolution spatial transcriptomics to deconstruct the immune remodeling and niche architecture during treatment. **Methods:** Single-cell 5′ RNA-seq paired with scBCR/scTCR-seq was performed on longitudinal BM aspirates from 11 RRMM patients treated with anti-BCMA or GPRC5D bispecifics at baseline (n = 13) and sequential on-treatment timepoints. In parallel, high-resolution spatial transcriptomics (Xenium 5 K) was performed on longitudinal BM trephine biopsies derived from n = 3 MM patients, at distinct disease stages: pre-treatment, MRD-negative remission, and relapse. Spatial analyses included proximity modeling, cell-cell interaction inference, and niche ecology reconstruction. **Results:** Single-cell profiling of 132,192 cells revealed therapy-specific yet convergent immune remodeling patterns. $CD8^+$ T cells expanded across both cohorts. NK cells also showed significant expansion following therapy (pre-therapy vs. anti-BCMA, adjusted p = 0.017; pre-therapy vs. anti-GPRC5D, adjusted p = 0.05). The T/NK compartment showed divergent trajectories: anti-BCMA therapy reduced CD4 central memory and regulatory T cells while expanding CD4 cytotoxic-like and CD8 TEMRA-like 2 subsets; conversely, GPRC5D therapy expanded CM $CD4^+$/$CD8^+$ T cells and NK-like_2/TEMRA-like_1 $CD8^+$ subsets. We observed also a direct effect on plasmacytoid dendritic cell upon BCMA therapy, rather than anti-GPRC5D. Longitudinal spatial transcriptomics captured a dynamic, stage-specific evolution of the BM ecosystem. Pre-treatment, the BM was immunologically active and non-compartmentalized, with PCs distributed across homogeneous niches and T-proximal subsets enriched in IFN/stress programs (STAT1, MX1, APOL6). At MRD-negative remission, niches underwent a profound non-malignant reorganization, showing drastic PC reduction,alongside expansion of granulocytic, stromal, and erythroid components suggesting restoration of hematopoietic system. At relapse, PCs returned closer to T cells than at baseline. These relapsed, T-proximal PCs exhibited a high-intensity inflammatory/IFN signature (STAT1, MX1, IFIT1/2, IFI44L, GBP1). Rather than immune exclusion, the relapsed niche ecology was highly specialized, featuring the coexistence of functionally insufficient, T-proximal niches and immune-permissive stromal/myeloid niches. **Conclusions:** Our integrated single-cell and spatial landscape refines the paradigm of therapeutic resistance in RRMM, proving that TCE relapse is driven by a chronically inflamed, immune-subversive ecosystem, characterized by a protective stromal and myeloid architecture. These multidimensional insights open unprecedented avenues for rational combination strategies designed to dismantle the protective niches of resistant clones.

PA-461

Stage- and Subset-Specific Immune Checkpoint Remodeling in the Bone Marrow Microenvironment of Multiple Myeloma Compared Across B-Cell Malignancies

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Introduction: The bone marrow (BM) immune microenvironment is progressively remodeled during plasma cell malignancy evolution, yet how immune-checkpoint reprogramming in multiple myeloma (MM) relates to the broader B-cell malignancy spectrum is poorly defined. We profiled inhibitory and co-stimulatory checkpoints across BM immune compartments to delineate stage-specific remodeling in MM and contextualize it against other B-cell non-Hodgkin lymphomas. **Methods:** Using high-parameter flow cytometry panels and mass cytometry (CyTOF), we quantified inhibitory (PD-1, CTLA-4, LAG-3, TIM-3, TIGIT, BTLA, 2B4) and co-stimulatory (ICOS, CD27, DNAM-1, 4–1BB, OX40) receptors across B-cell, T-cell, NKT, gamma/delta T-cell and NK-cell subsets. The MM continuum comprised healthy donors (HD, n = 25), MGUS (n = 17), newly diagnosed MM (NDMM, n = 57) and relapsed/refractory MM (n = 72; on-treatment n = 27, off-treatment n = 12). A parallel cohort spanned seven B-cell malignancy subtypes (B-CLL, hairy cell leukemia [HCL], mantle cell lymphoma [MCL], marginal zone B-cell lymphoma [MZBL], follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL], Waldenstrom macroglobulinemia [WM]). Comparisons used Kruskal-Wallis/Mann-Whitney tests; progression-free survival (PFS) was assessed by Kaplan-Meier and Cox models. **Results:** MM progression featured depletion of mature/memory and activated B cells, NDMM-specific plasmablast/plasma-cell expansion, early CD4+ expansion with CD8+ cytotoxic reduction, and reduced NK-cell frequency. Checkpoint remodeling was extensive and subset-specific: broad PD-1 downregulation with

subset-restricted increases in TIGIT, TIM-3, LAG-3 and BTLA on T cells; reduced PD-1, TIM-3, TIGIT and 2B4 on mature B cells; CTLA-4 loss on activated B and plasmablast/plasma compartments; and reconfigured innate signaling (NK: low TIM-3/4–1BB/OX40, high DNAM-1/TIGIT/2B4). Low TIGIT (mature B), low CTLA-4 (plasma cells, CD3+DN T), low ICOS (CD3+DN T) and high OX40 (plasma cells) were associated with superior PFS. Across the wider B-cell malignancy spectrum, shared programs emerged: PD-1 loss on helper T/NKT cells and OX40 loss on T/NK cells in nearly all subtypes, T-cell CD27 upregulation, and NK TIM-3 loss with 2B4 gain. WM was distinctive, showing elevated PD-1/PD-L1/PD-L2 and TIGIT on B, T and NK cells, contrasting with the PD-1 loss seen in MM; high effector T/NK and low myeloid-dendritic/myelocyte frequencies tracked with favorable OS/PFS in WM. **Conclusions:** MM entails extensive, stage- and subset-specific remodeling of inhibitory and activating immune checkpoints in the BM that carries prognostic value. Comparison with six additional B-cell malignancies reveals both conserved axes (PD-1/OX40 loss, CD27 gain) and disease-specific divergence, most strikingly checkpoint upregulation in WM. These data nominate biomarker-driven, subset-resolved checkpoint targets for immunotherapy in MM and related B-cell malignancies. The study was supported by VEGA 2/0127/26; APVV-24–0471, APVV-23–0482, APVV-20–0183, APVV-19–0212.

PA-462

STAT3 Inhibitors Inducing DNA Damage in Multiple Myeloma Cells and Enhancing the Anti-Tumor Effects of NK Cells

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Introduction: To investigate the anti-tumour cellular effects and mechanisms of DNA damage-induced activation of NK cells by STAT3 inhibitors in MM cells. **Methods:** Using data of MMRF-CoMMpass studies to identify the prognostic value of STAT3 and PARP1. Using CCK-8 to explore the Half-maximal inhibitory concentration (IC50) of STAT3 inhibitor C188–9 in MM cell lines U266 and RPMI-8266. Using flow cytometry (FCM) to evaluated the apoptosis and the expression of MICA/B in MM cells. Using western-blot to measure the level of STAT3, H2AX and ATM. We co-cultured MM cells with NK cells and measure the activation of NK cells and the level of apoptosis of MM cells by using FCM. **Results:** By using the data of MMRF-CoMMpass, we found that patients with higher expression was associated worse prognosis. The IC50 of C188–9 in U266 was 23.07μM while in RPMI-8226 was 44.16μM. The C188–9 can significantly induce the level of apoptosis and expression MICA/B of MM cells. Western blot should that inhibition of STAT3 could elevated the levels of H2AX and ATM. For PARP1 inhibitor BYK204165, it had no effect on the apoptosis and the level of MICA/B. However, when it combined with C188–9, it could induce higher levels of apoptosis and expression of MICA/B of MM cells. Western blot also verified higher level of H2AX and ATM when C188–9 combined with BYK204165. With the cotreatment of C188–9 and BYK204165, we found upregulation of NKG2D, perforin and granzyme B and heightened cytotoxicity in NK cells in Coculture of NK cells with the MM cells. **Conclusions:** We found STAT3 inhibitor induces apoptosis and DNA damage in MM cells and STAT3 inhibitor combined with PARP1 inhibitor induced apoptosis and DNA damage in MM cells and mediated the high expression of MICA/B in MM cells. What's more, STAT3 inhibitor combined with PARP1 inhibitor induces DNA damage in MM cells, mediates high expression of MICA/B in MM cells, and activates the anti-tumour effect of NK cells.

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Stem Cell Mobilization After Two Cycles in the Anti-CD38 Era: Does Earlier Timing Improve Apheresis Outcomes?

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Introduction: Autologous Stem Cell Transplantation (ASCT) remains the standard of care in Multiple Myeloma (MM) and is a feasible option for other plasma cell disorders. Anti-CD38 exposure has been associated with poorer apheresis outcomes, increasing interest in early mobilization to ensure access to ASCT. While experience after 3–4 cycles has been widely recommended, some authors suggest that mobilization after 2 cycles could benefit apheresis outcomes. **Methods:** We conducted a retrospective study including patients with MM and other plasma cell disorders undergoing peripheral blood stem cell mobilization at our (January 2024-May 2026). Clinical and mobilization-related variables were collected. Patients were compared according to mobilization after 2 versus >2 cycles. Analyses were performed using Stata 17 (StataCorp): Student's t-test for continuous variables, proportion tests for categorical variables, and a multivariable GLM (gamma distribution, log link) to identify predictors of peripheral blood CD34+ cell concentration. **Results:** A total of 117 procedures in 110 patients were analysed. Median age at diagnosis was 59 years (IQR 55–64), and 51.3% were male. Most patients had MM (92.3%), underwent apheresis in frontline therapy (96.6%) and had received anti-CD38 antibodies (97.4%) and IMiDs (90.6%). Predominant response prior to apheresis was RP (38.6%), followed by VGPR (36.8%) and CR (14.5%). Overall, 42.7% underwent apheresis after 2 cycles. Compared with the 2-cycle group, patients mobilized after >2 cycles required a higher G-CSF dose (8.63 vs 7.89 μg/kg/12 h;

p 0.017) and showed a trend toward a longer administration (5.34 vs 5.02 days: p = 0.095). However, early mobilization after 2 cycles was not associated with differences in mobilization or apheresis outcomes, including poor mobilizer rate (46.3 vs 36%; OR 1.53, 95% CI 0.72–3.24; p = 0.27) plerixafor use (43.3% vs 38%; OR 1.53, 95% CI 0.59–2.63; p = 0.56), peripheral blood CD34 concentration (19.99 vs 20.79/μL; p = 0.77), CD34/Kg yield (3.23 vs 3.12 × 106/Kg; p = 0.65), >1 apheresis day (36.4 vs 32%; OR 1.21, 95% CI 0.56–2.64; p = 0.62) or mobilization failure (4.5 vs 8%; OR 0.54, 95% CI 0.12–2.52; p = 0.43). In multivariable analysis, age >65 years, prior intensive chemotherapy and bone marrow infiltration >60% at diagnosis were independently associated with lower CD34 counts, whereas the number of induction cycles had no significant impact. **Conclusions:** In the anti-CD38 era, stem cell mobilization remains an effective procedure. Our results suggest early mobilization after 2 cycles may reduce G-CSF requirements prior to apheresis, without impacting procedural outcomes or need for rescue mobilization strategies.

PA-464

Stem Cell Support As a Salvage Therapy For Prolonged Severe Hematological Toxicity Following Car-T Cell Therapy

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Introduction: Although CAR-T cell therapy has revolutionized clinical outcomes for patients with relapsed/refractory hematologic malignancies, its application is associated with distinct adverse effects. In addition to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), CAR-T therapy frequently induces hematological toxicity. Notably, prolonged and severe impaired hematopoietic recovery constitutes a major cause of secondary infections, bleeding events, and increased non-relapse mortality. Given that CD34+ stem cells have been successfully utilized to treat graft failure or poor graft function following allogeneic and autologous stem cell transplantation, stem cell infusion (without conditioning regimens) may represent an effective salvage approach for growth factor-refractory and transfusion-dependent CAR-T-associated cytopenias. However, its role in CAR-T-related hematological toxicity remains unclear, and relevant clinical experience is limited. **Methods:** This study retrospectively analyzed 25 patients who received stem cell infusions for prolonged severe cytopenia (defined as an absolute neutrophil count < 0.5×10^9/ L and/or platelet count < 20×10^9/ L on day 28 post-infusion) following CAR-T therapy between November 2023 and October 2025. The cohort included 11 patients with diffuse large B-cell lymphoma (treated with CD19 CAR-T) and 14 patients with multiple myeloma (treated with BCMA CAR-T). The primary outcomes were engraftment and hematopoietic reconstitution (time to engraftment, cumulative incidence of engraftment) and survival outcomes. **Results:** Among the 18 patients with poor neutrophil engraftment, 17 (94.4%) achieved successful engraftment, with a median time to engraftment of 11 days and a 30-day cumulative incidence of engraftment of 88.9%. Of the 24 patients with poor platelet engraftment, 21 (87.5%) achieved successful engraftment, with a median ti me to engraftment of 16.5 days and a 30-day cumulative incidence of engraftment of 75.0%. Neutrophil, platelet, and hemoglobin levels on day 30 and day 90 post-stem cell infusion were significantly improved compared to baseline levels pre-infusion ($P < 0.001$). Subgroup analysis revealed no statistically significant differences in engraftment time or cumulative incidence of engraftment among patients receiving different stem cell types ($CD34^+$stem cells, MSCs, or combined infusion) (all $P > 0.05$). At the 12-month follow-up, the best overall response rate (ORR) was 88.0%, the complete remission (CR) rate was 80%, and the 1-year progression-free survival and overall survival rates were both 78.4%. **Conclusions:** Stem cell infusion represents a safe and effective salvage treatment strategy for patients experiencing prolonged severe cytopenia after CAR-T therapy. It facilitates rapid and durable hematopoietic reconstitution withoutcompromising the long-term anti-tumor efficacy of CAR-T cells. Notably, MSCs demonstrated comparable efficacy to $CD34^+$stem cells in promoting hematopoietic recovery.

PA-465

Stem-like CD8+ Memory Effector T Cells Are Prognostic and Predictive of Response in Transplant-Eligible Newly Diagnosed Patients Receiving VRd and Autologous Stem Cell Transplant

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Introduction: Increasing evidence suggests that T cell-mediated anti-tumor immune responses rely on the establishment of biologically distinct, long-lived memory T cells, which express dual properties of naïve CD8+ T cells and antigen-experienced effector T cells. We hypothesize that a self-renewing phenotype of these stem-like CD8+ memory effector cells represents a unique aspect of CD8+ T cell biology and predict response to multiple myeloma therapies in transplant eligible NDMM patients. **Methods:** We analyzed single-cell RNA-seq data from ~232,000 CD8+ T cells obtained from 335 treatment-naive newly diagnosed multiple myeloma (NDMM) patients in the CoMMpassTM Study. We identified a pre-exhausted,

self-renewing T-cell population (TSEM) with a CD39-/CD69- stem-like phenotype and used non-negative matrix factorization (NMF) to derive gene expression modules. We assessed the final SEM signature for association with progression-free survival (PFS) using Kaplan-Meier analyses and multivariable Cox models adjusted for age, BMI, gender, self-reported race, IMS-IMWG 2025 consensus genomic risk score, and frontline treatment. A prespecified SEM score-by-treatment interaction was tested with a likelihood ratio test. **Results:** We identified 17,437 CD8+ T cells with a TSEM -like transcriptional program and refined these to 7,133 TSEM cells, yielding five 100-gene NMF modules. Module 4 (the SEM signature) was associated with improved PFS in univariate analysis (HR 0.85, 95% CI 0.74–0.97; p = 0.02) and remained independently prognostic after adjustment for other modules (HR 0.73, 95% CI 0.54–1.00; p = 0.047). Median-based stratification of the SEM signature score further separated patients by PFS (log-rank p = 0.046), with the strongest effect in those treated with RVd and ASCT (p = 0.0022). Among RVd/ASCT-treated patients (N = 163), the association with PFS remained significant in a multivariable analysis (HR 0.69, 95% CI 0.54–0.88; p = 0.003). The SEM signature also showed a significant treatment interaction (p = 0.037), was enriched in patients achieving complete and stringent complete response as opposed to progressive disease following RVd and ASCT. Our SEM signature also outperformed existing myeloma immune signatures in predicting favorable outcome. **Conclusions:** The SEM signature describes distinct CD8T cell biology in myeloma that has been well characterized in solid tumors. However, fewer studies explored the clinical relevance of this phenotype in myeloma. We show that the SEM signature captures a biologically meaningful effector memory phenotype linked to treatment benefit. Current efforts are focused on evaluating whether this signature is also enriched in patients treated with CAR-T cell and bispecific antibody therapies, which will help determine its utility across distinct immunotherapy settings.

PA-466

Survival Outcomes Associated with Daratumumab Use in Multiple Myeloma: A Retrospective Real-World Cohort Analysis

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Introduction: Daratumumab-based regimens have improved outcomes in newly diagnosed and relapsed/refractory multiple myeloma (MM). However, real-world evidence from Latin America remains limited. We evaluated survival outcomes associated with daratumumab exposure in a real-world cohort of MM patients treated at a referral center. **Methods:** We conducted a retrospective single-center study including adult MM patients diagnosed between January 2019 and December 2025. Patients were stratified according to daratumumab exposure at any treatment line. Clinical, demographic, cytogenetic, transplant, and treatment data were collected from institutional records. Overall survival (OS) and progression-free survival (PFS) were analyzed using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Statistical analyses were performed using IBM SPSS Statistics. The study was approved by the Institutional Research and Ethics Committee, and informed consent was waived due to its retrospective design. **Results:** A total of 462 patients were included. Median age at diagnosis was 62 years (IQR 53–69), 55.3% were male, and 24% of evaluable patients had high-risk cytogenetics. Overall, 29.7% underwent autologous hematopoietic stem cell transplantation. Daratumumab was administered to 168 patients (36.4%), whereas 294 (63.6%) never received the drug. Patients exposed to daratumumab were younger (57.5 vs 64 years) and more likely to undergo transplantation (47.9% vs 16.5%). OS data were available for 348 patients. Median OS was not reached in the daratumumab group versus 43.4 months in non-exposed patients. Daratumumab exposure was associated with a reduced risk of death (HR 0.22, 95% CI 0.13–0.36; p < 0.001), with significant differences on Kaplan–Meier analysis (log-rank p < 0.001). PFS data were available for 345 patients. Median PFS was 66.2 months in daratumumab-exposed patients versus 27.0 months in non-exposed patients. Daratumumab use was associated with a lower risk of progression or death (HR 0.52, 95% CI 0.37–0.72; p < 0.001). **Conclusions:** This large real-world Latin American cohort demonstrated a strong association between daratumumab exposure and improved OS and PFS. Although patients receiving daratumumab were younger and more likely to undergo transplantation, and survival analyses may be influenced by treatment-selection and immortal time biases, these findings provide relevant real-world evidence supporting the clinical impact of anti-CD38 therapies in resource-limited settings.

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Survival Trends in Patients with Newly-Diagnosed Multiple Myeloma: A Retrospective, 10-Year, Population-Based Analysis (2010–2019)

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Introduction: Although survival improvements associated with the introduction of IMIDs and proteasome inhibitors in multiple myeloma (MM) have been well documented, a limited number of real-world studies have evaluated further survival gains with therapeutic advances in the past decade. The objective of this study was to examine changes in survival in patients diagnosed with MM since 2010 at a large regional Canadian cancer centre, through

comparison of cohorts by period of diagnosis. **Methods:** All patients seen for newly-diagnosed MM between January 2010-December 2019 at BC Cancer–Surrey were included for analysis, and divided into two cohorts based on period of diagnosis (cohort 1, 2010–2014; cohort 2, 2015–2019). Treatment history, including initial regimen, use of autologous stem cell transplant (ASCT), and exposure to specific novel agents throughout disease course, was compared between cohorts. The primary outcome comparison was survival from diagnosis for both cohorts, with subgroup analysis based on frontline ASCT use. **Results:** 308 patients were included (cohort 1, n = 121; cohort 2, n = 187). Median age at diagnosis for the whole population was 71 years, with 31% of patients over age 75 at diagnosis. No differences in age or R-ISS stage distribution were observed between cohorts (p = NS). 24% of patients in each cohort underwent ASCT in first-line therapy, and 76% received non-ASCT-based regimens. Median follow-up was 4.0 years for the whole population. Among patients undergoing ASCT, a higher proportion of patients in cohort 2 received lenalidomide maintenance therapy (61% vs. 17%, p < 0.001). Among ASCT-ineligible patients, the majority of patients in both cohorts received bortezomib-containing first-line regimens (66% of overall population), but a higher proportion of patients in cohort 2 received lenalidomide-containing first-line therapy (23% vs. 8%, p < 0.001). A higher proportion of patients in cohort 2 received anti-CD38 monoclonal antibody therapy during their disease course, in all cases for relapsed disease (33% vs. 13%, p < 0.001). Median survival from time of diagnosis was 5.0 years for cohort 2 and 3.7 years for cohort 1, with no statistically significant difference between cohorts (p = 0.45). Among patients undergoing first-line ASCT, median survival from diagnosis was numerically superior in cohort 2 (8.6 vs. 3.7 years, p = 0.08), but no difference in survival was observed between cohorts among non-ASCT patients (3.9 vs. 3.4 years, p = 0.6). **Conclusions:** In this real-world population of newly-diagnosed MM patients, with a median age at diagnosis >70 and over 75% of patients ASCT-ineligible, improvements in survival over a 10-year period were seen among patients receiving ASCT in first-line therapy, but not among non-ASCT patients. Significant differences in treatment between cohorts included higher use of post-ASCT lenalidomide maintenance and higher exposure to anti-CD38 monoclonal therapy in the later cohort, potentially accounting for survival improvements within the ASCT subgroup.

PA-468

Surzetoclax: A Potentially Best-in-class BCL-2 Inhibitor for the Treatment of Multiple Myeloma with t(11;14) Translocation or High BCL-2 Expression

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Introduction: Cancer cells evade apoptosis by disrupting the balance between pro-survival (BCL-2, BCL-XL, BCL-W, MCL-1, BFL-1) and pro-apoptotic (e.g., BAX, BAK, BAD, BIM, NOXA, PUMA) members of the BCL-2 protein family. BCL-2 is critically important for the survival of hematologic malignancies, as shown by the clinical effectiveness of BCL-2 inhibitors in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), multiple myeloma (MM), and acute myeloid leukemia (AML)1. Here we describe the discovery of surzetoclax (ABBV-453), a next generation BCL-2 inhibitor, and characterize its pre-clinical activity. **Methods:** A medicinal chemistry campaign led to the discovery of surzetoclax. Potency, selectivity and on-target MOA was subsequently determined in biochemical and cell-based assays with defined BCL-2 family-dependences coupled with assessments of PK parameters and tumor growth inhibition (TGI) in xenograft models. **Results:** Structure-based design yielded surzetoclax, a structurally constrained BCL-2 inhibitor with exceptional potency, selectivity and attractive PK properties. In vitro, surzetoclax possessed sub-nM affinity for BCL-2 and robust selectivity over related proteins BCL-XL and MCL-1. This strong affinity translates into potent induction of cell death in the acute lymphocytic leukemia (ALL) cell line, RS4;11 (EC50 = 4.7 nM), that relies on BCL-2 for survival, with markedly reduced activity in cell lines dependent on BCL-XL (Molt-4 EC50 = 2.85 μM) or MCL-1 (H929 EC50 >10 μM). The cellular activity of surzetoclax is on-target and mechanism-based as shown by reduced BCL-2:BIM complexes and the rapid caspase-dependent externalization of annexin-V. This activity profile is further evident in t(11;14) positive MM cell lines which express high levels of BCL-22, 3 and are sensitive to surzetoclax-mediated cell death in vitro. In xenograft models of hematologic malignancies, surzetoclax demonstrated durable monotherapy at low doses. TGI of the RS4;11 model was superior to that achieved with clinically relevant BCL-2 inhibitors venetoclax, sonrotoclax or lisaftoclax at equivalent doses and schedules. In the t(11;14) positive KMS-27 MM xenograft, surzetoclax was at least five-fold more potent on an exposure-normalized basis than other BCL-2 inhibitors. Importantly, surzetoclax combined effectively with daratumumab and dexamethasone in the KMS-27 and the BCL-2 high RPMI-8226 MM xenograft models. The enhanced potency and oral clearance of surzetoclax potentially translates to a low projected efficacious dose and pill burden compared to other BCL-2 inhibitors in the clinic. **Conclusions:** These data identify surzetoclax as a potential best-in-class, next-generation BCL-2 inhibitor that is in a phase-1/-2 clinical trial for the treatment of patients with R/R MM (ClinicalTrials.gov ID: NCT06953960).

PA-469

Sustained CAR T-Cell Persistence Drives Long-Term MRD Negativity and Delays Progression in Relapsed/Refractory Myeloma: Updated Insights From the FUMANBA-1 Trial

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Introduction: Equecabtagene autoleucel (eque-cel) induces deep minimal residual disease (MRD) negativity in relapsed/refractory multiple myeloma (RRMM). However, a subset of patients experience MRD conversion after initial negativity. We explored baseline characteristics and peripheral-blood vector copy number (VCN) persistence to understand mechanisms of MRD conversion and generate hypotheses on the optimal CAR-T therapeutic window. **Methods:** In this exploratory, post-hoc analysis of FUMANBA-1 (NCT05066646), MRD-negative RRMM patients were stratified into MRD-sustained (n = 61) and MRD-conversion (n = 41) groups. VCN persistence (event = VCN below limit of detection) was assessed by Kaplan-Meier and unadjusted Cox regression. Hierarchical relationships among time-to-progression (TTP), MRD-negativity duration, and VCN persistence were evaluated using Kendall's tau-b. All analyses were hypothesis-generating. **Results:** Compared with MRD-sustained patients, the MRD-conversion group had more del (17p) (26.8% vs 13.1%), higher bone-marrow plasma-cell burden (> = 50%: 26.8% vs 11.5%), shorter diagnosis-to-enrollment interval (31.1 vs 54.0 months), and more bridging therapy (61.0% vs 41.0%), indicating higher-risk, more rapidly progressing disease. Median VCN persistence was longer in the MRD-sustained group (463 vs 272 days; HR 0.73, 95% CI 0.42–1.26; P = 0.2568), a ~191-day numerical advantage that did not reach statistical significance, likely reflecting heavy censoring. Correlation analysis revealed a consistent benefit chain: TTP correlated strongly with MRD-negativity duration (tau-b = 0.736, P < 0.0001), moderately with VCN persistence (tau-b = 0.306, P < 0.0001), and VCN persistence correlated with MRD-negativity duration (tau-b = 0.185, P = 0.006). **Conclusions:** Longer in-vivo VCN persistence of eque-cel was associated with sustained MRD negativity and prolonged TTP, supporting peripheral cellular persistence as a candidate pharmacodynamic correlate of durable disease control. Notably, VCN was measured in peripheral blood; persistent CAR-T cells likely also reside in the bone marrow where MRD is assessed, which may further strengthen the observed VCN-MRD correlation. Patients with del(17p), high tumor burden, and rapid disease evolution appeared more susceptible to earlier VCN clearance and MRD conversion. These hypothesis-generating findings, limited by small sample size and lack of adjustment, may inform strategies to prolong VCN persistence and support evaluating CAR-T at earlier treatment lines.

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Synchronous Non-CLL MBL and Plasma Cell Neoplasms: Clinical and Biological Implications of Potential Links

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Introduction: The increased sensitivity of flow cytometry has led to a higher incidence rate of synchronous plasma cell neoplasms (PCN) and low-count monoclonal B-cell lymphocytosis (MBL). Whether this co-occurrence is coincidental or biologically relevant remains unclear. MBL is categorized as either CLL-type or non-CLL-type. Epidemiologically, the coexistence of CLL-type MBL is more common. In this retrospective cohort, we identified a rare set of PCN patients with synchronous non-CLL-type MBL (after excluding lymphoplasmacytic lymphoma) and investigated the clinical and biological relationship between the two clonal populations. **Methods:** We retrospectively reviewed medical records of PCN patients diagnosed at our center from July 1, 2017, to June 30, 2025. Clinical and laboratory data, treatment responses, and survival outcomes were analyzed. **Results:** The median follow-up time was 23.5 months. Among eleven patients, 63.6% were male, with a median age of 66 years. Diagnoses included one MGUS, two SMM, and eight MM patients. Notably, all patients presented with bone pain and radiologically confirmed bone lesions; none had lymphadenopathy or hepatosplenomegaly. Six patients showed discordant light-chain restriction between the MBL and PCN clones. Infections, predominantly respiratory, occurred in 63.6% of patients. Cytogenetic abnormalities included IgH translocation, del(13q),

and gain(1q) (each 54.5%), and MYC translocation (11.1%); no del (17p) or del(1p) was detected. Six patients underwent V(D)J sequencing for minimal residual disease (MRD) assessment, all revealing at least two distinct clones; however, the cellular origin (B-cell vs. plasma-cell) of these clones could not be definitively assigned. Among six patients with MBL clone assessment, all achieved hematologic responses. In four of these patients, the MBL clone was cleared. Among the eight MM patients, the median time to next treatment was 31.9 months. And the median overall survival was 51.4 months. **Conclusions:** We describe a rare cohort of PCN patients with synchronous non-CLL-type MBL. In those receiving bortezomib-based therapy, the MBL clone regressed in all evaluable cases, suggesting a possible common clonal precursor. Despite the indolent nature of MBL, these patients exhibited a higher incidence of infection compared to contemporaneous PCN patients without MBL, implying that dual B-cell and plasma-cell clonal expansion may exacerbate immune suppression. PCN with non-CLL-type MBL should be carefully distinguished from lymphoplasmacytic lymphoma, and regular monitoring of the MBL clone is recommended.

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Systematic Review and Meta-Analysis of Tocilizumab Prophylaxis for Cytokine Release Syndrome (CRS) in Bispecific Antibody Therapy for Multiple Myeloma

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Introduction: Background. T-cell–redirecting bispecific antibodies are highly effective in heavily pretreated multiple myeloma but commonly cause cytokine release syndrome (CRS) during step-up dosing, often requiring hospitalization. Prophylactic administration of a single dose of tocilizumab before the first dose has been proposed to prevent CRS. Objective. To synthesize all available evidence on whether prophylactic tocilizumab reduces CRS incidence and severity without compromising safety or efficacy, to estimate the pooled CRS rate and the controlled relative risk, and to examine the influence of dose and timing of tocilizumab. **Methods:** PRISMA 2020–guided review. Databases (PubMed, Cochrane, Embase, Google Scholar) and ClinicalTrials.gov were searched with MeSH terms and keywords for tocilizumab, prophylaxis, CRS, bispecific, teclistamab, talquetamab, elranatamab, linvoseltamab, cevostamab, and multiple myeloma. Any-grade CRS proportions (single 8 mg/kg dose before the first step-up dose) were pooled by a random-effects Freeman–Tukey model; relative risk was pooled (DerSimonian–Laird) across the three studies with comparator arms. Heterogeneity was quantified with I^2. Prespecified separate analyses examined pre–second-dose timing, the 4 mg/kg low dose, and cevostamab; a sensitivity analysis excluded the overlapping MajesTEC-1 cohort. **Results:** Ten studies met inclusion. Across 11 cohorts (293 patients) the pooled any-grade CRS incidence with an 8 mg/kg dose before the first step-up dose was 9.0% (95% CI 2.8–17.5; I^2 = 0%), versus ~72–91% historically; grade ≥3 CRS was 0% (Wilson 95% CI 0–1.3%)in the same cohort and 0.48% (95% CI ~0.1–1.7%) across all prophylaxis cohorts. By agent the pooled estimate was 8.5% (teclistamab) and 16.7% (talquetamab). Three studies provided a no-prophylaxis comparator. In each, prophylaxis sharply reduced CRS: the Danish ABCD nationwide cohort (8% vs 69%), the Emory single-centre study (26.3% vs 73.3%), and the cevostamab study (35.7% vs 90.9%). In the three controlled comparisons the pooled relative risk for any-grade CRS was 0.28 (95% CI 0.15–0.53), and for grade 2 CRS 0.11 (95% CI 0.03–0.35). A low (4 mg/kg) dose (adjusted OR 0.21) and pre–second-dose timing (26.3%) were also effective but yielded numerically higher rates than the standard 8 mg/kg pre-first-dose schedule. A single prophylactic dose introduced no new safety signals with no increased incidence of grade ≥3 neutropenia or infections. Among the cohorts that reported ICANS with an 8 mg/kg dose before the first step-up dose, the pooled incidence was 2.7% (95% CI 0.1–9.5%; I^2 = 0%; crude 11/244) and nearly all events were grade 1–2 and resolved with CRS resolution. **Conclusions:** A single prophylactic dose of tocilizumab before the first step-up dose consistently and substantially reduces CRS — to a pooled 9% with almost absence of grade ≥3 events. This low rate of CRS with prophylactic tocilizumab could lend to safe adoption of bispecifics in academic and community practices.

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Systematizing Expert Multiple Myeloma Consultation in a Large Healthcare System Leads to Better Patient Outcomes: A Pragmatic Implementation Study

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Introduction: To measure the effect of implementing an early referral expert consultation program for all patients with newly diagnosed multiple myeloma (NDMM) on expert consultation rates and clinical effectiveness outcomes, including autologous stem cell transplant (ASCT) rates and overall survival. **Methods:** We conducted a pragmatic, retrospective, type III hybrid effectiveness-implementation cohort study measuring performance at 11 primary oncology clinic sites and a transplant center (Center) in the Western United States using a non-randomized pre-post study design and multi-level hierarchical modeling adjusting for pre-identified covariates and a service region random effect. Beginning April 2023, referring providers (RPs) were encouraged to refer all NDMM

patients for early expert consultation with a Center hematologist, regardless of ASCT eligibility. Expert consultation (in-person or virtual) included review of the initial treatment plan, current therapies and required testing, and full evaluation of ASCT eligibility and timing. Implementation strategies to promote referral included use of a system-level clinical implementation team, delivery of patient education materials and RP education including via a community-based tumor board. Primary implementation and clinical outcomes included expert consultation rates and overall survival, respectively, stratified by transplant eligibility status. An adjusted cox proportional hazards regression was used to examine transplant rates and overall survival. **Results:** From January 2018 to June 2025, 46 RPs and MM specialists cared for 268 patients with NDMM with no cancer history (male, 61.2%; mean age, 67.8 years [standard deviation, 11.6]; Consensus Genomic Staging high risk, 11.6%; transplant eligible, 69.8%). Providers referring ≥75% of NDMM patients increased from 50.0% to 70.6% (adjusted OR, 6.69 [95%CI, 1.14–39.30]). Among all patients, the percent of patients referred increased from 68.4% to 77.3% (adjusted OR, 3.23 [95%CI, 1.31–7.98]) increasing consultation rates from 63.9% to 74.6% (adjusted OR, 2.89 [95%CI, 1.27–6.57]). The non-referral rate among eligible patients declined 40% from 15.9% to 9.5% (adjusted OR, 0.38 [95%CI, 0.12–1.18]). Service outcomes improved including significant increases in cytogenic testing (adjusted OR, 6.72 [95%CI: 2.05–22.04]) and receipt of CD-38 antibodies (adjusted OR, 9.07 [95% CI, 4.68–17.56]). Overall survival improved significantly among transplant eligible referred versus not-referred patients (HR 0.34 [95%CI, 0.14–0.83]). Transplantation rates did not vary significantly post intervention. **Conclusions:** Implementation of an early referral expert consultation was associated with increased patient access and use of advanced NDMM services. Expert referral in multiple myeloma may improve survival independent of any transplant-specific effects, highlighting its potential benefit for clinical translation of new innovations in dynamic care environments.

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T- and NK-Cell Immunomodulatory Reprogramming by Cemsidomide, a Novel and Potent MonoDAC® Degrader, in Relapsed/Refractory Multiple Myeloma: Biomarker Results from CFT7455–1101 Arm B2 Cohort

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Introduction: Relapsed/Refractory Multiple Myeloma (RRMM) patients who are pentadrug-exposed face limited options and have immune compartments compromised by disease and prior therapies. Cemsidomide is a novel, highly potent oral Cereblon-based IKZF1/3 MonoDAC® degrader with retained activity in lenalidomide- and pomalidomide-resistant models. Here we characterize its immunomodulatory profile in combination with dexamethasone (DEX) from patients dosed in CFT7455–1101, arm B2 cohort. **Methods:** 62 patients were included in this analysis and received daily cemsidomide orally on a 14 days on/14 days off schedule across four different doses levels (37.5 ug [n = 8], 62.5 ug [n = 15], 75 ug [n = 20], 100 ug [n = 19]), and DEX weekly. Predose whole blood was collected at C1D1, C1D7, C1D14, C1D21 and C2D1. T- and NK- cell subsets were profiled by multiparameter flow cytometry. Serum cytokines were measured using MSD S-plex proinflammatory panel 1. **Results:** Cemsidomide elicited a coherent immune activation signature across dose levels with concordant changes in soluble and cellular readouts. Serum IL2 increased 4- to 6-fold from baseline at C1D7 and C1D14 (on-treatment) before returning to baseline levels during off-treatment. This is consistent with upregulated IL2 transcription levels via IKZF1/3 degradation, despite concurrent DEX. Additional key cytokines such as IFNγ and TNFα rose following the same IL2 pattern (3–4 fold and 2–3 fold respectively). At the cellular level, CD4 + and CD8+ T-cells upregulated HLA-DR (~ 3 fold), with CD8+ HLADR rising from 13–16% at baseline to 50–58% at C1D14, a remarkable 3- to 4-fold, with CD38+/HLA-DR+ co-expression confirming activation specificity. Within the proliferating CD8+ compartment, the Ki67+ pool enriched for a non-senescent CD57- phenotype, shifted from 65–77% at baseline to 85–91% at C1D14, indicative of preferential expansion of proliferative fit effectors. These proliferating cells largely retained Gzmb and perforin expression (~65–75% Ki67+/Gzmb+; 70–85% Ki67+/Perforin+), demonstrating that the expanding population was armed for cytotoxicity. By C1D21, serum cytokines and cellular activation markers returned to baseline levels, defining a cyclical pharmacodynamic pattern aligned with the dosing schedule. NK populations were maintained or expanded across treatment, with dose-dependent increases in Gzmb MFI (up to 2.5-fold) and HLA-DR (up to 7-fold) within the cytokine- producing CD56bright subset. CD314 on mature cytotoxic NK was preserved or upregulated. **Conclusions:** Cemsidomide with dexamethasone combination produced a coherent cyclical immune reprogramming signature with IL2-led Th1 cytokine induction concordant with broad CD4+ and CD8+ T-cell activation, expansion of non-senescent armed CD8+ effectors, and dose-dependent NK cytotoxic enhancement with maintained CD314 expression. The clinical response during CFT7455–1101 supports continued development, including evaluation in combination with T-cell and other immune-based therapies.

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T Cell Engager Therapy Impairs Antiviral Immunity Through Depletion of Viral-Reactive CX3CR1+ CD8+ T Cells in Multiple Myeloma

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Introduction: T cell engagers (TCEs) are highly effective in multiple myeloma (MM), yet the T-cell subsets driving optimal responses remain unclear. We observed that TCE efficacy varied with T-cell differentiation state. Given our previous finding that anti-BCMA TCEs expand CX3CR1+ CD8+ T cells, we investigated the role of T-cell differentiation, particularly CX3CR1+ CD8+ effectors, in TCE-mediated cytotoxicity and viral susceptibility post-TCE therapy. **Methods:** Peripheral T cells from healthy donors were sorted into naïve (Tnaive), effector memory (Tem), CD4+, and CD8+ subsets and evaluated for Teclistamab-mediated cytotoxicity against MM cells. CX3CR1+ and CX3CR1− CD4+/CD8+ T cells from healthy donors and MM patients were compared for cytotoxicity, cytokine production, and viral reactivity using CEF- or CMV pp65-pulsed T2 cells. Longitudinal samples from TCE-treated MM patients were analyzed by CITE-seq to assess CD8+ CX3CR1+ T-cell dynamics and their association with viral infections. **Results:** Tem cells demonstrated significantly superior TCE-mediated cytotoxicity compared with Tnaive cells. This was validated in patient-derived samples, where a higher proportion of Tem cells correlated with enhanced killing function. Similarly, CD8+ T cells exhibited greater tumor killing than CD4+ T cells; however, this difference was largely attributable to subset composition, as CD8+ T cells were predominantly Tem whereas CD4+ T cells were enriched for Tnaive cells. Consistently, CD4+ Tem and CD8+ Tem subsets showed comparable killing capacity, indicating the importance of differentiation state rather than CD4/CD8 lineage. CX3CR1+ T cells, a highly differentiated effector population generated during chronic antigen exposure and TCE treatment, displayed markedly enhanced cytotoxicity compared with CX3CR1− counterparts. CD8+ CX3CR1+ cells expressed higher levels of HLA-DR and secreted increased amounts of CCL3, CCL4, CCL5, granzyme A/B, perforin, soluble FasL, and TRAIL, consistent with potent antiviral and antitumor activity. Importantly, CD8+ CX3CR1+ T cells were highly susceptible to activation-induced cell death (AICD), with limited recovery following activation and TCE treatment. These findings suggest that prolonged TCE engagement progressively depletes this pool, potentially favoring sustained antitumor activity at the expense of antiviral immunity. Longitudinal single-cell RNA and TCR sequencing of T cells from TCE-treated MM patients revealed increased TCR clonality, reduced repertoire diversity, and depletion of virally reactive, including CMV-specific, TCRs during therapy. Together, these findings suggest that viral reactivations in TCE-treated patients may result from depletion of primed antiviral CD8+ CX3CR1+ T cells. **Conclusions:** Our data identify CD8+ CX3CR1+ T cells as key mediators of both antitumor and viral immunity. Prolonged TCE therapy depletes these virally reactive effectors through activation-induced cell death, contributing to viral infections and immune dysfunction in MM patients.

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Tandem Autologous Stem Cell Transplantation in High-Risk Newly Diagnosed Multiple Myeloma: Results from the Argentine Group for Bone Marrow Transplantation and Cellular Therapy (GATMO-TC)

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Introduction: Tandem autologous stem cell transplantation (ASCT) remains a consolidation strategy for selected patients with newly diagnosed multiple myeloma (NDMM) and high-risk features. We report a national multicenter GATMO-TC experience. **Methods:** This retrospective, multicenter, observational study included patients with NDMM who underwent tandem ASCT as consolidation in Argentina between January 2014 and March 2025. Progression-free survival (PFS) and overall survival (OS) were estimated from first ASCT using Kaplan-Meier curves and compared with the log-rank test. **Results:** Eighty-six patients from 11 transplant units were included. Median age at first ASCT was 52.5 years (range, 34–70), and the median interval between ASCT1 and ASCT2 was 100 days (range, 20–267). R-ISS was I in 9 (10.4%), II in 43 (50.0%), and III in 34 (39.6%). High-risk cytogenetic abnormalities included del (17p) in 29 (33.7%), chromosome 1 abnormalities in 16 (18.6%), t (4;14) in 10 (11.6%), t(14;16) in 7 (8.1%), and ≥2 high-risk abnormalities in 20 (23.2%). Extramedullary disease was present in 23 (26.7%) patients and plasma cell leukemia in 10 (11.6%). The most frequent induction regimens were VRd (n = 40, 46.5%), CyBorD (n = 14, 16.3%), VTD (n = 10, 11.6%), Dara-VRd (n = 10, 11.6%) and Dara-VTD (n = 7, 8.1%); 12 (13.9%) received PACE-like chemotherapy and 12 (13.9%) required >1 line before ASCT. Response deepening was observed, with complete response or better increasing from 28 (32.5%) post-induction to 51 (59.3%) after

ASCT1 and 67 (77.9%) after ASCT2. After a median follow-up of 31.5 months (range, 6–136) from first ASCT, median PFS and OS were not reached. The 12- and 36-month PFS rates were 92% and 61%, and the 12- and 36-month OS rates were 96% and 80%. No transplant-related deaths occurred within 100 days after ASCT2. In the post-ASCT2 analysis, patients achieving stringent complete response showed longer PFS (median, 74 months; 36-month, 80%) compared with complete response (median, 36 months; 36-month, 44%) and < VGPR (median, 27 months; 36-month, 41%; P = 0.0698). PFS after ASCT2 did not differ according to the number of high-risk cytogenetic abnormalities (P = 0.249) or extramedullary disease (P = 0.94). **Conclusions:** In this national GATMO-TC experience, tandem ASCT was feasible in selected patients with high-risk NDMM, including those with adverse cytogenetics, extramedullary disease, and plasma cell leukemia. Tandem ASCT was associated with response deepening, encouraging PFS and OS, and no early transplant-related mortality, supporting its role as a consolidation approach for high-risk NDMM in contemporary practice.

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Targetable Mitotic Spindle Defects Underpin High Risk, Genetically Unstable Multiple Myeloma

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Introduction: Multiple myeloma patients who develop drug resistance and experience the poorest outcomes frequently have myeloma genomes marked by chromosomal instability (CIN). However, mechanisms driving CIN in myeloma remain poorly understood, and precision therapeutics to exploit the underpinning processes have not been identified. Centrosome amplification and/or abnormal clustering has been linked to genomic instability in B cell malignancies, including myeloma. We hypothesized that CIN in myeloma is driven by mitotic spindle instability and may be synthetically targeted. **Methods:** To identify mitotic spindle defects leading to CIN, we profiled mitosis across myeloma cell lines by live cell imaging, immunofluorescence, and sensitivity to a tool PLK4 inhibitor (PLK4i), which perturbs spindle assembly by centrosome depletion. Cell lines were classified as PLK4i-sensitive (IC50 < 50 nM) or -resistant, and genes identified whose copy-number status (DepMap-derived) predicted classification. These genes were intersected with genome-wide CRISPR screen hits in PLK4i-treated myelomas to identify candidate determinants of PLK4i sensitivity. Clinical relevance was assessed using the CoMMpass dataset. **Results:** We found PLK4i sensitivity in ~50% myelomas, characterized by mitotic catastrophe cell death following failure of functional bipolar spindle formation, revealed by live-cell imaging. Failure of bipolar spindle assembly occurred due to inefficient spindle pole focusing. In contrast, PLK4i-resistant myelomas were able to assemble functional bipolar spindles despite efficient PLK4i-induced centrosome depletion. The PLK4i-sensitive myelomas did not display 17q23 gain/TRIM37 overexpression or p53 dependence, both previously associated with PLK4i sensitivity in breast cancer cells [1]. CRISPR screening identified depletion of regulators of passive microtubule crosslinker NuMA – in particular its localization to the spindle – to mitigate sensitivity. Intersection of these regulators with genes in regions where loss or gain correlated to PLK4i sensitivity identified extra copies of the gene UBXN2B (p37) as a candidate driver of sensitivity. Excess p37 depleted polar localisation of NuMA, destabilising the spindle pole, so rendering pole focusing critically dependent on centrosomes. However, targeted knockdown of UBXN2B extra copies conferred PLK4i resistance: normal p37 levels restored NuMA polar accumulation, restoring spindle stability. In the CoMMpass dataset, we found top quintile UBXN2B expression in NDMM to have prognostic impact comparable to IMWG high-risk status. **Conclusions:** We demonstrate for the first time how mitotic defects underpin CIN in myeloma, and identify a predictive biomarker for precision targeting. High expression or extra copies of UBXN2B serve as a marker for (a) a subset of myelomas with poor outcomes and (b) potential efficacy of PLK4 inhibitors in this patient group.

Reference:

1. Yeow *et al.*, *Nature* 2020 585(7825):447–452.

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Targeting c-Myc Expression and Function in Multiple Myeloma Through a Novel PIM2 Kinase-Independent Approach

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Introduction: Multiple myeloma (MM) remains incurable for almost all patients because of adaptive upregulation of pro-survival mechanisms, progressively greater resistance to therapy and persistent relapsing disease. Although MM is a cMyc-driven cancer, its targeting remains a major therapeutic challenge. We reported PIM2, an oncogenic serine/threonine kinase, with a significant role in key signaling pathways that support survival and confer chemotherapy resistance in MM cells, to be overexpressed in patient CD138+ cells. Our novel PIM2-selective non-ATP competitive inhibitor JP11646 (JP) showed high efficacy against MM not only due to inhibition of kinase activity, but also to an unexpected downregulation of PIM2 mRNA and protein, as well as cMyc, in vitro and in vivo. We hypothesized that oncogenic PIM2 regulates cMyc expression and function through a previously unreported kinase-independent (Ki) mechanism. **Methods:** We employed knockdown of PIM2 (KD) and

overexpression (O/E) of either wild type (WT), kinase-dead (K61A) of kinase absent (DK) PIM2 molecule in MM cell lines. We generated specific small molecules inhibitors, structural analogs of JP: CpdA, with no kinase inhibitory effect (kinase-independent -Ki) holding similar potency with JP and CpdB, kinase-only inhibitor, similar with AZD1208 (AZD) in potency. **Results:** Exogenous expression of either PIM2 WT or K61A and DK mutants significantly upregulated survival regardless of a functional kinase. PIM2 O/E cells (WT, K61A or DK), challenged with either serum starvation, bortezomib or melphalan, overcame the inhibitory effect on viability induced in the vector control. RNA-seq GSEA analysis, showed Hallmark MYC Targets V1 gene set exhibited strong negative enrichment in PIM2 KD cells compared to their control in MM.1S cells. Ki inhibitor CpdA and dual inhibitor JP, significantly inhibited MM cell's viability, decreased PIM2 and cMyc mRNA and protein expression in striking contrast with CpdA and AZD. These effects were replicated in primary human CD138+ cells and in the tumors harvested from a MM.1S mouse xenograft model. AZD had minimal therapeutic activity compared to the significant anti-MM efficacy of JP in vivo in a immunocompetent model implanted i.v. with Vk*Myc MM cells. PIM2 co-immunoprecipitated with cMyc regardless of a functional kinase domain and this binding was disrupted by Ki PIM2 inhibitors, results confirmed by PLA assays. Hallmark MYC Targets V1 gene set exhibited strong negative enrichment while DEG sets co-clustered in hierarchical heatmap analysis in JP and CpdA treated cells compared to CpdB that shared zero DEGs with either compound and clustered with DMSO, supporting a PIM2 Ki correlation with cMyc activity signature. This observation was confirmed by c-Myc occupancy enrichment decrease at CDK4 promoter only by Ki inhibitors. **Conclusions:** cMyc transcriptional activity can be therapeutically targeted by PIM2 allosteric/non-ATP-competitive inhibitors like CpdA.

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Targeting HUWE1 in Multiple Myeloma: Enhanced Bortezomib Activity and Development of a Novel High-Throughput HUWE1 Screening Assay

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Introduction: HUWE1 is a promising therapeutic target in multiple myeloma (MM) and our lab developed a novel HUWE1 inhibitor QDD-7. HUWE1 is implicated in many oncogenic processes. Recent evidence demonstrated that HUWE1 promotes c-MYC multimer formation at stalled replication forks, protecting cells from replication-associated DNA damage. As bortezomib induces c-MYC multimerisation, we investigated the mechanistic basis of combining HUWE1 inhibition with bortezomib and developed a high-throughput screen to identify novel HUWE1 inhibitors. **Methods:** MM cell lines (JJN3, OPM2, KMS12 and MOLP8) were treated with bortezomib (BTZ) and QDD-7 simultaneously or sequentially using a 4-hour pre-treatment. Cell viability was assessed using CellTiter-Glo® and drug interactions were analysed using the Bliss synergy model (SynergyFinder+), where >10 indicates synergy, −10 to 10 shows an additive effect and <−10 antagonistic. DNA damage was evaluated by immunoblotting and immunofluorescence foci analysis. Apoptosis was assessed by immunoblotting and Caspase-Glo® luminescent assays. Immunofluorescence studies assessed c-MYC localisation following BTZ and QDD-7 treatment. HUWE1 auto-ubiquitination activity was measured using UbiQapture™ assays and a newly developed fluorescence polarisation-based primary ubiquitination assay using full-length HUWE1 and UbFluor substrate. **Results:** QDD-7 inhibited HUWE1 activity across MM cell lines and associated with a reduction of c-MYC expression ($p < 0.05$), along with induction of γH2AX and caspase-3 cleavage ($p < 0.05$), indicating DNA damage and apoptosis respectively. Combination studies demonstrated BTZ pre-treatment produced the strongest response (Bliss score ≥16.82), whereas simultaneous treatment produced additive effects (Bliss score ≥1.58). Combination treatment increased DNA damage compared with single agents, shown by enhanced γH2AX expression ($p < 0.0001$) and increased BRCA1 foci formation, while reducing c-MYC expression and increasing cleaved caspase-3 levels. Preliminary immunofluorescence studies demonstrate altered c-MYC and BRCA1 co-localisation following BTZ and QDD-7 treatment, supporting disruption of c-MYC-mediated replication stress responses; quantitative analysis is ongoing. To facilitate future drug discovery, a novel fluorescence polarisation-based HUWE1 ubiquitination assay was developed and optimised for high-throughput screening. Preliminary evaluation of QDD-7, along with the HUWE1 inhibitor BI8622 showed measurable inhibitory activity, supporting the platform for identification and optimisation of next-generation HUWE1 inhibitors. **Conclusions:** These findings further support HUWE1 as a therapeutic target in MM and demonstrates HUWE1 inhibition enhances the activity of BTZ through increased DNA damage, suppression of c-MYC-associated replication stress responses and apoptosis induction. The development of a robust primary HUWE1 activity assay establishes a platform for the discovery and optimisation of more potent and selective HUWE1 inhibitors.

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Targeting Lactate Metabolism in Multiple Myeloma to Enhance CAR-T Cells Antitumor Function

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Introduction: Altering tumor cell metabolism is a promising therapeutic target for multiple myeloma(MM). Increased glucose metabolism in multiple myeloma cells ensures a high proliferation of

tumor cells, but also produces excess lactic acid, which suppresses the immune microenvironment.Here,we intend to discovery targeting lactate metabolism in multiple myeloma to enhance immune cell like CAR-T cells antitumor function,which will lead a new therapy methods for both MM cell and CAR-T cell. **Methods:** we analyse of the correlation between the lactate level of TME and the function of its immune cells in patients with myeloma.next,the effect of exogenous lactate on immune cells were detected. Furthermore, the effect of MCT inhibitors combined with MPC inhibitors in the regulation of proliferation, apoptosis, and cell cycle in MM cells were analyse.last,the effect of targeting lactate metabolism of MM cell on immune cell function were analysed in MM patient-derived BMMNCs co-culture system and MM load NSG mice model. **Results:** The results of the analysis indicate the immune suppression in MM patients which may realted to the lactate level in MM patients. By synergistically inhibiting the monocarboxylate transporters (MCT) pathway and the mitochondrial pyruvate carrier (MPC) pathway, which may simultaneously inhibit the lactate efflux and blocking the entry of lactate-converted pyruvate into the mitochondria,it will lead to acidify the intracellular environment of the MM cells and activate oxidative stress of tumor cells. At the same time, with reduce of the extracellular acidification rate, the immunosuppressive microenvironment is alleviated, the effector immune cell (T cell and CAR-T cell) function get be restored and enhanced the anti-tumor effect in vitro and in MM load NSG mice model experiments. **Conclusions:** Our results indicated that targeting lactate metabolic in MM cell can enhance the efficiency of CAR-T cells in MM patients.

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Targeting NFIL3-MYC Axis as a Novel Therapeutic Strategy in High-Risk Relapsed-Refractory Multiple Myeloma

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Introduction: Aberrant activation of Notch signaling promotes drug resistance in multiple myeloma (MM), which limits the treatment outcomes and increases the risk of relapse in patients. However, direct inhibition of Notch pathway with γ-secretase inhibitors (GSI) leads to severe gastrointestinal side effects. Hence, the need to identify safe and selective druggable Notch effectors remains high. **Methods:** Transcriptome profiling was conducted on Notch-depleted MM.1S cells with short hairpin RNA (shRNA) knockdown or GSI treatment to identify Notch-dependent candidate genes. Subsequently, a focused shRNA library targeting selected genes was performed in NOTCH1-overexpressing U266-N1ΔE cells under selective pressure of lenalidomide, melphalan, or bortezomib. Those genes, which were significantly depleted by shRNAs in the remaining drug-resistant cell clones compared to DMSO treated controls, were identified as high-potential targets. From the top hits on the screen, we selected nuclear factor interleukin 3 regulated (NFIL3) and further validated it as a direct NOTCH1 target via ChIP-seq analysis and reporter assays. The NFIL3 expression profile was analyzed in patient cohorts of the MMRF CoMMpass study and a local published validation cohort from Würzburg to determine its prognostic potential. We further targeted NFIL3 using shRNAs or the oleanane-type triterpenoid saponin Raddeanin A (RA) to demonstrate its mechanistic specificity and treatment efficacy in vitro and in vivo. **Results:** Through functional genomic screens, we identified NFIL3 as a novel therapeutic target. Reduced cell growth and viability of human and murine MM cells were observed using shRNAs against NFIL3 or RA treatment in vitro. This finding was confirmed in vivo using the murine MOPC315. BM model, where RA-loaded polymer micelle nanocarriers were designed to improve compound solubility and to minimize toxicity. RA further reduced osteolytic bone lesions through blocking osteoclast development and activity in vivo. Immunoblotting revealed increased cleaved caspase-3 levels and decreased c-MYC expression following NFIL3 inhibition, indicating NFIL3 as a repressor of the MYC oncogenic signaling axis in MM cells. Notably, RA showed effective anti-tumor activity against patient-derived MM cells with high-risk cytogenetics and after failure of BCMA-directed immunotherapies. Higher NFIL3 expression was associated with high-risk cytogenetic abnormalities, higher tumor burden, and worse prognosis in patients, suggesting NFIL3 as a critical therapeutic vulnerability in high-risk, multidrug-resistant MM. **Conclusions:** In conclusion, we identified upregulation of NFIL3 as a novel mechanism for drug resistance in high-risk relapsed-refractory MM. RA targets the NFIL3-MYC axis and shows potent anti-MM effects, providing a novel therapeutic strategy for multi-refractory disease even after failure of current immunotherapies.

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Targeting of BIRC3 Sensitises Multiple Myeloma Cells to Proteasome Inhibitors

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Introduction: Despite significant advances in the treatment of multiple myeloma (MM) development of therapy resistance remains a clinical challenge. Thus, elucidation of resistance mechanisms and identification of novel targets is crucial to advance treatment and overcome resistance. Network analysis of 20 MM cell lines was performed using SynLeGG (Synthetic Lethality with Gene Expression and Genomics) to predict genes which could be targeted

to increase sensitivity to proteasome inhibitors (PIs), which are a cornerstone of MM therapy. This analysis identified BIRC3 as a potential target gene. BIRC3 codes for an inhibitor of apoptosis protein which is largely involved in regulating both the canonical and non-canonical NF-κB pathways. The aim of this study was to validate BIRC3 as a PI-sensitiser gene and to investigate its potential as a therapeutic target in MM. **Methods:** Five MM cell lines (JJN3, U266, OPM2, KMS18, AMO1) representing diverse cytogenetic subgroups were analysed, along with a PI-resistant model of U266. BIRC3 was silenced using siRNA-mediated knockdown (KD) or chemically inhibited using SMAC mimetics (SM) BV-6 and tolinapant. Combination treatments with SMs and PIs were analysed using SynergyFinder to calculate Bliss Synergy scores. Scores <−10 indicate antagonism, −10 to 10 indicates an additive relationship, and >10 indicates synergism. **Results:** siRNA-mediated KD of BIRC3 significantly reduced viability of MM cell lines compared to control siRNA ($p < 0.05$) and yielded sensitisation to carfilzomib (CFZ). Subsequent analysis using BV-6 in combination with PIs (carfilzomib/bortezomib) across five cell lines revealed at least an additive relationship between these drugs (Bliss Synergy score ≥ 5.08). Pre-treatment with BV-6, to allow for effective BIRC3 degradation, followed by PI treatment further enhanced the synergistic effect (Bliss Synergy score ≥ 12.71). Furthermore, this combination is effective in PI-resistant U266 cell lines (Bliss Synergy score ≥ 40.11). Western blot analysis demonstrated cleavage of caspases-3/-8/-9 at 18hrs, suggesting an induction of both intrinsic and extrinsic apoptotic cell death. Combination treatment induced nuclear translocation of p52 and RelB which is indicative of non-canonical NF-κB activation and was accompanied by significantly increased TNFα secretion ($p < 0.0001$). Importantly, similar synergistic effects were observed using a clinically relevant SM, tolinapant (Bliss Synergy score ≥ 12.44), further confirming BIRC3 as a PI-sensitiser gene. **Conclusions:** The results of this study reveal that BIRC3 is a PI-sensitiser gene which, when targeted therapeutically, increases PI sensitivity even in PI-resistant cells. Future work will aim to further delineate the role of TNFα signalling in SM/PI-induced cell death. Ultimately, the discovery of this synergistic drug combination could have important implications in developing new strategies to overcome treatment resistance in MM.

PA-482

Targeting p300/CBP to Overcome IMiD Resistance

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Introduction: ImmunoModulatory Drugs (IMiDs) are a backbone therapy for myeloma, thus overcoming IMiD-resistance will improve outcomes. Recently, bromodomain inhibition of the H3K27 acetyltransferases p300 and CBP has been shown to be effective in combination with IMiDs, even in IMiD resistant patients. We sought to understand how p300/CBP inhibition works in combination with IMiDs. **Methods:** Seven MM cell lines were treated with the p300/CBP inhibitor CCS1477/Inobrodib and/or pomalidomide (Pom). Cell viability was measured by flow cytometry. Drug synergy was determined using the Zip model. Protein levels were determined by immunoblot for MYC, IRF4, p300, CBP, IKZF1/3. H3K27ac was measured by CUT&RUN and gene expression determined by RNA-seq. p300/CBP and IKZF1/3 interactions were determined by co-immunoprecipitation and proximity ligation assay. The dependency of EP300 (encodes p300) and CREBBP (encodes CBP) was assessed using CRISPR/Cas9 competition assays. **Results:** Pom treatment showed growth inhibitory effects in NCI-H929, JJN3, MM1.S (GI50 ~100–200 nM), but limited to no cytotoxicity in all cell lines tested (IC50 >400nM), consistent with previous reports. In contrast, CCS1477 showed both a robust dose dependent growth inhibition (GI50 < 200 nM, all cell lines) and cytotoxicity (IC50 < 200 nM, 6/7 cell lines). Reduced MYC and IRF4 expression following CCS1477 treatment was observed across all cell lines. CRISPR/Cas9 targeting of EP300 and CREBBP showed EP300 to be essential for growth whereas CREBBP was largely dispensable. CUT&RUN showed a 50% global reduction of H3K27ac with CCS1477. This manifested in pronounced transcriptional downregulation in Pom-sensitive cells, whereas resistant RPMI8226 had fewer downregulated genes. Combined CCS1477 and Pom dose matrices showed synergy in Pom responsive cells (ZIP >10; NCI-H929, MM1.S, JJN3), but not Pom-resistant cells. Both co-immunoprecipitation and proximity ligation analyses showed robust interactions between p300/CBP and IKZF1/3 in Pom-sensitive cells (MM1.S, NCI-H929), but diminished interactions in Pom-resistant (RPMI8226) cells. **Conclusions:** These data indicate p300/CBP inhibition is effective in both IMiD-sensitive and resistant cells. Chromatin analysis suggests p300/CBP are responsible for the majority of H3K27ac in myeloma, explaining the broad sensitivity to targeting p300/CBP. Synergy of Pom and CCS1477, however, appears to be more pronounced in models that are Pom-sensitive and correlates with stronger interactions between IKZF1/3 and p300/CBP. Genetic experiments indicate p300 is the critical regulator of myeloma cell growth and p300-specific strategies should be considered. These data provide clues about the mechanistic basis for synergy between IMiDs and p300/CBP inhibitors with implications for ongoing clinical trials.

PA-483

TARGET-LATAM Targeted Bispecific Antibodies Against BCMA and GPRC5D in Relapsed/Refractory Multiple Myeloma A Real-World Comparative Analysis from the GELAMM Group

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Introduction: Bispecific antibodies (BsAbs) have emerged as a novel treatment for relapsed/refractory multiple myeloma (RRMM), demonstrating remarkable response rates in pivotal clinical trials. However, real-world data, particularly from Latin America (LATAM), remains scarce. The TARGET-LATAM study reports BCMA and GPRC5D results across LATAM centers, providing the first large-scale real-world evidence of their effectiveness and tolerability in this region. **Methods:** This is a retrospective multicenter study from the GELAMM group. Of 346 TCE-exposed RRMM patients, 124 received BsAbs targeting BCMA (teclistamab or elranatamab) or GPRC5D (talquetamab). Normality was assessed using the Kolmogorov-Smirnov test; non-parametric tests were applied when $p < 0.05$. Categorical variables were compared using chi-square or Fisher's exact test; continuous variables with the Mann-Whitney U test. To minimize selection bias, propensity score matching (PSM) was performed using nearest-neighbor 1:1 algorithm with a caliper of 0.2 SD, adjusting for age, ISS stage, cytogenetic risk, prior autologous stem cell transplantation (ASCT), and extramedullary disease, yielding 57 matched pairs (n = 114). **Results:** The matched cohort was 62.9% male, with a median age of 56 years (IQR 26–79). ISS: I 22.6%, II 43.5%, III 32.3%. High cytogenetic risk in 18.5%, prior transplantation in 34.7%, and extramedullary disease in 22.6%. Refractoriness: triple 29%, quadruple 37.1%, penta-refractory 27.5%. Mean treatment duration 12.85 months (95% CI 9.2–16.5). Median PFS was 10.7 vs 10.3 months for BCMA and GPRC5D arms, respectively ($p = 0.8$). Median OS was 15.1 vs 19.0 months ($p = 0.7$). Infectious toxicity was significantly higher in the BCMA arm (62% vs 18.8%; $p = 0.001$). Grade ≥3, as well as infectious toxicity: 35.2% vs 12.5% ($p = 0.150$) and Hypogammaglobulinemia (< 400 mg/dL): 77.1% vs 50% ($p = 0.013$). **Conclusions:** In this Latin American cohort of heavily pretreated RRMM patients, anti-BCMA (teclistamab/elranatamab) and anti-GPRC5D (talquetamab) bispecific antibodies demonstrated comparable efficacy in PFS and OS after propensity score matching. However, anti-BCMA therapy was associated with significantly higher rates of any-grade infectious toxicity ($p < 0.001$) and hypogammaglobulinemia < 400 mg/dL ($p = 0.013$), underscoring the importance of close infectious-disease monitoring and immunoglobulin replacement strategies in this population.

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Teclistamab as a Novel "Neuro-Rescue" Strategy for Refractory Neuropathy in POEMS Syndrome with Sustained Hematologic Response

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Introduction: POEMS syndrome is a multisystemic disorder closely associated with abnormal clonal plasma cells, primarily manifested as polyneuropathy. A key therapeutic goal is eradication of the pathogenic plasma cell clone to improve neurological function, survival, and quality of life. Although autologous hematopoietic stem cell transplantation (ASCT) and the application of new drugs have improved the overall prognosis, a clinical dilemma of "hematologic-neurologic response dissociation" persists: severe polyneuropathy (PN) may show minimal improvement for months despite achieving hematologic remission (HR). Currently, there is no standard treatment strategy for these patients who are "non-relapsed but neurologically refractory". BCMA/CD3 bispecific antibodies (e.g., Teclistamab) can rapidly eliminate plasma cells via T-cell redirection, but their effect on improving persistent PN in POEMS syndrome has not been reported. **Methods:** This is a retrospective case report of a patient with POEMS syndrome whose neurological symptoms showed inadequate improvement after induction therapy with the DRd (daratumumab, lenalidomide, dexamethasone) regimen, followed by sequential treatment with Teclistamab. **Results:** A 36-year-old female diagnosed with POEMS syndrome (polyradiculoneuropathy, monoclonal plasma cell-proliferative disorder:M protein 7.97 g/L, markedly elevated VEGF, organomegaly). At the initial diagnosis, her Overall Neuropathy Limitations Scale (ONLS) score was 3, indicating inability to walk independently (wheelchair-dependent). Induction therapy with DRd achieved partial HR at 6 months (M-protein 2.81 g/L) and sustained PR at 1 year, with normalization of VEGF. However, her neurological symptoms

plateaued with no functional improvement (ONLS score remained 3). Despite her refusal to ASCT, stem cell collection and cryopreservation still performed at 6 months after DRd treatment. Given that neurological function recovery had entered a plateau phase, she was switched to Teclistamab treatment after informed consent. Teclistamab was administered with step-up dosing (0.06 mg/kg → 0.3 mg/kg → fixed 30 mg weekly). After one month of treatment, she achieved very good partial hematologic response (M-protein 0.71 g/L). Notably, her neurological function improved significantly: ONLS score decreased to 2, reflecting regained ability to walk independently. The patient is still undergoing continuous treatment. **Conclusions:** This case demonstrates that switching to Teclistamab effectively reversed the "neurologic improvement plateau" in a POEMS syndrome patient with sustained hematologic remission on DRd therapy, serving as a successful "neuro-rescue" strategy. It highlights the potential of T-cell redirecting therapy to address the critical unmet need of hematologic-neurologic dissociation. The favorable initial safety and "off-the-shelf" availability support its further investigation in this setting.

PA-485

Teclistamab for Relapsed/Refractory Multiple Myeloma in Latin America: A Real-World Analysis from the GELAMM Registry

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Introduction: Background: Teclistamab (TEC), a BCMA × CD3 bispecific antibody, demonstrated significant clinical activity in heavily pretreated patients (pts) with relapsed/refractory multiple myeloma (RRMM) in MajesTEC-1. However, real-world (RW) data from Latin America remain scarce. Aims: To evaluate the effectiveness and safety of TEC in RRMM pts treated in routine clinical practice across Latin America. **Methods:** We conducted a retrospective multicenter study of RRMM pts treated with TEC within the Grupo de Estudio Latinoamericano de Mieloma Múltiple (GELAMM) Registry. Consecutive pts treated between January 2023 and April 2026 were included. Baseline characteristics, treatment outcomes, and adverse events (AEs) were collected from participating centers. Responses were assessed per IMWG criteria. Primary endpoints included overall response rate (ORR), ≥VGPR, CR/sCR, progression-free survival (PFS), overall survival (OS), and safety. **Results:** Eighty-four pts from Argentina (n = 54), Mexico (n = 20), Uruguay (n = 5), Paraguay (n = 3), and Peru (n = 2) were included. Median age was 61.2 years (range, 33–82), 59.5% were male, and median prior lines of therapy (LOT) was 3 (range, 1–7). Prior autologous stem cell transplantation (ASCT) had been performed in 67.9%, while 38.1% were penta-drug refractory. High-risk cytogenetics, ISS stage III, and extramedullary disease (EMD) were present in 23.8%, 36.9%, and 21.4%, respectively. Median time from diagnosis to TEC initiation was 4.4 years. Among 80 response-evaluable pts, ORR was 72.6%, including sCR in 28.6%, CR in 25.0%, VGPR in 14.3%, and PR in 4.8%. Overall, 67.9% achieved ≥VGPR and 53.6% achieved CR/sCR. At a median follow-up of 10.2 months (95% CI, 6.4–14.0), median PFS was 16.9 months (95% CI, 10.0–23.8), while median OS was not reached. CRS occurred in 62.0% of pts, with grade ≥3 CRS in 1.2%. ICANS occurred in 6.0%, including 1.2% grade ≥3 events. Infections occurred in 64.3%, with grade ≥3 infections in 31.0%. Hypogammaglobulinemia was observed in 75.0%, and 76.2% received IVIG replacement. Among pts developing CRS, 38.0% received tocilizumab alone and 21.0% dexamethasone alone. **Conclusions:** This GELAMM Registry analysis represents one of the largest RW Latin American experiences with TEC reported to date. TEC demonstrated substantial clinical activity, deep responses, and encouraging survival outcomes despite a high proportion of heavily pretreated and penta-drug refractory pts. The safety profile was manageable and consistent with the known toxicity spectrum of BCMA-directed bispecific antibodies, supporting the integration of TEC into routine clinical practice across Latin America.

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Teclistamab plus Daratumumab (Tec-Dara) Versus Real-World Physician's Choice of Therapy for Relapsed/Refractory Multiple Myeloma: Comparative Effectiveness Based on an Indirect Treatment Comparison

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Introduction: Tec-Dara significantly improved progression-free (PFS) and overall survival (OS) vs standard-of-care (SoC; Dara +

dexamethasone + pomalidomide or bortezomib [DPd/DVd]) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) and 1–3 prior lines of therapy (LOTs), in the phase 3 MajesTEC-3 study (NCT05083169). Based on these unprecedented results, Tec-Dara received US approval for the treatment of RRMM with ≥1 prior LOT including a proteasome inhibitor (PI) and immunomodulatory agent. To evaluate Tec-Dara vs SoC in RW clinical practice, we performed indirect adjusted comparisons to assess the effectiveness of Tec-Dara vs real-world physician's choice (rwPC) of therapy. **Methods:** Individual pt data from MajesTEC-3 included pts who received Tec-Dara (N = 291; CCO, Aug-1–2025). An external cohort was created from the US Flatiron Health database, including pts who met key MajesTEC-3 criteria such as 1–3 prior LOTs, including a PI and lenalidomide (pts with 1 prior LOT were lenalidomide refractory), no prior BCMA-exposure or anti-CD38 mAb refractoriness (N = 4224 observations from 2959 pts [Jan-2016–Oct-2025]). Inverse probability of treatment weighting (IPTW) was used to adjust for imbalances in the following: refractory status, cytogenetic risk, ISS disease stage, time to progression on last LOT, ECOG performance status, age ["base-case" set], hemoglobin, no. of prior LOT, time since diagnosis, prior transplant, race, sex, type of MM, and creatinine clearance ["full-model" set]. Weighted Cox proportional hazards models were used to estimate the hazard ratios (HR) for PFS, OS, and time to next treatment (TTNT). Primary analysis used all observations per pt; sensitivity analysis used first observation only. **Results:** After reweighting, baseline characteristics were balanced across cohorts. The most common RW regimen was DPd (15.2%). Per base-case adjustment, pts treated with Tec-Dara had significantly improved PFS vs rwPC (HR, 0.12; 95% CI, 0.08–0.16); P < 0.001); adjusted median PFS, NR vs 9.9 mo, respectively. Tec-Dara also significantly improved OS vs rwPC (HR, 0.51; 95% CI, 0.37–0.70; P < 0.001); median OS, NR vs 68.0 mo. Similarly, Tec-Dara significantly prolonged TTNT (HR, 0.18; 95% CI, 0.13–0.23; P < 0.001); median TTNT, NR vs 12.5 mo. Full-model adjustment results also significantly favored Tec-Dara for PFS (HR, 0.11 [95% CI, 0.08–0.15]), OS (HR, 0.50 [95% CI, 0.36–0.70]), and TTNT (HR, 0.17; 95% CI, 0.13–0.22]; all P < 0.001). Sensitivity analyses results were consistent with those from the primary analysis. **Conclusions:** Using IPTW-adjusted indirect comparisons in a large US RW cohort, Tec-Dara outperformed rwPC across a broad range of regimens in real-world practice, with significant improvements in PFS, OS and TTNT. These findings extend MajesTEC-3 results beyond the trial setting and support Tec-Dara as a robust, immunotherapy-based, steroid-sparing SoC with convenient dosing, in 2L+ RRMM in routine clinical practice.

PA-487

The Changing Landscape of Thrombosis in Multiple Myeloma: Temporal Trends from a Real-World Longitudinal Cohort

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Introduction: Thromboembolic events are frequent non-hematologic complications of Multiple Myeloma(MM). This study aimed to quantify the prevalence of thromboembolic events in Mexican MM patients. **Methods:** We conducted a multicenter retrospective cohort study of patients aged > = 18 years from October 97 to October 2025. Thromboprophylaxis strategies included none, antiplatelet therapy, or anticoagulation (DOACs, VKAs, or LMWH). Patients were stratified into the pre-DOAC and DOAC-access eras. The sample size was calculated assuming an expected incidence of 10%, a 95% confidence level, and an absolute precision of 3%. The required sample size was 384. Normality was assessed using the Kolmogorov- Smirnov test. Comparisons between groups were performed using Student's t- test. The association between categorical variables was tested using the chi-square test. Time-to-event analyses were conducted using Kaplan-Meier curves and the log-rank test. Multivariable analyses included logistic regression and Cox proportional hazards models. **Results:** A total of 517 patients were included. Men accounted for 53.6%, and women for 46.4%, with a mean age at diagnosis of 55.8 years. Renal involvement was present in 26.9%, and bone disease in 49%. Elevated DHL was observed in 14.9%, and 33.7% recived ASCT. The median IMPEDE- VTE score was 6.71 (5–9, RIC 4). Baseline characteristics were similar between groups with and without thrombotic events. According to IMPEDE-VTE, 13% were low risk, 29.4% intermediate risk, and 56%. 75% high risk. 84.7% received thromboprophylaxis, mainly aspirin (42.6%), DOACs (31%), and vitamin K antagonists (9.9%). Major bleeding occurred in 0.4%. The prevalence of thromboembolic events was 8.3%. The mean time to thrombosis for the entire cohort was 4.4 months (95% CI 2.3–6.9 months). In the pre-DOAC-access era, the incidence of thrombotic events was 10.9% (n = 35/322), compared with 4.1% (n = 8/195) in the DOAC-access era (p = 0.007). Kaplan-Meier analysis in the pre-DOAC group showed a median time to thrombosis

of 2.867 mo (95% CI, 0.220–11.380) vs 5.8 mo (95% CI, 0.440–5.94) in the DOAC era ($p = 0.002$). Cox regression did not identify independent predictors of thrombosis. Logistic regression demonstrated significantly lower odds of thrombosis with anticoagulation compared with antiplatelet therapy ($p < 0.001$). **Conclusions:** In conclusion, this real-world evidence study reported a prevalence of thromboembolic events of 8.3%. Our findings demonstrate a substantial reduction in thromboembolic events after the introduction of DOAC access. These data support the growing role of DOACs as an effective antithrombotic prophylaxis in multiple myeloma.

PA-489

The Impact of Pomalidomide-Containing Induction on Stem Cell Mobilization and Engraftment in Newly Diagnosed Multiple Myeloma: A Single Center Experience

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Introduction: Autologous stem cell transplantation (ASCT) remains the standard intensification therapy for eligible patients with newly diagnosed multiple myeloma (NDMM). While lenalidomide-based regimens have been associated with impaired hematopoietic stem cell (HSC) mobilization, clinical data regarding the potential impact of pomalidomide (POM)-containing induction on mobilization outcomes remains extremely limited. We conducted a study to evaluate the effect of POM-based induction on HSC mobilization, collection, and engraftment in transplant-eligible NDMM patients. **Methods:** This retrospective cohort study analyzed consecutive NDMM patients who underwent HSC mobilization with high-dose cyclophosphamide (HD-CTX) plus pegylated granulocyte colony-stimulating factor (PEG G-CSF) at a single center between January 2023 and December 2025. Patients were divided into two groups based on whether their induction regimen contained POM (POM group) or not (Control group). To minimize confounding factors, propensity score matching (PSM) was performed to balance baseline characteristics between the groups. **Results:** Overall, 111 consecutive transplant-eligible NDMM patients were included, with 33 patients receiving POM-containing induction and 78 serving as controls. After 1:1 matching, 33 patients were identified in each cohort. In the matched population, the incidence of poor mobilization was comparable between the two groups (36.4% vs. 30.3%, $p = 0.794$). However, patients in the POM group received a significantly higher number of plerixafor (PXF) doses ($p = 0.030$). The total CD34+ cell yield was significantly lower in patients exposed to POM (median 5.81×10^6/kg) compared to controls (median 7.29×10^6/kg, $p = 0.011$). Additionally, a significantly lower proportion of POM-treated patients reached the optimal collection goal of $\geq 6 \times 10^6$ CD34+ cells/kg (45.5% vs. 72.7%, $p = 0.044$). Despite the lower total cell yield, the median CD34+ cell dose infused at transplant was comparable between groups ($p = 0.151$), and all patients achieved successful hematopoietic recovery with similar neutrophil and platelet engraftment times. **Conclusions:** POM-containing induction significantly reduces total CD34+ collection yields and increases PXF requirements. However, it does not preclude the successful harvest of the minimum HSC doses required for transplantation, nor does it compromise post-transplant engraftment. For patients receiving POM-based induction, a risk-adapted mobilization strategy utilizing chemotherapy-based mobilization and on-demand PXF should be employed to ensure successful HSC collection and subsequent ASCT.

PA-490

The Myeloma Biomarker Glutaminyl Cyclase Is a Novel Post-Translational Modifier of Immunoglobulin Light Chains

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Introduction: There has been increasing interest in blood-based protein biomarkers that predict the future development of multiple myeloma (MM). Three groups have independently reported that higher levels of glutaminyl peptide cyclotransferase (QPCT) predict the development of MM. However, its function in plasma cell and myeloma biology are unknown. QPCT and its isoform QPCT-like (QPCTL) convert N-terminal glutamine (Q) and glutamate (E) to pyroglutamate (pE). Classically, this protects hypothalamic hormones from N-terminal peptidases, but it is also a drug target in amyloidogenic disorders like Alzheimer's. While N-terminal pE has been found on human antibodies for several decades, it is widely believed to be spontaneous and of no functional consequence. We now show that QPCT and or QPCTL actively modify light chain immunoglobulins in myeloma cell lines and that inhibition of this activity does not affect myeloma cell viability. **Methods:** Immunoglobulin N-terminal amino acids from humans, mice and macaques were tabulated using data from the Observed Antibody Space. 4 MM cell lines and 3 non-MM blood cancer cell lines were treated with the QPCT inhibitor PBD150 and the dual QPCT and QPCTL inhibitor SEN177. Light chains were examined using isoelectric focussing at 24 hours and cell viability was assessed at 48 and 96 hours. Survival as a function of QPCT mRNA expression was assessed within the 977 patients of the COMMPASS cohort using the log-rank test. **Results:** 60% and 73% of heavy and lambda immunoglobulins begin with Q respectively. In comparison, < 1% of kappa light chains begin with Q but 30% begin with E. These features are evolutionarily conserved, being shared with C57BL/6 mice and Rhesus macaques. Isoelectric focussing revealed that treatment with SEN177, reduced the major light chain isoform in lambda secreting cell lines and resulted in the emergence of one new species in U266B1 and two new species RPMI-8226 and L-363. No changes were observed for JJN-3 kappa light chains, nor were changes

observed when using the QPCT selective inhibitor PBD150. Despite higher levels of QPCT transcript being favourably prognostic for overall survival within the COMMPASS cohort ($p = 0.032$), SEN177 and PBD150 had no impact on cell viability in any of the lines tested. **Conclusions:** The strong conservation of N-terminal Q and E in immunoglobulin heavy and light chains suggests functional importance and show they are potential substrates for QPCT(L). We have shown that either QPCT, or more likely QPCTL, modify light chains and that in the absence of their activity, a second modification can occur. Ongoing work will measure light chain secretion via ELISA, characterise the new light chain isoforms with mass spectrometry, and confirm the isoform responsible following knock-down. It remains unclear whether QPCT actively drives MM progression and why higher baseline tumour expression of QPCT is favourably prognostic.

PA-491

The Relationship Between Minimal Residual Disease in Peripheral Blood Autologous Stem Cell Grafts and the Efficacy and Prognosis of Multiple Myeloma

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Introduction: Despite novel anti-cancer therapies, autologous hematopoietic stem cell transplantation (ASCT) remains first-line standard care for eligible multiple myeloma (MM) patients. Post-ASCT relapse remains a major unmet clinical challenge. While graft minimal residual disease (gMRD) prognostic value has been studied for two decades, conclusions remain inconsistent and its clinical utility is not fully established. This study aimed to examine gMRD's association with post-ASCT response depth and long-term outcomes, confirm its independent prognostic value, and evaluate its utility combined with traditional risk stratification systems. **Methods:** This prospective, multi-center cohort study enrolled 176 MM patients undergoing first ASCT between January 2023 and September 2025. gMRD was detected by 10-color flow cytometry (sensitivity: 10^{-6}). Primary endpoints were progression-free survival (PFS) and overall survival (OS). Survival curves were generated by Kaplan-Meier method, with log-rank test for group comparisons. Multivariate Cox proportional hazards model adjusted for age, high-risk cytogenetic abnormalities (HRCA), Revised International Staging System (R-ISS) stage, pre-transplant response, $CD34^+$ cell dose, and autograft absolute lymphocyte count (A-ALC) to verify gMRD's independent prognostic value. **Results:** 176 patients were enrolled. gMRD status was stratified at 1×10^{-6}, with 117 (66.5%) gMRD-negative and 59 (33.5%) gMRD-positive patients. Baseline characteristics were balanced between groups. At 3 months post-ASCT, gMRD-negative patients had significantly higher complete response/strict complete response (CR/sCR) rates, while gMRD-positive patients more often achieved very good partial response (VGPR) ($p < 0.001$). Survival analysis confirmed 1×10^{-6} as the optimal gMRD prognostic cut-off for our detection system. At this threshold, gMRD-negative patients had significantly better PFS ($p = 0.004$), with a clear separation trend in OS curves. Combined analysis of gMRD and traditional risk indicators showed that among HRCA patients, gMRD-negative patients had significantly better PFS ($p = 0.009$); among R-ISS stage III patients, both PFS and OS were significantly better in gMRD-negative patients ($p < 0.001$; $p = 0.038$). Multivariate analysis showed that after adjusting for all confounders, gMRD positivity was an independent adverse prognostic factor for both PFS (HR = 5.55, $p < 0.001$) and OS (HR = 4.85, $p = 0.041$). Subgroup analysis confirmed stable prognostic value of gMRD across all subgroups, including HRCA, R-ISS stage II/III, and age ≥60 years, enabling refined risk re-stratification of high-risk populations. **Conclusions:** gMRD is an independent, reliable prognostic biomarker reflecting tumor burden and predicting deep remission and long-term post-ASCT survival. Combining gMRD with traditional risk stratification significantly improves the accuracy of prognostic evaluation, providing a critical basis for individualized risk stratification and treatment optimization after ASCT.

PA-492

The Role of Prehabilitation in Individuals Undergoing CAR-T Therapy for Relapsed or Refractory Multiple Myeloma

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy has transformed outcomes for patients with relapsed/refractory multiple myeloma (R/R MM). However, benefits are limited by treatment-related toxicities. Published evidence suggests that approximately one-third of CAR-T recipients experience significant skeletal muscle loss within 30 days of infusion. Despite increased recognition of the need for supportive prehabilitation strategies, prehabilitation has not been adopted into standard clinical practice. To improve this clinical gap, we designed a pilot study to evaluate the feasibility, acceptability, and safety of a remote prehabilitation program in

patients with R/R MM considered for CAR-T therapy. **Methods:** This was a single-arm study including older adults (age 60+) with R/RMM considered for CAR-T therapy at Mayo Clinic in Rochester, MN. The intervention utilized a personalized exercise-based prehabilitation program delivered remotely using the Connected mHealth mobile app with at least 4 weeks duration from apheresis until CAR-T infusion, supported by remote physiological monitoring and weekly check-in calls. Primary outcomes included feasibility, acceptability, and safety. Secondary exploratory outcomes included changes in physical function (SPPB), frailty (IMWG and Fried), skeletal muscle mass measured using BIA, and CAR-T-related adverse events. **Results:** Ten participants enrolled in the program from August 2025 to February 2026. The age range was 62–83 years old (median 70 years old); two participants were female. Among those, nine proceeded to CAR T-cell infusion. The intervention duration was 4 to 8 weeks. There were no serious adverse events attributable to the program. Adherence was high, with participants completing a mean of 86.9% of prescribed sessions. Nine of ten participants successfully utilized the mobile application and heart rate monitor throughout the intervention. All patients expressed they had met their functional goals and would suggest program to loved ones. At the time of infusion, all evaluable participants demonstrated improvement in at least one physical function domain following prehabilitation. Four participants continued to demonstrate functional improvements at 30 days post infusion. Skeletal muscle mass increased from baseline to post-prehabilitation in the majority of participants, although declines from baseline mass were observed following infusion. Among infused participants, cytokine release syndrome (CRS) was limited to grade 0–1 events, with no cases of high-grade CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), or 90-day mortality. One participant experienced delayed neurologic toxicity which was resolved with IVIG and steroids. All participants after CAR-T infusion achieved minimal residual disease negativity by day 30. **Conclusions:** In this pilot, the intervention demonstrated feasibility, acceptability, and safety, with preliminary favorable effects on muscle health and physical function.

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The Royal Marsden NHS Foundation Trust Experience of Implementing The Binding Site EXENT Analyser and Its Use in the MyTrack Myeloma Pathway

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Introduction: Multiple myeloma (MM) is a relapsing, remitting, haematological malignancy with ~6000 new UK cases annually. Many patients are on active treatment requiring minimal residual disease (MRD) monitoring via bone marrow (BM) biopsy and serum protein electrophoresis (SPE). SPE measures monoclonal protein (M-protein) but lacks sensitivity and specificity. The EXENT (The Binding Site, part of Thermo Fisher Scientific) uses mass spectrometry to deliver significantly improved sensitivity and specificity. The Royal Marsden NHS Foundation Trust (RMH) became the first UK clinical laboratory to implement the EXENT in April 2026. We describe its implementation and key role within the revolutionary patient-centred diagnostic pathway: MyTrack Myeloma. **Methods:** EXENT uses Matrix-Assisted Laser Desorption Ionisation Time-of-Flight (MALDI-TOF) to quantify, isotype, and track patient-specific M-protein. It has a limit of quantitation of 0.015 g/L and identifies the M-protein unique molecular mass with a precision of ±4 m/z, enabling precise monitoring throughout treatment and beyond, whilst minimising interferences. Challenges to the introduction of the EXENT included: management buy-in, cost (capital and reagents), space, verification, education, nomenclature and IT. MyTrack Myeloma is a precision diagnostic pathway combining comprehensive baseline MRD risk profiling (clonoSEQ next generation sequencing MRD), risk profiling/staging (MMProfiler SKY92), genetics (IMS-IMWG 2025), and peripheral blood MRD via EXENT. This enables a patient's individual risk profile to be identified and treatment adapted accordingly. High-risk patients can receive intensified therapy, while low-risk patients may enter treatment breaks with EXENT-based monitoring. This approach supports improved outcomes, quality of life, and resource utilisation. **Results:** Collaboration with financial, clinical, and senior leadership enabled adoption of this cutting-edge technology in a tertiary specialist cancer centre. Linking the EXENT with other technology to enable a pioneering diagnostic pathway for MM strengthened the business case for the use of expensive reagents. Capital funding was obtained via the RMH cancer charity as the patient benefit was clear. Implementation required staff training and development of new reporting approaches. Verification was a challenge as SPE is not the ideal gold standard, but it highlighted the strengths and limitations of the EXENT. Although MyTrack Myeloma is currently limited to privately insured or self-pay patients, it has been designed to be applicable to all patients, and we are exploring routes for NHS access. **Conclusions:** As MM survival improves, avoiding over- and under-treatment while maintaining quality of life is critical. EXENT, within the MyTrack Myeloma pathway, enables minimally invasive, precise MRD monitoring and supports informed clinical decision-making. Despite implementation challenges, its potential to improve patient outcomes makes it a valuable advancement in MM care.

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The VRD Regimen Improves Clinical Outcome via Overcoming the Adverse Impact of KRAS Mutations in Newly Diagnosed Multiple Myeloma

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Introduction: Multiple myeloma (MM) exhibits profound molecular heterogeneity, with the RAS/RAF pathway mutated in 50% of patients. However, its prognostic significance remains controversial. This study evaluates whether the triplet regimen VRD (bortezomib, lenalidomide, dexamethasone) influences clinical outcomes by affecting the RAS/RAF pathway in newly diagnosed MM (NDMM), and validates the in vitro phenotypic impact of the hotspot KRAS Q61H mutation on drug susceptibility. **Methods:** We retrospectively analyzed 169 NDMM patients with NGS of CD138-sorted plasma cells (April 2019-June 2024). Based on front-line treatment, patients were categorized into a non-VRD group (n = 48; receiving BD, BCD, RD, or ID) and a VRD group (n = 121). Median follow-up was 42.63 months. Response and survival data were analyzed. In vitro, we stably overexpressed the KRAS Q61H mutation via lentiviral transfection in the RPMI-8226 cell line (KRAS-8226), using empty vectors as controls. Cell proliferation and sensitivity to bortezomib (BOR) and lenalidomide (LEN), alone and combined, were monitored via CCK-8 assays. **Results:** The most common mutations of primary sorted plasma cells were KRAS (24.23%), NRAS (14.43%), TP53 (8.25%), and BRAF (6.19%). KRAS was the most prevalent, with Q61H as the core variant (50%). KRAS mutations were not correlated with baseline high-risk factors such as R-ISS III, HRCAs, or TP53 mutation. In the non-VRD group, KRAS mutations were associated with significantly inferior survival outcomes [PFS: P = 0.015; OS: P = 0.107]: 1-year and 2-year PFS rates for KRAS-mutated vs. wild-type were 65% vs. 87% and 36% vs. 73%; 4-year OS rates were 43% vs. 64%. In the VRD group, KRAS-mutated patients exhibited significantly superior PFS(P = 0.001), with 2-year PFS rates of 81.3% vs. 60.7% and 4-year PFS rates sustained at 81.3% vs. 37.0%. Meanwhile, these patients showed an improved trend in OS (P = 0.095), with 4-year OS rates of 89.2% vs. 80.9%. Other mutations (NRAS, BRAF, TP53) in the VRD group did not significantly affect survival outcomes. Multivariable analysis confirmed KRAS mutation as an independent PFS predictor, favorable in VRD but opposite in non-VRD. In vitro, KRAS-8226 cells exhibited exponential proliferation (P < 0.0001) and primary resistance to both bortezomib (BOR IC50 >100 nM) and lenalidomide (LEN IC50 >100 μM) monotherapies. However, combined treatment (40 nM BOR + 100 μM LEN, 72 h) drastically killed mutant cells with impaired viability of 40% (P < 0.0001), demonstrating robust synergistic inhibition. **Conclusions:** Our study suggests that VRD as front-line treatment effectively overcomes the adverse impact of KRAS mutations as in patients with non-VRD regimens and improves survival. In vitro data confirm that KRAS Q61H drives aggressive proliferation refractory to single-agent treatment, while it is effectively reversed by the dual BOR/LEN combination. Further molecular mechanism needs to be investigated.

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Three-Dimensional Single-Cell Telomere Profiling Reveals Distinct Multiple Myeloma and AL Amyloidosis Clones in Overlapping Plasma Cell Disorders

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Introduction: Light-chain (AL) amyloidosis and multiple myeloma (MM) are both clonal plasma cell dyscrasias with distinct biological and clinical features. AL diagnosis still requires demonstration of a monoclonal protein and a confirmatory tissue biopsy showing amyloid deposition. Peripheral blood (PB)–based liquid biopsy approaches for the diagnosis or risk stratification of AL amyloidosis have not been established. We previously demonstrated that three-dimensional (3D) telomere profiling of circulating plasma cells isolated from PB can distinguish MM from AL amyloidosis at diagnosis. This study investigated whether single-cell telomere analysis could identify distinct intrapatient plasma cell subpopulations in clinically overlapping MM/AL cases. **Methods:** Circulating tumor cells (CTCs) were isolated from peripheral blood samples of 22 patients with newly diagnosed MM (n = 17) and AL amyloidosis (n = 5), and their telomere profiles were analyzed using TeloView®. Hierarchical clustering and canonical discriminant analysis were performed using standardized single-cell quantitative telomeric features. Two MM patients with clinically suspected but pathologically unconfirmed AL amyloidosis were selected for additional analysis. 3D-telomere parameters of individual circulating plasma cells from these cases underwent single-cell cluster analysis to evaluate intrapatient clonal heterogeneity and relationship to established MM and AL telomere profiles. **Results:** Consistent with our previous findings, hierarchical cluster analysis of telomeric parameters clearly separated AL amyloidosis from MM profiles, with distinct telomere-based clustering patterns. Two MM cases with strong clinical suspicion for concurrent AL amyloid clustered with the AL amyloidosis cohort. The patients were too sick to undergo a confirmatory biopsy for pathological confirmation of AL amyloidosis, but these two clinically overlapping MM/AL cases were subsequently analyzed at the cell level to investigate potential internal subpopulations. Cell-level clustering of the telomeric profiles identified two distinct clusters in both cases, with CDA showing strong separation

between clusters (Wilks' λ = 0.038 and 0.028, respectively; p < 0.0001 for both analyses). Subsequent comparative analysis demonstrated that one cellular subcluster grouped with MM cases, while the second grouped with AL amyloidosis cases. These findings suggest the coexistence of biologically distinct plasma cell populations with different telomere architectures within individual patients. **Conclusions:** Single-cell spatial 3D telomere profiling of peripheral blood circulating plasma cells identified distinct MM-like and AL-like cellular populations within clinically overlapping cases. These findings, for the first time, demonstrate the ability of telomere-based liquid biopsy analysis to detect intrapatient clonal heterogeneity and suggest its potential utility for non-invasive characterization of complex plasma cell dyscrasias.

PA-496

Thrombin Time Reflects SPI1-Driven Neutrophil Activation and Predicts Inferior Outcomes in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is frequently accompanied by coagulation dysfunction, which manifesting overt bleeding or thrombosis that impacts patient prognosis. Previous researches suggest that myeloid cell inflammatory activation can perturb coagulation homeostasis, implying that coagulation dysfunction may reflect immune cell activation within the bone marrow tumor microenvironment (BM-TME). Whether routine coagulation parameters can serve as accessible clinical surrogates for BM-TME immune status remains unclear. **Methods:** We retrospectively analyzed clinical data from 170 newly diagnosed MM (NDMM) patients. Cox regression analyses identified independent prognostic factors. Bulk RNA sequencing of bone marrow mononuclear cells identified differentially expressed genes, enriched pathways, and key hub genes via protein-protein interaction network analysis. Single-cell transcriptomic data from 27 healthy donors and 173 MM patients were integrated for further characterization. **Results:** Lower thrombin time (TT) was an independent predictor of inferior progression-free survival (HR = 1.575, 95% CI 1.073–2.314, P = 0.021). SPI1 emerged as a central hub gene enriched in myeloid activation and inflammatory pathways, with its target genes highly enriched in neutrophil functional regulation. Immune infiltration analysis demonstrated a significantly higher neutrophil proportion in the low-TT group, while MMRF cohort analysis showed that SPI1 expression was significantly correlated with neutrophil abundance. Single-cell transcriptomic analysis confirmed progressive SPI1 upregulation in BM neutrophils from normal bone marrow to MM (P < 2.2e-16) and identified 6 neutrophil subclusters. The SPI1high subset, characterized by elevated of PTGES, IL1A/IL1B, and CCL3/CCL4, exhibited the strongest inflammatory response signature and was markedly enriched in MM (P < 0.0001). Additionally, a four-variable prognostic model incorporating ISS stage, SPI1 expression, sex, and age achieved a C-index of 0.707 and a 5-year AUC of 0.839 in the MMRF cohort. **Conclusions:** Lower TT is associated with inferior prognosis in MM and may reflect SPI1-driven pro-inflammatory neutrophil activation, linking coagulation dysfunction and immune remodeling. SPI1 own potential value as both a prognostic biomarker and an immunologically relevant therapeutic target in MM.

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Timing and Resolution of Talquetamab-Related Dysgeusia in Relapsed/Refractory Multiple Myeloma (RRMM): Longitudinal Waterless Empirical Taste Test and Patient Reported Outcomes Profiles From TALisman

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Introduction: In MonumenTAL-1, talquetamab (Tal) elicited durable responses in patients (pts) with RRMM. Dysgeusia is common with Tal, but current assessment tools are limited. The Waterless Empirical Taste Test (WETT), an objective tool employing taste strips, is used in TALisman to evaluate taste changes over time and the impact of prophylactic interventions for dysgeusia, including the neurological inhibitor clonazepam. Prior TALisman data showed dysgeusia occurs as early as 2 weeks after Tal initiation and begins to recover 3–4 months after starting Tal. We report updated data from the Tal-only cohort and initial data on clonazepam oral disintegrating tablet as a prophylactic intervention for dysgeusia. **Methods:** The phase 2 ongoing TALisman (NCT06500884) study has been

previously described. Briefly, pts with RRMM receive experimental prophylaxis for 7 days before the first Tal step-up dose or Tal-only as a control. Co-primary endpoints are incidence of dysgeusia and severe dysgeusia, time to severe dysgeusia, and dysgeusia improvement at the end of 3 and 7 months per WETT. **Results:** As of April 2026, 84.0% of 25 pts in the Tal-only cohort completed ≥3 cycles and 52.0% completed ≥6 cycles; 92.9% and 7.1% of 14 pts in the clonazepam (Tal+clon) cohort completed ≥3 and ≥6 cycles, respectively. Across cohorts, median age was 65.0 yrs; 59.0% were male. Adverse events led to dose modifications of Tal in 52.0% (Tal-only) and 64.3% (Tal +clon). By WETT, dysgeusia (any severity) occurred in 84.0% of pts with Tal-only and 92.9% with Tal+clon. Severe dysgeusia occurred in 56.0% and 85.7%, respectively. Median time to dysgeusia was 8 (Tal-only) and 4 days (Tal+clon); median time to severe dysgeusia was 75 and 8 days, respectively. The highest rates of dysgeusia/severe dysgeusia by WETT (Tal-only) occurred at cycle 3 (71.4%). The component WETT scores (Tal-only) with the highest mean change from baseline at timepoints through cycle 3 were sweet (–3.13), salty (–2.95), and sour (–2.18). Improvement in dysgeusia (any severity) was observed in 58.8% of pts with Tal-only and 58.3% with Tal+clon at the end of month 3, and in 66.7% (Tal-only) at the end of month 7. Further data on WETT taste components, patient-reported taste function, and oral health experience will be presented at the congress. **Conclusions:** Dysgeusia by WETT improves as early as 3 months after Tal initiation, with 67% showing improvement after 7 months. Clonazepam prophylaxis did not improve incidence, onset, or resolution of dysgeusia, although low numbers limit definitive conclusions. The highest proportion of pts with dysgeusia/severe dysgeusia by WETT occurred during cycle 3, with the largest changes observed in the sweet, salty, and sour components of the taste profile. The innovative study design of TALisman enables investigation of additional prophylactic interventions for dysgeusia to help clarify expectations for pts, caregivers, and healthcare providers, and facilitate ongoing treatment and clinical benefit from Tal.

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Tissue-Defined Antigen-Immune States Reveal Actionable Evolution in Extramedullary Myeloma

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Introduction: Extramedullary multiple myeloma (EMD-MM) is a major mode of failure after T-cell-redirecting therapy. Sequencing after BCMA or GPRC5D exposure often assumes linear antigen loss, yet EMD may behave as a tissue-compartmentalized ecosystem in which target expression, gene dosage and immune access evolve independently of archival marrow data. We explored whether serial EMD profiling could define decision-relevant antigen-immune states for adaptive cellular therapy. **Methods:** In an investigator-initiated prospective precision cellular-therapy cohort, 8 patients with relapsed/refractory MM and biopsy-confirmed EMD underwent repeat EMD or paired marrow/EMD assessments at prospectively defined disease or treatment-decision timepoints. IHC assessed BCMA, GPRC5D, CD38, CD138, CD19 and CD70. Available specimens underwent flow cytometry, multiplex IHC for CD3/CD8/PD-1, and targeted testing of immune-target or escape genes. Profiles were interpreted before treatment allocation to support target confirmation, avoidance, re-entry or investigational antigen use. **Results:** Median age was 58 years (range, 46–71); 5 patients were female. EMD involved soft tissue, chest wall, pelvic/iliac, breast/chest-region and combined marrow/soft-tissue sites. Serial profiling identified four clinically relevant states. First, target extinction was documented: one post-immunotherapy lesion showed GPRC5D copy-number loss (1.14 copies) with near-absent protein, supporting avoidance of GPRC5D escalation. Second, target attenuation was observed after BCMA-directed pressure, with GPRC5D decreasing from 40% to 5% and from 50% to undetectable in two patients. Third, target gain occurred, as one patient acquired GPRC5D expression from 0% to 50% after BCMA CAR-T failure, creating a new actionable window. Fourth, noncanonical target emergence was seen: BCMA ranged from lesion-level loss to high expression (80%-90%), one BCMA-dim lesion showed focal CD19 co-expression of approximately 70%, and bilateral EMD lesions in one patient expressed CD70 at 70%-80%. These findings changed, refined or contraindicated candidate targets in real time. Evaluable microenvironment studies showed immune-sparse/excluded lesions, with CD3+ cells 0.92%-15.76%, CD8+ cells 0.09%-0.51% and low PD-1/CD3 co-localization (< 6%). Target-concordant decisions were followed by serologic or radiographic benefit in selected cases, whereas poor immune fitness, heavy tumor burden or infection limited benefit despite target availability. **Conclusions:** Serial EMD profiling reveals that post-immunotherapy relapse is not a simple linear antigen-loss event, but a tissue-defined antigen-immune ecosystem shaped by target extinction, attenuation, gain, ectopic expression and immune exclusion. Real-time lesion-based remapping can govern target selection and avoidance beyond archival marrow data, providing a translational framework for adaptive cellular therapy in immune-refractory EMD-MM.

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TNFRSF17 Fusions as Clonal Drivers in Newly Diagnosed Multiple Myeloma

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Introduction: B cell maturation antigen (BCMA), a key regulator of B cell proliferation and survival, is preferentially expressed on mature B lymphocytes and plasma cells and notably overexpressed on multiple myeloma (MM) plasma cells. Encoded by TNFRSF17

(16p13.3), BCMA, specifically its extracellular domain (ECD), is a central therapeutic target of CAR T cell, bispecific antibody and antibody-drug conjugate therapies in MM. Structural TNFRSF17 alterations have predominantly been described as acquired resistance mechanisms following BCMA-directed therapy, typically involving biallelic deletions or mutations in the ECD. TNFRSF17 alterations in newly diagnosed MM (NDMM) are less well described but primarily involve monoallelic 16p deletions. Activating TNFRSF17 fusions at diagnosis, prior to BCMA-targeted therapy, have not been mechanistically characterized. **Methods:** NA. **Results:** Here we present a case of a 66 year-old female with IgA kappa NDMM in the setting of anemia and rising M-spike. Molecular profiling identified t(11;16)(p11;p13) [MDK::TNFRS17] fusion mRNA. The breakpoint of TNFRS17 occurred at exon 2, with exon 1 (encodes the ECD) missing in the fusion. The breakpoint of MDK occurred at exon 3, resulting in the MDK promoter driving transcription of the fusion product. The elimination of the ECD and the preserved transmembrane domain and cytoplasmic signaling tail predicts a ligand-independent signaling through spontaneous receptor clustering and TRAF recruitment, leading to constitutive activation of TNF receptor signaling pathways. Functional transcriptomic profiling of the patient's tumor demonstrated a non-canonical NF-κB activation signature with NFKB2 elevated 3.1-fold relative to median MM of an internal cohort ($Z = 3.4$), while the canonical pathway negative-feedback target NFKBIA was reduced to 0.30 of median ($Z = -0.75$) and NFKB1 remained at baseline ($Z = 0.36$). TRAF2 and TRAF3 transcripts were elevated 7.6-fold ($Z = 2.9$) and 5.7-fold ($Z = 3.2$) respectively, consistent with compensatory upregulation in the setting of chronic receptor-recruited proteasomal degradation of the TRAF2/TRAF3/cIAP complex. This molecular pattern is mechanistically distinct from the TRAF3-deletion subset of MM, in which TRAF3 transcript is reduced rather than elevated. A similarly noteworthy NDMM case was identified involving del(16)(p12.3p13.13) [RPS15A::TNFRSF17], in which the ubiquitously expressed RPS15A promoter drove transcription of TNFRSF17. **Conclusions:** Pre-treatment TNFRSF17 structural alterations have generally been described as loss-of-function events. These patients, with distinct pre-treatment TNFRSF17 fusions reframe this outlook, with these fusions serving as potential drivers of disease in NDMM. Here, we describe a novel mechanism of constitutive non-canonical NF-κB signaling. This case suggests that BCMA-targeting therapies may be less effective due to the splicing out of the ECD. This underscores the importance of comprehensive RNA profiling prior to utilizing BCMA-directed therapy.

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TP53 Isoform Switching Defines Functional States and Clinical Risk in Multiple Myeloma

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Introduction: TP53 alterations are established drivers of high-risk multiple myeloma (MM), yet they do not fully explain the biological and clinical heterogeneity observed in patients lacking canonical TP53 lesions. Alternative TP53 isoforms generated through promoter usage and splicing may represent an additional regulatory layer influencing p53 pathway activity. We investigated whether TP53 isoform expression defines biologically distinct functional states with prognostic relevance in newly diagnosed MM (NDMM). **Methods:** RNA sequencing data from 659 NDMM patients enrolled in the MMRF CoMMpass study were analyzed to quantify major TP53 isoforms, including p53FL, p53β, p53γ, Δ40p53α, Δ133p53α, and Δ133p53β. Isoform expression patterns were integrated with genomic, cytogenetic, and clinical data. Survival analyses were performed using Kaplan–Meier and multivariable Cox regression models. **Results:** TP53 isoform expression was highly heterogeneous across the cohort. p53FL and p53β were nearly universally expressed (95% and 99%, respectively), while co-expression of ≥3 isoforms occurred in 83% of patients. Isoform number was not associated with treatment response; however, Δ40p53α and Δ133p53β expression were significantly enriched in TP53 wild-type and del(17p)-negative cases ($p < 0.0001$). Notably, Δ133p53β expression was almost exclusively detected in p53FL-low/absent samples and consistently displayed high Δ133p53β/p53FL ratios ($p < 0.001$), suggesting a transcriptionally dominant state associated with constrained canonical p53 signaling. An integrated TP53 isoform-based classifier incorporating p53FL, p53β, p53γ, Δ133p53β, and cytogenetic features identified favorable ($n = 170$), intermediate ($n = 474$), and poor-risk ($n = 15$) groups. Compared with the favorable group, intermediate- and poor-risk patients showed significantly shorter progression-free survival (PFS) (HR 1.29, $p = 0.037$; HR 2.55, $p = 0.002$) and overall survival (OS) (HR 1.40, $p = 0.034$; HR 3.51, $p < 0.001$). Median overall survival was 102.4, 96.0, and 31.2 months, respectively. The classifier retained independent prognostic significance beyond established genomic staging systems, including International Myeloma Working Group-Consensus Genomic Staging (IMWG-CGS) (OS HR 2.86, $p = 0.029$), and identified an ultra–high-risk subgroup in combination with ISS stage III disease (interaction HR 3.95, $p = 0.035$). **Conclusions:** TP53 isoform balance defines distinct transcriptional and functional states in MM independent of canonical TP53 genomic alterations. In particular, Δ133p53β identifies a transcriptionally rewired, high-risk phenotype associated with markedly inferior survival. These findings establish TP53 isoform architecture as a novel layer of MM biology and support incorporation of isoform profiling into future molecular risk stratification frameworks. Acknowledgments AIRC19-IG22059, BolognAIL OdV.

PA-501

Transcriptomic Profiling Reveals t(11;14)-like Gene Expression Signature Predictive of Venetoclax Sensitivity in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is an incurable hematologic malignancy typically characterized by cytogenetic lesions detected by fluorescence in situ hybridization (FISH). Patients with t(11;14) often show higher BCL-2 expression and sensitivity to the BCL-2 inhibitor venetoclax. However, not all t(11;14)-positive patients respond, making FISH-based detection alone an imperfect biomarker. We hypothesize that venetoclax sensitivity is associated with a broader transcriptomic program that predicts drug response with greater precision than t(11;14) positivity by FISH. **Methods:** Ex-vivo drug response and RNA sequencing (RNA-seq) data were obtained from a Moffitt Cancer Center cohort (n = 111). Venetoclax response was quantified by integrating cell viability over 0–96 hours at the highest tested dose using the trapezoidal rule (AUC). Patients in the 1st (n = 37) and 3rd (n = 38) AUC tertiles were labelled sensitive or resistant respectively. A random forest classifier was trained on Moffitt RNA-seq using features characteristic of t(11;14) and applied to an external validation cohort with RNA-seq and ex-vivo drug response data (n = 39), assessed by ROC-AUC and F1 score. Differential expression, transcription factor inference, and gene set enrichment analysis (GSEA) were applied to characterize transcriptomic differences between response groups and evaluate classifier output. **Results:** Differential expression and transcription factor inference revealed venetoclax-sensitive patients were characterized by apoptotic regulation and immune engagement signatures, while resistant patients showed enriched proliferation and poorly differentiated tumor states. The classifier achieved ROC-AUC of 0.74 and F1 of 0.68 on Moffitt data (two-fold cross-validation), significantly outperforming t(11;14) FISH status within the cohort (McNemar's test, p = 0.002), and generalized well to the external cohort(ROC-AUC = 0.62, F1 = 0.67). Highly predictive features included chromosome 11 and 14 genes (e.g., CD3E, GPR135) and mitochondrial calcium signaling genes (e.g., SLC25A23). GSEA of correctly classified samples demonstrated sensitive patients were enriched for apoptotic pathways (KRAS, NF-kB) and resistant patients for proliferative programs (MYC, E2F, cell-cycle regulation). **Conclusions:** These findings suggest venetoclax sensitivity in t(11;14) myeloma is associated with a broader transcriptional program characterized by apoptotic priming and plasma cell differentiation, while resistance is associated with MYC-associated proliferative states. The transcriptome-based classifier outperformed t(11;14) FISH status and highlights the need for clinical validation to determine whether this approach predicts patient response in vivo.

PA-502

Transplant Utilisation Disparities Do Not Translate to Survival Disadvantage: Myeloma Outcomes in an Ethnically Diverse, Real-World South-East London Cohort

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Introduction: Autologous stem cell transplantation (ASCT) remains a cornerstone of first-line treatment for transplant-eligible multiple myeloma (MM). US studies have documented significantly reduced ASCT access among Black patients, yet those receiving equivalent treatment demonstrate equal or superior outcomes compared with White patients. South-East London has a distinctively diverse demographic profile. Building on our prior observation of lower ASCT utilisation among Black patients at our centre, this study examines whether that disparity translates into inferior long-term survival. **Methods:** We included transplant-eligible patients aged < 75 years diagnosed with MM between January 2013 and December 2022 at King's College Hospital and Princess Royal University Hospital. High-risk (HR) cytogenetics were classified according to the IMWG 2025 criteria. **Results:** 688 patients were analysed: 449 White, 167 Black, 33 Asian, 8 Mixed, and 31 Other. Mean age was 60.1 [30–74] years. Black (57.1 years) and Asian (54.2 years) patients were significantly younger than White patients (61.6 years). ASCT uptake was 70% in White, 54% in Black, and 82% in Asian patients — a disparity that persisted after adjustment for age, sex, deprivation, and cytogenetics (OR 0.35, 95% CI 0.23–0.54, p < 0.001 for Black vs White). Fifty-two percent of Black patients resided in the most deprived areas (IMD tertile 1) versus 15% of White and 27% of Asian patients. HR cytogenetics were identified in 21% of tested White, 17% of Black, and 16% of Asian patients. Median overall survival (OS) was 84.5 months for White, 122.6 months for Black, and not reached for Asian patients (log-rank p = 0.216). On multivariable logistic regression adjusted for age, sex, IMD, cytogenetics, and ethnic category, Black (OR 0.63, 95% CI 0.41–0.99, p = 0.042) and Asian patients (OR 0.38, 95% CI 0.15–0.96, p = 0.041) had significantly lower odds of death compared with White patients. Age, sex, and IMD were not independent predictors of mortality. HR cytogenetics was the strongest predictor of death (OR 4.46, 95% CI 2.74–7.26, p < 0.001). ASCT uptake was not independently associated with overall mortality. **Conclusions:** Despite marked disparities in ASCT

utilisation — with Black patients 65% less likely to receive transplant — OS was not significantly worse. Adjusted mortality odds were in fact lower, for Black and Asian patients compared with White patients. These findings are consistent with emerging evidence that, within a treated cohort, survival outcomes in Black patients are equivalent or superior once disease biology is accounted for. HR cytogenetics, not ethnicity or transplant status, was the dominant determinant of mortality. Limitations include the absence of progression-free survival data and comorbidity adjustment, and the relatively young age of Black patients may partly explain the OS advantage. A national multicentre study is needed to evaluate ASCT utilisation and ethnic disparities in survival across the UK.

PA-503

Treatment Deliverability Rather Than Chronologic Age Predicts Survival in Very Elderly Patients With Newly Diagnosed Multiple Myeloma: A Multicenter Real-World Study From China

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Introduction: Patients aged 80 years or older with multiple myeloma (MM) are substantially underrepresented in clinical trials. Consequently, treatment decisions are often influenced more by chronologic age than by disease biology or treatment feasibility. We evaluated clinical outcomes and prognostic factors in a multicenter cohort of very elderly patients with MM, with particular focus on treatment deliverability. **Methods:** We retrospectively analyzed 117 patients aged ≥80 years diagnosed with MM between 2013 and 2025 across eight Chinese centers. Survival outcomes were assessed according to age, ISS stage, and receipt of ≥4 treatment cycles. Cox regression, 4-month landmark analysis, treatment-deliverability analysis, and early-mortality assessment were performed. **Results:** The median age was 83 years (range, 80–92), and 76 patients (65.0%) were male. Eighty-seven patients (74.4%) were aged 80–84 years and 30 (25.6%) were aged ≥85 years. Among evaluable patients, ISS stage III, R-ISS stage III, and high-risk FISH were present in 68.3%, 31.4%, and 11.4% of patients, respectively. Forty-one patients (35.0%) received ≥4 treatment cycles. Among 113 OS-evaluable patients, the median follow-up was 43 months (range, 1–111) by the reverse Kaplan-Meier method. Median PFS and OS were 29 and 38 months, respectively, with 1-year and 2-year OS rates of 79.3% and 63.8%. No significant differences in PFS or OS were observed between patients aged 80–84 years and those aged ≥85 years. In contrast, patients with ISS stage III disease had significantly inferior PFS and OS compared with those with ISS stage I/II disease. High-risk FISH was not significantly associated with either endpoint. Receipt of < 4 treatment cycles was strongly associated with inferior survival. In multivariable analysis adjusting for age, sex, and ISS stage, receipt of < 4 cycles remained independently associated with worse OS (HR 2.657, 95% CI 1.362–5.184; P = 0.004). ISS stage retained independent prognostic significance for both OS and PFS, whereas age group was not independently associated with either endpoint. To address potential guarantee-time bias, a 4-month landmark analysis was performed among patients alive at 4 months. Receipt of ≥4 cycles remained associated with superior OS from the landmark (median OS, 53 vs 27 months; HR for < 4 cycles, 2.528; 95% CI 1.320–4.844; P = 0.004). To explore factors influencing treatment deliverability, logistic regression analysis was performed. Serum albumin < 35 g/L was associated with a lower likelihood of receiving ≥4 treatment cycles (OR 0.458, 95% CI 0.211–0.996; P = 0.049). Thirty-day and 90-day mortality rates were 0.9% (1/114) and 7.0% (8/114), respectively. **Conclusions:** Survival in very elderly MM patients was driven more by disease stage and treatment deliverability than by chronologic age. Strategies that improve treatment feasibility may enhance outcomes in this growing population.

PA-504

Treatment-Naïve GPRC5D-Negative Multiple Myeloma With t(11;14)

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Introduction: GPRC5D is one of the main actionable markers for immunotherapy development, particularly CAR T-cells and T-cell engagers. These have shown remarkable efficacy in relapsed/refractory multiple myeloma (RRMM), with response rates of 70–80%. However, a subset of treatment-naïve patients exhibits primary refractoriness due to the absence of GPRC5D expression, representing an uncharacterized population with distinct biological features. **Methods:** We analyzed whole-exome, whole-genome, and RNA sequencing data from 549 newly diagnosed myeloma (NDMM) patients in the CoMMpass study to identify those with low GPRC5D expression. Clinical validation was performed in 32 RRMM patients enrolled in two anti-GPRC5D CART trials (NCT04555551,

NCT05431608) and 117 patients treated with Talquetamab. GPRC5D protein expression was assessed by the MSKCC immunohistochemistry (IHC) assay. **Results:** Low GPRC5D RNA expression was observed in 54/549 (9.8%) NDMM patients, with only 16.4% (9/54) harboring GPRC5D deletions. These were typically monoallelic and large, in striking contrast to the focal and often biallelic GPRC5D alterations observed in RRMM patients progressing after anti-GPRC5D therapies. These patients also showed significant enrichment for t(11;14) ($p < 0.0001$), a low presence of high-risk features (ie, TP53 or gain1q), and displayed Cyclin 2 (CD2)-like gene expression programs characteristic of B-cell-like myeloma. In the subsequent clinical validation, 26 RRMM patients under anti-GPRC5D CART were assessed by IHC and FISH; all negative cases but one (ie, low tumor content) exhibited t(11;14) and demonstrated primary refractoriness with significantly shorter progression-free survival. In line with prior findings (Gupta et al. Blood 2021), all four refractory B-cell-like t(11;14) patients subsequently responded to Venetoclax. As additional validation, in the Talquetamab cohort (n = 117), patients with t(11;14) and prior Venetoclax sensitivity showed no GPRC5D expression and primary refractoriness to anti-GPRC5D. **Conclusions:** This study identifies a strong association of GPRC5D negativity with a t(11;14), B-cell-like profile, and genomically indolent myeloma subgroup, potentially conferring refractoriness to anti-GPRC5D therapy. As this group accounts for 10% of NDMM, and GPRC5D protein measurement can be performed by IHC, this represents a feasible and accessible biomarker for immunotherapy selection in myeloma. Importantly, these patients usually have a genomically indolent profile and are particularly sensitive to anti-BCMA therapies (Maura et al. BiorXiv 2025). The integration of FISH and IHC is ready for clinical use and could be very helpful in optimizing treatment allocation while avoiding ineffective therapies and associated toxicities.

PA-505

Treatment of Waldenstrom Macroglobulinemia Associated With AL Amyloidosis With Teclistamab

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Introduction: Waldenström macroglobulinemia (WM) is a rare indolent B-cell lymphoma. Immunoglobulin-related AL amyloidosis is an uncommon but severe complication, affecting approximately 3% of WM patients and conferring a poor prognosis. Rapid and deep elimination of pathogenic light chains is critical for organ recovery. However, treatment options remain limited for patients with relapsed/refractory WM complicated by AL amyloidosis. BCMA is highly expressed on lymphoplasmacytic lymphoma/WM tumor cells, representing a promising therapeutic target. **Methods:** We report a 50-year-old female patient with WM who developed progressive IgM-λ–associated systemic AL amyloidosis (cardiac involvement) after zanubrutinib and bendamustine-rituximab treatment. The patient had high BCMA expression (97.38%) on bone marrow lymphoplasmacytic cells and was treated with the BCMA-targeted bispecific antibody teclistamab. **Results:** Teclistamab induced a rapid and deep hematologic response: dFLC normalized within 4 weeks; IgM decreased from 24.38 g/L to 0.3 g/L; serum and urine immunofixation became negative. The patient achieved very good partial response (VGPR). Clinically, cardiac function improved significantly with recovery of global longitudinal strain (GLS), and hoarseness was relieved. The treatment was manageable with grade 2 cytokine release syndrome (CRS) resolved by tocilizumab. **Conclusions:** To our knowledge, this is the first report demonstrating that teclistamab can induce rapid, deep, and durable hematologic and organ responses in a patient with WM-associated AL amyloidosis. BCMA-targeted therapy represents a novel and effective strategy for this high-risk population, supporting further clinical development.

PA-506

Treatment Outcomes in Primary Plasma Cell Leukaemia: A Single-Centre Experience of Novel Therapeutic Modalities Including Haploidentical Transplantation and Bispecific Antibody Therapy

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Introduction: Plasma cell leukaemia (PCL) is a rare and aggressive plasma cell dyscrasia defined by ≥5% circulating plasma cells per the 2021 IMWG criteria, classified as primary (pPCL) or secondary (sPCL). Despite advances including daratumumab-based induction regimens, outcomes remain dismal. We present a single-centre retrospective analysis of pPCL, with a focus on novel treatment strategies including haploidentical allogeneic stem cell transplantation (allo-SCT) and bispecific antibody therapy. **Methods:** We performed a retrospective review of all patients with pPCL managed at a single tertiary referral centre (King's College Hospital, London) between 2021 and 2026. Three patients had been diagnosed under pre-2021 PCL diagnostic criteria. **Results:** Ten patients were included; median age at diagnosis 58 years (range 38–78), 90% male, with heterogeneous ethnic backgrounds (3 White, 4 Black, 3 unstated). Median follow-up was 29.6 months (range 9.3–137.1). Lines of therapy received: 1 line (n = 3), 2 lines (n = 3), 4 lines (n = 2), 5 lines (n = 2). Induction regimens comprised D-VTD (n = 6), KRD via HOVON-129 (n = 1), VCD→CRD (n = 1), and VTD→DT-PACE (n = 2). High-dose melphalan (MEL200) auto-SCT was performed in 80% of patients, including one tandem auto-auto SCT. Five patients underwent tandem auto-allo SCT; donors comprised one matched sibling, one voluntary unrelated donor, and three haploidentical donors. Two patients received elranatamab: one achieved their first complete remission (CR) at fifth-line therapy and subsequently

proceeded to allo-SCT; the other demonstrated a response at fourth line despite active CNS disease infiltration. Median overall survival (OS) was 53.7 months; OS rates at 12, 24, and 36 months were 100%, 83%, and 83%, respectively. Notably, two patients who relapsed following allo-SCT achieved deep remission with further lines of therapy. Four deaths occurred: one following relapse after third-line therapy; two following haploidentical transplantation; and one from intracranial haemorrhage secondary to thromboprophylaxis during fifth-line therapy (OS 137.1 months). **Conclusions:** These findings suggest that the incorporation of novel treatment modalities may improve outcomes in pPCL. Allo-SCT appeared to confer durable benefit even following post-transplant relapse, consistent with ongoing graft-versus-myeloma immune surveillance. Haploidentical transplantation expands donor availability for patients from ethnic minority backgrounds — particularly Black patients, who face a disproportionately elevated risk of pPCL. Nevertheless, further refinement of haploidentical transplant protocols is required to mitigate treatment-related mortality. Elranatamab demonstrated clinically meaningful activity at later lines of therapy, including in the context of CNS disease infiltration. Extended follow-up will be necessary to establish the durability of these responses, and prospective validation in larger cohorts is warranted.

PA-507

Treatment Patterns and Outcomes in Primary Plasma Cell Leukemia: A Single-Center Case Series

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Introduction: Primary plasma cell leukemia (pPCL) is an aggressive plasma cell neoplasm with poor outcomes. pPCL patients are excluded from randomized trials, and optimal treatment sequencing remains unclear. Proteasome inhibitor–immunomodulatory drug (PI-IMiD) combinations with anti-CD38 antibodies and autologous stem cell transplantation (ASCT) may improve outcomes [1]. We report a retrospective review of pPCL patients treated with daratumumab-based quadruplet (DQ), ASCT, during induction and maintenance of pPCL. **Methods:** We conducted a retrospective study of 11 patients diagnosed with pPCL per IMWG criteria at our institution from 2021 to 2026. Baseline demographics, laboratory data, cytogenetics, R-ISS staging, treatment regimens, best response per IMWG response criteria, ASCT status, and survival outcomes were studied. Descriptive statistics were used to summarize patient characteristics and outcomes. **Results:** The median age at diagnosis was 65 years (range 58–82); 7 (63.6%) were female, and 10 (91%) were non-Hispanic. High-risk cytogenetics were seen in 9 (81.8%) patients. 9 (81.8%) patients had beta 2 microglobulin ≥ 5.5. The median LDH was 335 U/L. R-ISS staging was III in 91%. Cytotoxic regimen (CyBorD 45.5%; VTD-PACE 27.3%) was used initially if patients exhibited acute organ failure at presentation, followed by daratumumab-based combinations (Dara-KRd or Dara-VRd). All 11 patients (100%) received DQ therapy during their treatment course, 5 (45.5%) patients received one cycle of cytotoxic chemotherapy followed by transition to DQ as frontline therapy, and 2 (18%) patients received upfront DQ. Six patients (54.5%) underwent ASCT. The overall response rate was 63.4% (n = 7). Of responders, 1 (14.2%) had a complete response, 5 (71.4%) had VGPR, and 1 (14.2%) had PR. Two patients (18%) developed progressive disease, of whom one received talquetamab as a bridge to CAR-T cell therapy. At a median follow-up of 13.2 months (range 1–38), 9 (81.8%) remained alive. Progression-free survival events were observed in 4 of 9 (44.5%), while 5 (55.6%) patients remained progression free. 2 of 11 patients (18%) developed early aggressive relapse and succumbed to progressive disease. Median overall survival (OS) was not reached. **Conclusions:** In this retrospective review of pPCL, DQ regimens were universally incorporated into therapy. ASCT was performed in the majority of patients. Updated disease status will be provided at the time of conference. Our data adds to the growing body of real-world evidence supporting anti-CD38–based strategies with ASCT consolidation in pPCL.

Reference

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PA-508

Trends and Disparities in Infection Associated Mortality Among Older Adults with Multiple Myeloma: A CDC WONDER Analysis from 1999 to 2023

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Introduction: Multiple myeloma (MM) associated immune dysfunction and treatment related immunosuppression confer an increased susceptibility to infection related mortality. However, population level longitudinal trends and demographic disparities remain incompletely characterized. This study examined national mortality trends from 1999 to 2023 among older adults with MM to identify vulnerable populations and inform targeted infection prevention strategies. **Methods:** CDC WONDER data were extracted using ICD-10 codes for MM (C90.0) and infectious causes including sepsis (A40–41), fungal infections (B35–49), pneumonia (J12–J18), and urinary tract infections (N39.0). Age-adjusted mortality rates (AAMR) per 1,000,000, standardized to the 2000 U.S. population, were calculated among adults aged ≥65 years. Temporal trends were

assessed using Joinpoint regression from 1999 to 2023. Analyses were stratified by sex, race/ethnicity, state and place of death. **Results:** A total of 37,560 infection associated deaths occurred among MM patients. The majority of deaths occurred in medical facilities (77.8%), followed by nursing or long term care facilities (7.7%). Overall AAMR decreased from 1999 to 2018, increased transiently during 2018 to 2021 (APC +3.63%), and then declined sharply to near pre-2018 levels. Among males, AAMR declined from 55.2 in 2004 to 40.9 in 2012 (APC −3.81%; $p < 0.05$), followed by reversal with an increase to 42.3 in 2020. Female mortality demonstrated a sustained downward trend, decreasing from 31.4 in 2004 to 23.1 in 2011 (APC −3.37%; $p < 0.05$) and further to 20.6 in 2023 without reversal. Across racial groups, Non-Hispanic Black populations consistently exhibited nearly double the AAMR compared with other groups. From 1999 to 2012, AAMR declined significantly among both Non-Hispanic Black (APC −3.02%; $p < 0.05$) and Non-Hispanic White populations (APC −3.30%; $p < 0.05$), followed by stabilization among Non-Hispanic Whites and a modest increase among Non-Hispanic Blacks. In contrast, Hispanic or Latino populations demonstrated a sustained decline from 1999 to 2023 (APC −1.29%; $p < 0.05$). State level AAMRs varied widely, with rates in the District of Columbia nearly threefold higher than in Maine. **Conclusions:** Infection related mortality among older MM patients declined from 1999 to 2018 but increased during 2018–2021. Racial and geographic disparities persisted throughout the study period. Despite advances in treatment, MM patients remain vulnerable to surges in infection related mortality in the setting of emerging infectious threats. Certain subgroups bear a disproportionately high infection related mortality burden. Targeted prevention strategies, improved infection management, and further investigation are therefore needed to reduce infection related mortality across the MM population.

PA-509

Trial in Progress: Isatuximab and Iberdomide as Immunotherapy for High-Risk Smouldering Myeloma – The UK Myeloma Research Alliance MODIFY Clinical Trial

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Introduction: Interventional strategies for smouldering myeloma (SMM) have the potential to transform outcomes in myeloma but the optimal approach remains debated. Intensive regimens e.g. GEM-CESAR, are aimed at cure and have shown deep responses, but not all patients sustain MRD negativity or remain progression free. Immunomodulatory approaches with single agents, such as AQUILA, prolong time to progression but with modest depths of response. Our recent observations on T cell differentiation in SMM suggest that loss of immune control may be critical in the progression to myeloma. We designed the MODIFY trial using immunotherapies that induce deep responses while also acting to restore/enhance anti-tumour immune function thus improving survival. **Methods:** MODIFY is a multicentre phase 2 single-arm interventional study in SMM, based on the IMWG 4 category risk model, i.e. 20/2/20 plus high-risk cytogenetics. Patients are diagnosed with intermediate or high-risk SMM within 2 years of study entry or diagnosed with SMM within 5 years but only intermediate or high risk within the last 2 years. Patients receive isatuximab (1400 mg subcutaneous), iberdomide (Cereblon E3 ligase modulator, 1.0 mg) and dexamethasone (20 mg) for a fixed duration of 2 years (26 cycles). Isatuximab is given QW during cycle 1, Q2W in cycles 2–13 and Q4W in cycles 14–26. Iberdomide is given D1–21 in cycles 1–26 with dexamethasone 20 mg once weekly in cycles 1–4 only. Follow-up duration is 3 years. Co-primary endpoints are treatment deliverability, measured by treatment discontinuation before completion of 26 cycles and efficacy, measured by best overall response rate (ORR) by the end of treatment. Secondary endpoints include progression free survival (PFS) (defined as development of CRAB or SLiM CRAB), time to biochemical progression, MRD negativity rates, best ORR to subsequent therapy and overall survival. Patients with biochemical progression will be restaged and may continue on study if CRAB or SLiM-CRAB features remain absent. It is important to understand QoL impacts of therapy in SMM. In addition to using EORTC QLQ-C30, EORTC-MY20 and EQ5D-3L tools, we have designed bespoke questionnaires in partnership with patient and public involvement. Views on how SMM affects aspects of patients' lives, risk, perceived advantages and disadvantages of treatment, treatment effects and duration and ongoing QoL will be captured alongside reasons for declining the MODIFY study.Translational studies will investigate tumour genomics, effects of therapy on innate and adaptive immune function, and correlatives with depth of response and timing to progression to overt myeloma. A key strength of MODIFY will be the use of a parallel cohort from COSMOS, a prospective UK MRA multi-centre observational study of SMM to act as a control.Trial progress: Ten patients have been recruited with a target of 63. Last patient first visit is projected in November 2027. **Results:** n/a. **Conclusions:** n/a.

PA-510

Trial in Progress: Phase 1 Trial of Arlocabtagene Autoleucel (Arlo-cel) Plus Mezigdomide (MEZI) or Elranatamab (ELRA) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Arlo-cel (BMS-986393) is an investigational GPRC5D-targeted CAR T cell therapy being studied in RRMM. MEZI is an investigational, oral CELMoD optimized for maximal Ikaros/Aiolos degradation in MM. ELRA is a bispecific BCMA-directed CD3 T-cell engager (TCE) that redirects T cells to BCMA-expressing MM cells. All three have distinct tumoricidal mechanisms; MEZI and ELRA are also immunostimulatory. ELRA can stimulate endogenous T cells, and MEZI can enhance endogenous and CAR T cells; based on preclinical data, a TCE or CELMoD plus arlo-cel may enhance the depth and/or durability of response. This multiarm trial (NCT06121843) evaluates arlo-cel combinations, including with MEZI (arm B) or ELRA (arm D) as maintenance therapy, to determine safety and tolerability, establish each combination's recommended phase 2 dose (RP2D), and evaluate efficacy and PK in pts with RRMM. **Methods:** This multicenter, open-label, phase 1 trial comprises dose finding (part 1) and dose expansion (part 2) cohorts. Eligible pts are ≥18 y with measurable RRMM and ECOG PS of 0–1. Pts must have received ≥3 (part 1) or 1–3 (part 2) prior antimyeloma regimens. Prior therapies must include an IMiD, proteasome inhibitor (PI), anti-CD38 monoclonal antibody, and if eligible, auto-HSCT (part 1) or an IMiD and PI (part 2). Key exclusion criteria are prior GPRC5D-targeted therapy (arms B and D), MEZI (arm B), ELRA (arm D), and BCMA-targeted therapy (part 2, arm D). Bridging therapy may be given before lymphodepletion, prior to arlo-cel infusion. In part 1, pts will receive an arlo-cel IV infusion on day 1 (D1; 75 × 106 [dose level 1] or 150 × 106 [dose level 2]). MEZI or ELRA may begin on D60 after arlo-cel. MEZI (0.6 mg oral QD) is administered on D1–21 of 28-day cycles (C) until PD/unacceptable toxicity. ELRA is administered SC with step-up dosing in C0 (12 mg and 32 mg), followed by 76 mg on C0D8, then Q2W followed by Q4W. Dose escalation/de-escalation uses a Bayesian optimal interval design, with DLTs evaluated for 28 days after first exposure to combination therapy. Pts receive study treatment until PD, treatment completion (arm D), an AE requiring discontinuation, or consent withdrawal. RP2D selection is based on DLT rate across dose levels and cumulative safety, efficacy, and PK/pharmacodynamic data. In part 2, the safety/efficacy of arlo-cel plus MEZI or ELRA at the selected RP2D will be evaluated in 20–40 pts per arm. Primary endpoints are frequency/severity of AEs, serious AEs, AEs of special interest, AEs leading to discontinuation/death, and RP2D establishment for each combination. Secondary endpoints include ORR, CRR, VGPRR, and arlo-cel kinetics. Pts will undergo post-treatment follow-up for response, survival, long-term toxicity, and lentiviral vector safety, with rollover to a separate long-term follow-up trial for ≤15 y after arlo-cel. **Results:** Enrollment began February 2024 and is ongoing. **Conclusions:** This trial will evaluate arlo-cel combinations, including with MEZI and ELRA maintenance, in RRMM.

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Tryptophan Metabolism Plays a Substantial Role in Multiple Myeloma Survival

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Introduction: Multiple myeloma (MM) is a hematological malignancy caused by abnormally proliferating plasma cells in the bone marrow. It is considered incurable, as patients go through cycles of treatment, remission and treatment-resistant relapse, with almost none remaining disease free long term. Early-stage MM depends on the Bone Marrow Microenvironment (BMME) for survival. We have previously shown that MM interacts with BMME Dendritic Cells (DC) which induces DC production of Indolamine Dioxygenase 1 (IDO1), which catabolizes tryptophan (TRP) to kynurenine (KYN). The production of KYN activates pro-survival pathways in MM through the activation of the transcription factor Aryl Hydrocarbon Receptor (AHR). We now show that MM cells can produce KYN independently of DCs through expression of the TRP metabolizing enzyme TDO. **Methods:** Patient RNA expression data were taken from the CoMMpass database. We measured MM cell lines U266, 8226, MM1S and KMS11 for expression of TRP metabolizing enzymes with western blot and qPCR. TRP metabolizing enzyme Tryptophan 2,3-Dioxygenase (TDO) was or inhibited with TDO-specific inhibitor 680C91. AHR activation was measured through qPCR of CYP1a1, a transcriptional downstream target. KYN production was measured by ELISA. KMS11 cells were treated with 680C91, then underwent bulk RNAseq and were analyzed using

gene set enrichment analysis. **Results:** CoMMpass patients with the highest quartile of TDO expression have significantly lower rates of progression-free and overall survival. Three of our cell lines 8226, MM1S and KMS11 express TDO, while U266 does not. Inhibiting TDO with the non-competitive inhibitor 680C91 significantly reduced MM cell survival in TDO+ MM cell lines. Inhibiting TDO reduced KYN production. Inhibiting TDO also reduced AHR activation as shown by expression of downstream target CYP1a1 in TDO+ MM cell lines, but did not affect a TDO- MM cell line. Treatment with AHR ligand TCDD rescued MM cell viability from TDO inhibitor-induced cell death, indicating that TRP metabolism to KYN is important to MM survival. RNAseq with KMS11 cells revealed that cells treated with TDO inhibitor 680C91 had significantly reduced expression of genes involved in MYC signaling, AHR signaling, cholesterol homeostasis and fatty acid metabolism; 680C91-treated KMS11 cells had upregulated expression of genes involved in TNFa signaling through NFkB, hypoxia and apoptosis. **Conclusions:** MM depends on TRP metabolism for survival both in the BMME and as it becomes independent of it. MM cells express TDO, which supports MM survival through the activation of AHR. We now show evidence that TRP metabolism in MM also supports survival through MYC signaling and through upregulation of metabolic pathways, such as fatty acid metabolism which MM is reliant on as a primary energy source. TRP metabolism is a novel treatment target in MM and could lead to more effective killing, especially in relapse/refractory disease.

PA-512

Tunneling Nanotubes Sustain Transmitophagy and Apoptotic Resistance in Multiple Myeloma

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Introduction: Tunneling nanotubes (TNTs) are F-actin-based intercellular structures that enable long-distance transfer of organelles and cargoes between cells. TNT-mediated communication is enhanced under metabolic stress conditions, including oxygen and glucose deprivation (OGD), key features of hypoxic tumor niches. Multiple myeloma (MM) develops within the bone marrow (BM), a metabolically heterogeneous microenvironment characterized by steep oxygen and nutrient gradients. However, the contribution of TNT-mediated mitochondrial trafficking to MM adaptation within hypoxic BM niches remains poorly understood. **Methods:** We developed a co-culture model recapitulating metabolic conditions of the MM niche by exposing the human MM cell line JJN3 and primary bone marrow stromal cells (BMSCs) to oxygen-glucose-serum deprivation (OGD). Mitochondrial membrane potential ($\Delta\Psi m$), apoptosis, mitochondrial trafficking, lysosomal interactions and TNT dynamics were investigated using oxygen-tunable 4D holotomography and confocal microscopy. **Results:** OGD markedly reduced mitochondrial membrane potential ($\Delta\Psi m$) in JJN3 cells, while BMSCs maintained mitochondrial stability. In heterotypic co-cultures, BMSCs significantly protected JJN3 cells from OGD-induced apoptosis. OGD also promoted TNT network formation among BMSCs. Under OGD conditions, mitochondrial transfer from JJN3 cells to BMSCs was significantly increased. Transferred tumor-derived mitochondria displayed a fragmented/post-fission phenotype and localized within actin-rich intracellular compartments in recipient BMSCs. Confocal analyses revealed increased association between transferred mitochondria and lysosomal structures under OGD, consistent with activation of transmitophagy-related processes. Connexin-43 enrichment at intercellular contact sites suggests a potential role for gap junction in TNT-mediated mitochondrial trafficking. Notably, TNTs connecting BMSCs showed punctate tumor-derived mitochondria interacting with lysosomes, suggesting that stromal TNT networks may redistribute damaged MM mitochondria across the stromal syncytium. Then, TNT formation was disrupted using Cytochalasin-D prior to co-culture under OGD conditions. TNT disruption significantly impaired the protective effect exerted by BMSCs against OGD-induced apoptosis in JJN3 cells, supporting a functional role for stromal TNT networks in MM cell adaptation to metabolic stress. **Conclusions:** Our findings identify stromal TNT networks as dynamic mediators of mitochondrial handling and metabolic support within hypoxic MM niches. TNT-mediated redistribution of damaged tumor-derived mitochondria toward BMSCs appears associated with lysosomal processing pathways consistent with transmitophagy and contributes to stromal protection against metabolic stress-induced apoptosis. Targeting TNT-dependent mitochondrial communication may therefore represent a novel therapeutic strategy to disrupt microenvironment-driven metabolic adaptation in multiple myeloma.

PA-513

Underrepresentation in Randomized Clinical Trials Identifies a High-Risk Real-World Population in Newly Diagnosed Multiple Myeloma

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Introduction: Randomized clinical trials (RCT) establish the standard of care in multiple myeloma (MM). However, restrictive eligibility criteria may limit the generalizability of their findings to routine clinical practice. The prevalence of trial ineligibility among real-world patients with newly diagnosed MM (NDMM) and its impact on survival outcomes remain incompletely defined. **Methods:** We conducted a retrospective real-world cohort study of patients with NDMM who initiated frontline treatment between 2018 and 2026. Data were obtained from the prospective registry of the Brazilian Myeloma Group (GBRAM). Trial eligibility was assessed according to harmonized criteria derived from pivotal frontline phase 3 RCT. Patients were classified as trial-ineligible according to the presence of at least one trial exclusion criterion. The objectives of the study were to quantify the underrepresentation of real-world patients in pivotal frontline RCT, identify causes of trial ineligibility, characterize baseline features, and evaluate overall survival (OS) according to trial eligibility. Survival was estimated using the Kaplan–Meier method and compared using Cox proportional hazards models. **Results:** A total of 2,825 patients were included in the analysis. Overall, 41% of patients would have been excluded from participation in pivotal frontline RCT. The most frequent reasons for trial ineligibility were creatinine clearance < 30 mL/min (20.3%), hemoglobin < 7.5 g/dL (14.7%), and ECOG performance status >2 (11.8%). Trial-ineligible patients were more frequently aged ≥75 years (19.4% vs 15.0%), had ISS stage III disease (66.5% vs 25.5%), had bone involvement (74.7% vs 66.0%), and were transplant-ineligible (45.1% vs 38.2%) than trial-eligible patients. Trial-ineligible patients experienced significantly inferior OS compared with trial-eligible patients (median OS, 51 vs 86 months; HR, 2.10; 95% CI, 1.81–2.44; P < 0.001). Early mortality was higher among trial-ineligible patients (2-year OS, 69% vs 86%). The adverse prognostic impact of trial ineligibility was consistent across transplant-eligible and transplant-ineligible subgroups (HR, 2.32 and 2.05, respectively; both P < 0.0001). In multivariable analysis adjusted for age ≥75 years, transplant eligibility, ISS stage III disease, and bone involvement, trial ineligibility remained independently associated with inferior OS (adjusted HR, 1.84; 95% CI, 1.49–2.26; P < 0.001). **Conclusions:** More than 40% of real-world patients with NDMM would have been excluded from participation in pivotal frontline RCT, resulting in substantial underrepresentation in routine clinical practice. Trial ineligibility identified a high-risk, clinically distinct population with advanced disease features and a twofold increased risk of death. These findings highlight important limitations in the generalizability of current MM trials and support the need for more inclusive study designs and greater integration of real-world evidence.

PA-514

Unequal Transition Towards Survivorship in Multiple Myeloma Across Europe, 2000–2022: A Population-Level Analysis

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Introduction: Survival in multiple myeloma has improved substantially over the past two decades, but the population-level consequences of this progress remain incompletely characterised. If premature mortality declines while more patients live longer with disease, the burden of multiple myeloma should shift from fatal health loss towards survivorship-associated morbidity. Whether this transition has occurred consistently across European countries is unclear. We assessed temporal changes in fatal and non-fatal multiple myeloma burden across Europe from 2000 to 2022. **Methods:** We conducted a secondary analysis of Global Burden of Disease estimates for European countries from 2000 to 2022. Age-standardised rates of incidence, prevalence, deaths, disability-adjusted life-years, years of life lost, and years lived with disability were extracted by country, year, sex, and European region. The primary derived metric was the years of life lost:years lived with disability ratio, interpreted as the relative balance between premature mortality and non-fatal survivorship-associated burden. Temporal patterns were assessed overall, by region, and across countries. **Results:** Across Europe, multiple myeloma burden shifted in composition between 2000 and 2022. Age-standardised years lived with disability increased to 127% of their 2000 level, whereas age-standardised years of life lost declined to 92%. The years of life lost:years lived with disability ratio decreased from 31.6 in 2000 to 23.1 in 2022, consistent with a relative shift away from mortality-dominated burden towards survivorship-associated health loss. However, this transition was incomplete and unequal. Eastern Europe retained the highest fatal-to-non-fatal burden ratio throughout the study period, despite improvement. Western and Northern Europe had substantially lower ratios by 2022, while Southern Europe remained intermediate. Country-level patterns showed persistent heterogeneity in both baseline burden composition and magnitude of change. **Conclusions:** Multiple myeloma in Europe is undergoing a measurable but incomplete transition from predominantly fatal towards survivorship-associated burden. The unequal pace of this transition suggests that therapeutic progress has not translated uniformly into population-level survivorship gains across European health systems. These findings support the need for continued mortality reduction, equitable access to effective therapies, and survivorship-oriented myeloma care models.

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Updated Exploratory Multivariable Analyses of Differential Impact of Duffy Genotype on PFS With Lenalidomide-Bortezomib-Dexamethasone (RVd) Alone or RVd+ASCT in Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: The erythrocyte Duffy null phenotype, which is associated with lower absolute neutrophil count, plays a key role in cytokine homeostasis, and has known effects on the inflammasome, is present in ~66% of African American (AA) and < 1% of White patients (pts) and may impact MM pathobiology. We previously reported analyses of progression-free survival (PFS) by Duffy genotype in an initial cohort in the DETERMINATION phase 3 trial exploring Duffy null status as a pathobiological explanation for differential relative PFS with RVd-alone vs RVd+ASCT in White (n = 540/722, 74.8%; median 44.3 vs 67.2 months; hazard ratio [HR] 1.67, 95%CI 1.29–2.15) and AA pts (n = 132/722, 18.3%; median not reached [NR] vs 61.4 months; HR 1.07, 95%CI 0.61–1.89). We report updated findings in an expanded cohort of ~500 pts. **Methods:** Pts were classified as C/C (Duffy null) or non-C/C (Duffy non-null) based on genomics analysis of baseline peripheral blood samples for SNP rs2814778. PFS was evaluated with Cox proportional hazards regression in univariate and multivariable models, with heterogeneity of treatment effect assessed by a test for interaction. **Results:** Of 670 enrolled pts with data on Duffy status, 12.8% (n = 86) had the Duffy null genotype (AA: 64.7%, n = 75/116; White/other race: 1.1%, n = 6/523). Of these, 493 pts randomized to RVd-alone (n = 238) and RVd+ASCT (n = 255) were included in PFS analyses; the cohort was broadly representative of the intent-to-treat population. Of the 493 pts, 53/81 (65.4%) AA and 5/408 (0.4%) White/other race pts were Duffy null. In Duffy null vs non-null pts, pooled PFS (arms combined) was similar (median 56.7 vs 62.5 months; HR 0.94, 95%CI 0.62–1.42). In Duffy non-null pts, PFS with RVd-alone vs RVd+ASCT (120/209 vs 85/225 events/pts; median 46.7 vs 67.5 months; HR 1.76, 95%CI 1.33–2.34) favored RVd+ASCT. Findings were consistent in an analysis of the limited number of AA Duffy non-null pts (6/13 vs 3/15 events/pts; median PFS 64.4 months vs NR; HR 5.29, 95%CI 1.20–23.4). In Duffy null pts, PFS with RVd-alone vs RVd+ASCT (9/29 vs 16/30 events/pts; median NR vs 44.0 months; HR 0.64, 95%CI 0.27–1.50; Duffy status interaction p-value 0.005) was not significantly different, but the HR favored RVd-alone. A similar trend was observed in AA Duffy null pts (8/25 vs 15/28 events/pts; median PFS NR vs 45.3 months; HR 0.66, 95%CI 0.27–1.60). On multivariable analysis, Duffy null vs non-null was a significant prognostic factor for longer PFS with RVd-alone with a lower HR (0.44) than for AA vs White/other race (HR 0.54). **Conclusions:** Duffy status was associated with a differential treatment effect more pronounced than previously observed by race in these exploratory analyses of DETERMINATION. In Duffy non-null pts, PFS favored RVd+ASCT, but in Duffy null pts PFS HRs favored RVd-alone, with similar trends in analyses restricted to AA pts. In multivariable analyses, Duffy status was prognostic for PFS with RVd-alone and a stronger prognostic factor than race. Updated data will be presented.

PA-516

Updated Results of Frontline BCMA CAR T-Cell Therapy in Newly Diagnosed Transplant-Ineligible Primary Plasma Cell Leukemia: A Phase 2 Study (CAREMM-002)

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Introduction: We previously reported the initial results of CAREMM-002 (NCT05979363), a prospective phase 2 study evaluating frontline BCMA CAR T-cell therapy in newly diagnosed, transplant-ineligible primary plasma cell leukemia. Here, we present updated efficacy and safety data with expanded enrollment and longer follow-up. Primary plasma cell leukemia remains an ultra-high-risk plasma cell neoplasm with poor outcomes, and prospective data for transplant-ineligible patients are limited. **Methods:** CAREMM-002 is an investigator-initiated, open-label, single-arm phase 2 study. Eligible patients had newly diagnosed primary plasma cell leukemia and were deemed ineligible for autologous stem cell transplantation because of age, frailty, comorbidities, or repeated stem-cell mobilization failure. Patients received 3–4 cycles of VRd-based induction, followed by lymphodepletion and a single infusion of

BCMA CAR T cells, then consolidation and maintenance. Primary endpoints were MRD negativity post-infusion and safety. **Results:** As of May 16, 2026, 22 patients were enrolled. Median age was 68 years (range, 54–75), 7 patients were aged ≥70 years, 11 were male, and 15 were CGS high-risk. Nineteen patients had received BCMA CAR T-cell infusion; 10 were receiving maintenance, 6 were receiving consolidation, and 3 remained in early post-infusion follow-up. Eighteen patients with available post-infusion response assessment were included in the current efficacy and safety analysis. The overall response rate was 100%, with stringent complete response in 16 of 18 patients (88.9%). All 18 patients (100%) achieved NGF-MRD negativity at 10^-5. At a median follow-up of 18.0 months, median progression-free survival, overall survival, and duration of remission were not reached. The estimated 12- and 24-month progression-free survival rates were 100% and 87.5%, respectively. Only one patient relapsed at 23.1 months after diagnosis, and no death were observed. Safety remained manageable. The most common grade ≥3 hematologic adverse events were lymphopenia in 18 patients (100%), leukopenia in 16 (88.9%), neutropenia in 14 (77.8%), thrombocytopenia in 5 (27.8%), and anemia in 4 (22.2%). Cytokine release syndrome (CRS) occurred in 13 patients (72.2%), all grade 1–2, with a median onset of 3 days and median duration of 3 days. No immune effector cell-associated neurotoxicity syndrome was observed. **Conclusions:** With expanded enrollment and longer follow-up, frontline BCMA CAR T-cell therapy continued to induce deep and durable responses with manageable toxicity in newly diagnosed, transplant-ineligible primary plasma cell leukemia. These updated CAREMM-002 data support further evaluation of early BCMA-directed cellular therapy for this ultra-high-risk population.

PA-517

Updated safety and efficacy results for linvoseltamab (LINVO) in patients (pts) with high-risk smoldering multiple myeloma (HR-SMM): Phase 2 LINKER-SMM1 trial

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Introduction: LINVO (BCMA × CD3 bispecific antibody) monotherapy is approved for triple-class exposed relapsed/refractory multiple myeloma (RRMM) after ≥3 therapies (EU) or ≥4 prior lines of therapy (USA). In HR-SMM, BCMA-targeted immunotherapy could leverage a more intact immune system to delay/prevent progression to active MM. Earlier data from the LINKER-SMM1 study showed a 100% overall response rate (ORR), a high rate of minimal residual disease (MRD) negativity at 10–6 sensitivity, and a tolerable safety profile in 24 pts. Here we report updated results. **Methods:** LINKER-SMM1 (NCT05955508) is an open-label Phase 2 study of LINVO monotherapy in adults with HR-SMM, with HR features defined by Mayo 2018 "20–2–20" or PETHEMA criteria. Treatment began with 3-week step-up dosing, followed by full dose LINVO 200 mg in 28-day cycles (C): Q1W for C1, Q2W for C2–5, and Q4W for C6–24. In Part 1 (P1, safety run-in, 6 pts), primary endpoints are the frequency of adverse events (AEs) of special interest (including Grade [Gr] ≥2 CRS and ICANS) and the frequency and severity of treatment-emergent AEs (TEAEs). In Part 2 (P2, expansion), primary endpoints are complete response (CR) rate and MRD negativity rate at 12 and 24 months (mos). **Results:** As of December 24, 2025, 36 pts were enrolled in P1 and P2 (median age 61 years [range 39–84]; 39% male; 94% ECOG PS 0). HR-SMM criteria were met in all pts: 83% (30/36) by "20-2-20," 64% (n = 23/36) by PETHEMA, and 47% (n = 17/36) by both. Median exposure was 8.4 mos (range 0–20). Median duration of follow-up was 8.6 mos (range 0–20; P1, 19.4 mos; P2, 7.3 mos). Of all 36 pts, 35 (97%) experienced ≥1 TEAE and 23 (64%) experienced Gr ≥3 TEAEs (no Gr 5; neutropenia was the only Gr 4 TEAE [n = 5]). CRS occurred in 15 pts (42%): all Gr 1 except for a single Gr 2 event, with 4 cases managed with tocilizumab. No pts experienced ICANS. Infections occurred in 33 pts (92%), with Gr 3 infections in 7 pts (19%), all resolved with routine clinical care. All pts received IVIG replacement therapy, pneumocystis pneumonia prophylaxis, and antiviral prophylaxis; antibacterial prophylaxis was used in 12 pts (33%). In pts completing ≥1 cycle of LINVO with at least C2 Day 1 assessment (n = 32), investigator-assessed ORR per IMWG criteria was 100% (≥VGPR 97%; ≥CR 69%). All responses were ongoing at data cutoff, with evidence of deepening over time and no progression to active MM. Among pts with ≥VGPR who were MRD evaluable by either clonoSEQ or EuroFlow, 100% achieved MRD negativity at a depth of 10-5 (n = 21/21) and 10-6 (n = 19/19, 2 indeterminate) sensitivity. **Conclusions:** With additional enrollment and follow-up (n = 36; median 8.6 mos) in LINKER-SMM1, LINVO monotherapy continued to demonstrate deep and ongoing responses (100% ORR, 97% ≥VGPR, 69% ≥CR) with a tolerable safety profile, supporting its role as a promising treatment strategy for HR-SMM. Further updated data as of May 2026 will be presented at the meeting. A Phase 3 registrational study is ongoing.

PA-518

Updated Safety of Isatuximab Subcutaneous At-Home Administration by On-Body Injector in Patients With Relapsed/Refractory Multiple Myeloma in the Phase 3 IRAKLIA Study

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Introduction: At-home administration of therapies for multiple myeloma may offer flexibility and convenience to support long-term disease control. At-home administration was studied in a subset of patients with relapsed/refractory multiple myeloma (RRMM) in IRAKLIA (NCT05405166), an ongoing, global, non-inferiority Phase 3 trial investigating isatuximab (Isa) subcutaneous (SC) vs intravenous (IV). Isa SC is administered using an on-body injector (OBI) with a small, hidden, retractable needle. We present an update for the safety and feasibility results of at-home Isa SC OBI administration by a health care provider (HCP) with data from an additional 93 at-home injections. **Methods:** In IRAKLIA, patients with RRMM aged ≥18 years with ≥1 prior line of therapy were randomly assigned 1:1 to Isa SC OBI (1400 mg; n = 263) or Isa IV (10 mg/kg; n = 268) weekly in Cycle (C)1, then every 2 weeks, + pomalidomide (4 mg/day, Day [D]1–21) + dexamethasone (40 mg [20 mg if aged ≥75 years] weekly) in 4-week cycles. After 5 cycles, at-home administration by an HCP was optional for Isa SC OBI patients on D15 from C6 onward (D1 visits from C6 remained clinic based). At-home eligibility depended on an absence of infusion reactions at C4 and C5, hematology test results at D1 of each cycle, investigator judgment, and patient willingness. During at-home visits, HCPs applied and disposed of Isa SC OBI, evaluated the injection site and vital signs, and completed documentation. For the first isatuximab injection at home, an additional assessment was performed 30 min after the end of the injection. Thereafter, local tolerability was assessed at end of injection. **Results:** In the ongoing IRAKLIA trial (cut-off date: August 29, 2025; median follow-up period: 21.75 months), 16 (6.1%) out of 263 patients treated with Isa SC OBI participated in at-home administration, with 148 injections performed. Most patients started at-home administration at C6 (n = 7), with the remaining patients starting at C7+ (n = 9). More than half (68.8%) switched to at-home administration and have not returned to the hospital for the D15 visit of their next cycle. The median injection duration was similar between clinic (13 min) and at-home administration (12 min). At-home administration was well tolerated with no new safety signals and a 100% completed injection rate. None of the at-home injections were interrupted. There was one injection-site reaction (grade 1) which consisted of injection-site swelling and resolved the same day. No other adverse events, systemic infusion reactions, or device events were associated with at-home administration. **Conclusions:** Updated data from the ongoing IRAKLIA trial showed that at-home administration by an HCP is feasible and well tolerated. Median injection time and success rate are consistent with in-clinic use. These data support the safety of Isa SC OBI administration at home by an HCP in addition to in the clinic, enabling more flexible, accessible, and comfortable care for patients with multiple myeloma.

PA-519

Upregulation of the S100A10-Annexin A2 Complex in Gain(1q) Myeloma

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Introduction: Gain of chromosome 1q (gain(1q)) is one of the most frequent cytogenetic abnormalities in multiple myeloma (MM) and is associated with aggressive disease biology and therapeutic resistance. Proteomic analysis provides an opportunity to identify the biologically relevant pathways in gain(1q) disease and uncover potential therapeutic vulnerabilities. **Methods:** Bone marrow aspirates were collected from patients with newly diagnosed MM (NDMM, n = 14) and relapsed/refractory MM (RRMM, n = 2). Following sucrose density centrifugation and magnetic sorting, CD138+ MM cells were isolated, and the protein fraction was quantified by whole proteome tandem mass tag labelled mass spectrometry (LC-MS). 1q status was determined by fluorescence in-situ hybridisation of CD138+ cells during routine diagnostic testing (gain(1q)+, n = 7, non-1q+, n = 9). Genomic DNA from patient samples and MM cell lines underwent targeted sequencing using the Myeloma Genome Project panel to identify recurrent genomic alterations associated with multiple myeloma, using matched peripheral blood DNA for germline filtering where available. **Results:** LC-MS proteomic analysis identified 146 proteins differentially expressed (logFC > 0, p < 0.01) in gain(1q) MM samples. Notably, several proteins encoded within the 1q locus, including S100A10, S100A6 and S100A4 were upregulated in this cohort. STRING analysis revealed strong interactions with annexin A2 (ANXA2), which was also significantly upregulated in the Gain(1q) cohort. A comparable trend toward increased expression of these targets was also observed in MM patient-derived xenograft models.

The S100A10 and ANXA2 proteins associate on the cell surface as a heterotetramer, functioning as a primary receptor for plasminogen activation that drives extracellular proteolysis, angiogenesis, and tissue remodelling, mechanisms well-documented to fuel tumour invasion and metastasis. Pathway enrichment analysis revealed Gain(1q)-associated proteins were linked to the enrichment of oxidative phosphorylation and mitochondrial respiration pathways, consistent with a metabolically active and aggressive cellular phenotype. Concurrent suppression of inflammation, immune response and adhesion-associated processes was also noted, suggesting altered interactions within the tumour-microenvironment. **Conclusions:** These findings identify a distinct gain(1q)-associated proteomic signature characterised by the upregulation of the S100A10-ANXA2 network and the enrichment of oxidative metabolic pathways highlighting potential mechanisms underlying the aggressive disease biology and therapeutic resistance in high-risk MM. Defining these mechanisms opens a promising novel therapeutic avenue for targeted therapeutic interventions in gain(1q) disease.

PA-520

Usage of Prophylactic Dexamethasone to Reduce Incidence and Severity of Toxicity after Ciltacabtagene Autoleucel

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Introduction: Cilta-cel is associated with substantial rates of CRS, ICANS, and NINT (non-ICANS neurotoxicity). High CAR-HEMATOTOX scores (≥ 2) correlate with increased risk for treatment-related toxicity. Data from the CARTITUDE trials identify CRS grade ≥ 2 and any-grade ICANS as risk factors for NINT. Currently, no established prophylactic strategy exists to mitigate severe toxicities for myeloma CAR-T therapies. We evaluated the impact of prophylactic dexamethasone on the incidence of grade ≥ 2 CRS in patients with CAR-HEMATOTOX scores ≥ 2 that received cilta-cel, with secondary objectives assessing other safety and efficacy endpoints. **Methods:** In this single-center retrospective cohort study, 31 patients received prophylactic dexamethasone 10 mg once daily administered on days 4–6 following cilta-cel infusion between February 24, 2025 and November 24, 2025. Outcomes were compared to a historical cohort of 28 patients who did not receive prophylaxis following cilta-cel between December 5, 2023 and June 22, 2025. Patients were included in either cohort if they had a CAR-HEMATOTOX score of 2 or higher at time of lymphodepletion and received cilta-cel. Comparative analyses between cohorts were performed using Fisher's exact test, Pearson's Chi-squared test, and Wilcoxon rank sum exact test. **Results:** Baseline characteristics were similar between cohorts. The median follow-up time was 6.0 months in the prophylaxis cohort and 14.8 months in the historical cohort (p = < 0.001). The incidence of grade ≥ 2 CRS was not significantly different between the prophylaxis and historical cohorts (13% vs 18%, p = 0.8). CRS onset was delayed with prophylaxis (median 7.5 vs 5.0 days, p = 0.009) and CRS duration was shorter (median 1 vs 2 days, p = 0.023). Rates of grade ≥ 3 CRS (0% vs 7%, p = 0.4), any-grade ICANS (16% vs 11%, p = 0.7), grade ≥ 3 ICANS (0% vs 7%, p = 0.4), severe infections (0% vs 11%, p = 0.1), and NINT (19% vs 7%, p = 0.3) were similar between cohorts. No cases of IEC-EC were observed in either cohort. Incidence of lymphocytosis, defined as an absolute lymphocyte count ≥ 3000 k/uL during cilta-cel expansion, were similar between cohorts (48% vs 32%, p = 0.2). Median cumulative dexamethasone or equivalent received in the first 30 days was significantly higher in the prophylaxis cohort (40 mg [30–635] vs 10 mg [0–320], p = < 0.001). At day 90, ORR were similar between the cohorts (87% vs 82%, p = 0.7), as were rates of CR or better (65% vs 43%, p = 0.1). **Conclusions:** Prophylactic dexamethasone 10 mg daily administered on days 4–6 following cilta-cel infusion in patients with CAR-HEMATOTOX scores ≥ 2 did not result in a significant reduction in the incidence of grade ≥ 2 CRS. Prophylactic dexamethasone was associated with a significant delay in CRS onset and reduction in CRS duration. Day 90 treatment response rates appeared similar between cohorts, suggesting that prophylactic dexamethasone did not compromise early efficacy. Additional outcomes and follow-up will be available at time of presentation.

PA-521

Using Spatial Transcriptomics to Uncover the Unique Biology of Extramedullary Multiple Myeloma

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Introduction: In ~8% of multiple myeloma (MM) patients at diagnosis and ~40% of patients with relapsed disease, there are lesions external to the bone marrow (BM), defined as extramedullary multiple myeloma (EMM). Currently, there are no therapeutic approaches specifically developed for EMM and patient outcomes remain suboptimal even with immunotherapies such as CAR-T cell and bispecific antibodies. It is therefore critical to understand the biology of EMM to enable development of treatments specifically targeting its unique biology. This project aims to characterise the heterogeneity of gene expression in EMM, identify the unique transcriptional signatures compared to BM MM cells and to understand the impact of the EMM tumour microenvironment (TME) in contrast to the BM niche. **Methods:** Spatial transcriptomics data was generated from a retrospective cohort of 7 EMM

patients treated at the Peter MacCallum Cancer Centre. For 5 patients, tissue sections were profiled from EMM sites and a contemporaneous matched BM site using GeoMx for the BM and Visium HD for the EMM site. For the remaining 2 patients, both of which had multiple sites, the available tissue was limited with a low surface area, therefore unsuitable for Visium HD. Hence, nuclei were extracted from each EMM biopsy and were profiled on the same slide with the STAMP method and the Xenium 5k panel. Custom algorithms were developed using standard single cell and spatially aware analysis methods to analyse this data. **Results:** While there were similarities between the expression profiles of MM cells in the EMM and BM site of each patient, key genes and pathways unique to the EMM samples were identified. There was heterogeneity in expression of MM cells in the EMM site that can be linked to spatial location and proximity to different cell types of the TME. In patients with multiple sites of disease, there were shared and unique alterations in gene expression profiles between their EMM sites. In EMM samples, the main immune cells observed were Macrophages, T and NK cells. These immune cells were found in much higher numbers in the BM but with the addition of a sizeable neutrophil population. There were lower numbers of CD4+ T cells in these patient's BMs compared to the BM of myeloma patients without EMM. Overall, there was evidence of increased interaction and tumour infiltration by immune cells in the BM than EMM site. **Conclusions:** EMM cells have unique signatures, suggesting specific characteristics are required to survive outside the BM niche and potentially resulting in divergent evolution. The results suggest that EMM cells actively interact with the cells of the TME, which may support shaping a favourable niche outside the BM. Within patients, expression changes between EMM sites may suggest that it can seed further extramedullary involvement instead of multiple seeding events from the BM. This study increases the understanding of the unique biology of EMM which will help inform the creation of novel personalised treatments for EMM.

PA-522

Utility of Local Cytogenetic Testing for Risk-Stratified Therapy in Newly Diagnosed Multiple Myeloma: UKMRA RADAR Experience

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Introduction: Both UK and international studies in genetically-defined high risk (HR) multiple myeloma (MM) have reported high response rates and progression free survival with intensive induction and prolonged post-ASCT treatment strategies, providing the rationale for stratified therapy based on genetic risk. Whilst centralised testing in clinical trials enables uniformity and quality control, the use of local laboratories paves the way for genetic testing to be available for all patients. The UKMRA RADAR study uses local laboratories for cytogenetic (CGN) testing. **Methods:** RADAR is a national, multi-centre, risk-adapted, response-guided multi-arm, multi-stage phase II/III trial for patients with newly diagnosed MM eligible for ASCT. Patients received induction with VRDc (bortezomib, lenalidomide, dexamethasone and cyclophosphamide), followed by ASCT. Post-ASCT, HR patients were randomised to receive isatuximab or not, alongside VRD/R consolidation/maintenance whilst standard risk (SR) patients receive MRD-guided regimens. A protocol amendment (2022) included isatuximab for all HR patients within induction, consolidation and maintenance.Testing was undertaken in local CGN laboratories on CD138-selected bone marrow (BM). HR was assigned based on the presence of ≥2 of: t(4;14), t(14;16), t(14:20), del(17p), del(1p32), and gain(1q). Clone size cut-offs were 10% for IgH translocations and 20% for copy number changes. Results were centrally reviewed to assign risk in real-time by a genomics working group, according to a pre-defined trial-specific algorithm. **Results:** Recruitment closed on 01APR26. 1379 patients were recruited from 85 UK sites. Median age is 61 years, 58.8% male, 83.2% white. 24 local laboratories were used for CGN testing. 73% were assigned SR, 19.3% HR, 5.9% undefined and CGN reports were unavailable for 1.7%. Of the HR lesions, gain(1q) was most prevalent (36.0%), followed by t(4;14): 10.4%, del(1p): 9.8%, del(17p):9.7%, t (14;16):3.6% and t(14;20):1.2%. In 82.4%, risk was assigned from one BM sample. 195 (14.14%) had a second sample, with a success rate of 51%, giving an overall success rate of 89.3% of all patients. The median turnaround time (from D1 induction until site notified of result) was nine days. Note in some cases, risk was able to be assigned without full results equating to 92.6% being classified as SR or HR. **Conclusions:** RADAR demonstrates that risk-stratified treatment using local laboratories is feasible and quick. The majority of patients were successfully allocated to a risk-adapted treatment pathway following a first CGN test and over 90% in total with a second test. This model is applicable internationally and supports the infrastructure for accessible genetic risk-stratification for all newly diagnosed MM patients. However, infrastructure should be updated to include TP53 mutation testing to enable IMS-IMWG Consensus Genomic Staging. Funding: Cancer Research UK (C9203/A24078, C7852/A25447), Sanofi and Celgene: A BMS Company.

PA-523

Utilizing Epigenetic Profiling of Primary Multiple Myeloma Cells to Understand Enhancer Usage Across Myeloma Subtypes.

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Introduction: Multiple myeloma (MM) is a transcriptionally heterogeneous disease, with distinct gene expression programs associated with different MM subtypes. MM cells are known to upregulate the expression of important genes by activating oncogenic distal regulatory elements, known as enhancers. However, the extent to which differential chromatin states and enhancer usage drives subtype-specific gene expression in MM has not been fully explored. MM subtypes are distinguished by unique molecular drivers, many of which are direct regulators of chromatin and transcription, e.g. NSD2 in t(4;14) MM. These subtype-specific oncogenes may therefore contribute to differential gene expression via chromatin remodeling. Here, we comprehensively characterized the epigenetic landscape of t(11;14) and t(4;14) MM in primary patient material, to identify common and distinct regulatory elements that contribute to their transcriptional programs. **Methods:** We used TOPmentation (transcription factor-optimized ChIPmentation), a small cell-number chromatin immunoprecipitation (ChIP)-based approach, to generate genome-wide profiles of eight key histone modifications in CD138+ cells isolated from three t(11;14) and three t(4;14) patients. We used ChromHMM to functionally annotate the genome based on these histone modifications, and differential peak analysis to identify subtype-specific chromatin features, including differential enhancer usage. Key enhancers were linked to target genes using the chromatin conformation capture technique micro-capture-C. We compared these to transcriptional differences using MMRF CoMMpass RNA-sequencing data from t(11;14) and t(4;14) patients. **Results:** ChromHMM genome segmentation analysis revealed broadly conserved chromatin features between t(11;14) and t(4;14) patients, although specific areas of differential enrichment were identified in both active (H3K27ac, H3K4me1) and repressed (H3K9me3, H3K27me3) chromatin. Significant differences were observed at key loci, including subtype-specific genes such as MAF, CCND1/2 and CD19. Most enhancers were conserved, including at essential MM oncogenes, e.g. IRF4 and IKZF3, but approximately 5% were subtype-specific, with the majority more active in t(4;14) cells. Around 30% of the genes associated with these enhancers were differentially expressed between t(11;14) and t(4;14) MM patients in the CoMMpass dataset. These included genes previously associated with myelomagenesis and high-risk disease, e.g., TEAD1, PBX1 and DSG2. **Conclusions:** We have comprehensively profiled the epigenetic landscape of six MM patients. Overall, the chromatin profile of t(11;14) and t(4;14) MM is broadly similar, but we identified clear subtype-specific chromatin regulation able to explain differences in gene expression. These differentially enriched loci may represent potential vulnerabilities and targets for novel subtype-specific therapies.

PA-524

Venetoclax Synergizes with Circularly Permuted TRAIL Through DR5 Upregulation and BID-Dependent Crosstalk in Multiple Myeloma

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Introduction: Although Venetoclax has shown promising activity in multiple myeloma (MM), its clinical application is limited by resistance and restricted efficacy beyond selected molecular subgroups. Circularly permuted TRAIL (CPT, Aponermin) activates death receptor-mediated apoptosis and may complement Venetoclax-induced mitochondrial apoptosis. We therefore investigated the therapeutic efficacy and underlying mechanisms of CPT combined with Venetoclax in MM. **Methods:** Anti-myeloma activity of CPT and Venetoclax was evaluated in drug-resistant MM cell lines, primary CD138+ myeloma cells. Cell viability, apoptosis, caspase activation, mitochondrial membrane potential, RNA sequencing, flow cytometry, and protein expression analyses were performed. Drug synergy was assessed using Bliss scores. Correlations between biomarker expression and treatment response were evaluated in CD138+ primary patient samples. **Results:** CPT and Venetoclax demonstrated significant synergistic anti-myeloma activity across multiple myeloma cell lines, including bortezomib-resistant cells, as well as primary patient samples. RNA sequencing revealed upregulation of TNFRSF10B (death receptor 5, DR5) following Venetoclax treatment. Consistently, flow cytometric analysis confirmed increased surface expression of DR5, suggesting that Venetoclax sensitizes myeloma cells to CPT-mediated death receptor signaling. Therefore, combined treatment induced greater activation of Caspase-8, Caspase-9, and Caspase-3/7 than either monotherapy. In addition, combination treatment was associated with reduced total BID expression and enhanced mitochondrial membrane depolarization, consistent with BID cleavage and activation of mitochondrial apoptotic signaling. Concurrently, Venetoclax-mediated BCL-2 inhibition further promoted mitochondrial apoptotic priming and Caspase-9 activation. These findings indicate that Venetoclax enhances CPT-induced death receptor signaling through DR5 upregulation, while CPT amplifies mitochondrial apoptosis through BID-dependent crosstalk, resulting in dual-pathway apoptotic amplification. In primary CD138$^+$ myeloma samples, Bliss synergy scores positively correlated with DR4 and DR5 expression. ROC analysis demonstrated that DR4 and DR5 effectively predicted synergistic responses (AUC = 0.861 and 0.824, respectively), while

combined assessment further improved predictive performance (AUC = 0.935). Consistent with these ex vivo findings, a high-risk MM patient resistant to both proteasome inhibitors and immunomodulatory drugs achieved rapid serologic complete response following CPT–Venetoclax treatment. **Conclusions:** Venetoclax enhances CPT sensitivity through DR5 upregulation, whereas CPT promotes BID-dependent mitochondrial apoptotic amplification. DR4 and DR5 may serve as predictive biomarkers for this combination strategy. These findings provide a strong mechanistic and translational rationale for further clinical evaluation of CPT plus Venetoclax in relapsed/refractory MM.

PA-525

Venous Thrombosis in Newly Diagnosed Multiple Myeloma: A Multi-Institutional Study from India

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Introduction: Venous thromboembolism (VTE) is a recognized complication in newly diagnosed multiple myeloma (NDMM), and current thromboprophylaxis recommendations are largely based on risk stratification models developed in Western populations. Data on VTE from Asian populations remain limited. Given the well-recognized ethnic variations in the VTE incidence, we evaluated the incidence of VTE in a large multi-center Indian NDMM cohort and assessed the predictive performance of the IMPEDE VTE score. **Methods:** This multicenter retrospective study included adults with NDMM treated between January 2012 and December 2023 at three tertiary cancer centers in India. Patients lacking data required for IMPEDE VTE calculation or with follow-up < 6 months were excluded. Baseline demographic, clinical, and treatment-related variables were collected. Patients were stratified into low- (≤3), intermediate- (4–7), and high-risk (≥8) categories according to the IMPEDE VTE score. The cumulative incidence of VTE was estimated using the Fine–Gray competing-risk model, considering non-VTE-related death as a competing event. Model discrimination was assessed using the concordance index (C-index). **Results:** A total of 980 patients were analyzed. Median age was 62 years (range, 30–90), and 55% were male. According to the IMPEDE VTE score, 870 patients (89%) were classified as low-risk, 103 (10%) as intermediate-risk, and 7 (0.7%) as high-risk. The predominance of low-risk scores was largely attributable to universal Asian ethnicity (−3 points), frequent use of aspirin thromboprophylaxis (69%; −3 points), low prevalence of obesity (16%), prior VTE (1.2%), and central venous catheter use (1.7%), along with the absence of doxorubicin exposure. Overall, VTE occurred in 20 patients (2.0%). The cumulative incidence of VTE at 6 months for the entire cohort was 1.2% (95% CI, 0.5–1.9). Stratified by risk category, the 6-month cumulative incidence was 1.0% (95% CI, 0.3–1.7) in the low-risk group, 3.0% (95% CI, 0.0–6.2) in the intermediate-risk group, and 0% in the high-risk group. The observed incidences were substantially lower than those predicted by the IMPEDE VTE model. The score demonstrated poor discriminative ability, with a C-index of 0.532. Patients with VTE showed a trend toward poorer performance status (ECOG >2: 35% vs. 18%; p = 0.05) and higher prevalence of lower-limb weakness (23% vs. 10%; p = 0.08), although no variable achieved statistical significance. **Conclusions:** In this large multi-center Indian cohort, the incidence of VTE in NDMM was remarkably low. The IMPEDE VTE score showed poor predictive performance, suggesting limited applicability in this population. Most patients were classified as low risk likely reflecting the influence of Asian ethnicity and a low prevalence of major thrombotic risk factors. These findings suggest the need for prospective studies to develop specific VTE risk assessment tools for Indian patients with multiple myeloma.

PA-526

Waldenström Macroglobulinemia in a Resource-Constrained Setting: Clinical Characteristics, Treatment Patterns and Survival Outcomes from a 15-Year Cohort

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Introduction: Waldenström macroglobulinemia (WM) is a rare indolent B-cell lymphoproliferative disorder characterized by bone marrow infiltration and monoclonal IgM production. Data from low- and middle-income countries remain limited. We evaluated the clinical presentation, treatment patterns, and outcomes of patients with WM managed at a tertiary referral center. **Methods:** We performed a retrospective analysis of consecutive patients diagnosed with WM between January 2010 and December 2025 at a single center. Demographic, clinical, laboratory, treatment, and outcome data were extracted from institutional records. Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method. Prognostic factors were evaluated using univariate survival analyses. MYD88 mutation testing was not available during the study period and therefore molecular data were unavailable for all patients. **Results:** Sixty-nine patients were included. The median age at diagnosis was 60 years (range, 32–77), with a male predominance (78.3%). The most common presenting features were anemia (75.4%), constitutional symptoms (60.9%), lymphadenopathy

(43.5%), splenomegaly (31.9%), and hyperviscosity syndrome (13.0%). Median hemoglobin was 7.8 g/dL and median serum IgM level was 4,129 mg/dL. IPSS-WM risk stratification was available in 22 patients; 9 (40.9%) were low risk, 9 (40.9%) intermediate risk, and 4 (18.2%) high risk. Chemoimmunotherapy was the predominant first-line treatment (63.8%), followed by chemotherapy alone (20.3%) and bortezomib-based regimens (5.8%). Among evaluable patients, complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 7.2%, 5.8%, 42.0%, 2.9%, and 7.2% of patients, respectively. Response data were unavailable in 34.8% of patients. The overall response rate (≥PR) was 55.0% for the entire cohort and 84.4% among evaluable patients. After a median follow-up of 48 months, median event-free survival (EFS) and overall survival (OS) were 40 and 74 months, respectively. Forty EFS events and 23 deaths were recorded. On univariate analysis, anemia ($p = 0.007$) and constitutional symptoms ($p = 0.002$) were associated with inferior OS, while fever was associated with inferior EFS ($p = 0.043$). Constitutional symptoms demonstrated the strongest association with adverse survival outcomes. **Conclusions:** Patients with WM in this cohort presented with a high burden of symptomatic disease, particularly anemia and constitutional symptoms, suggestive of delayed diagnosis and advanced disease at presentation. Despite a relatively short EFS, overall survival remained prolonged, reflecting the indolent biology of WM and the benefits of sequential therapeutic strategies. These findings provide important real-world data from an LMIC setting and highlight the challenges posed by indolent malignancies requiring repeated interventions in resource-constrained healthcare systems.

PA-527

Whole Genome Sequencing of Circulating Multiple Myeloma Cells with a Novel Clinical Assay Enables Identification of Genetic Alterations Underlying Immunotherapy Resistance

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Introduction: Detecting genetic abnormalities is required during diagnostic workup and for potential individualization of therapy selection in multiple myeloma (MM) and its precursor conditions. Presently, this requires invasive bone marrow (BM) biopsies, hindering early detection, frequent longitudinal monitoring, and precise therapy selection. The standard for detecting genetic alterations in MM remains fluorescence in situ hybridization (FISH), which cannot detect point mutations and other clinically relevant alterations. Consequently, the IMS-IMWG guidelines were recently updated to require next-generation sequencing for the classification of high-risk MM. To address these needs, we recently launched GenoPredicta, a CLIA-approved LDT that comprehensively characterizes MM genomes with whole genome sequencing (WGS) from as few as 50 circulating tumor cells (CTCs) isolated from peripheral blood (PB) or tumor cells from BM and enables risk classification according to the new IMS-IMWG guidelines. **Methods:** Tumor cells were isolated from BM or PB samples using fluorescence-activated cell sorting (after immunomagnetic CD138+ enrichment for PB) and subjected to WGS. Copy number alterations, translocations, and single nucleotide variants and indels were identified with a fully automated pipeline that generates physician-ready clinical reports from raw sequencing data in ~6 h. **Results:** Here, we describe results from a cohort of 50 patients representing a mix of newly diagnosed and relapsed/refractory MM. Notably, ~95% of samples had at least 1 event not detectable by FISH, with ~40% having TP53 alterations resulting in high-risk classification according to the IMS-IMWG guidelines. Crucially, ~50% of samples had alterations in therapy target genes, with ~25% of samples showing biallelic alterations in targets of immunotherapies (e.g., BCMA and GPRC5D). The detected alterations ranged from large-scale deletions (Mb- to arm-level) to small focal deletions (kb-scale) and point mutations, emphasizing the advantage of WGS to comprehensively characterize MM genomes. In all instances, the resistance-conferring alterations were consistent with patients' prior lines of therapy. Comparison with FISH performed concomitantly or obtained from medical records showed complete recall by WGS conducted from either PB or BM. Finally, we show that in some cases, CTC-based profiling enables detection and characterization of residual disease when no tumor cells are detected in the BM. **Conclusions:** We demonstrate that WGS-based characterization of MM from BM or CTCs enables comprehensive profiling of MM genomes, including a large diversity of genetic resistance mechanisms only detectable by WGS. Moreover, CTC-based profiling, which is increasingly recognized for its independent prognostic value, will enable more frequent monitoring, enabling both early detection of such alterations and more precise selection and guidance of therapy.

PA-528

Whole Proteome Analysis of Multiple Myeloma Patient Samples Provides New Insights into IMiD/CELMoD Resistance

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Introduction: Analyses of large cohorts of primary samples from MM patients to understand resistance mechanisms have mostly been undertaken at the DNA/RNA level. However, whole proteome analysis is highly pertinent to understanding resistance to protein degraders such as immunomodulatory drugs (IMiDs) and next generation agents (CELMoDs), which are central to many MM treatment regimens. **Methods:** We analysed proteomic changes associated with relapse on lenalidomide (Len) therapy using paired baseline and relapse CD138+ samples from patients enrolled in the Myeloma XI trial. In a separate analysis we explored degradation profiles in patient MM cells (CD138+ samples from IMiD sensitive and resistant patients) treated ex vivo with IMiDs/CELMoDs (Len 10uM, pomalidomide [Pom] 10uM, iberdomide [Iber] 1uM and/or mezigdomide [Mezi] 1uM vs DMSO control over 4 h). All samples were analysed by TMT-labelled quantitative mass spectrometry. RNA expression and outcome were explored in the CoMMpass dataset for key proteins. **Results:** Paired baseline and relapse samples from 14 patients enrolled in Myeloma XI were analysed with ~7500 proteins identified. At relapse on Len, the expression levels of 91 proteins were upregulated ($log2FC \geq 0.5$, $p < 0.01$) and of 272 were downregulated ($log2FC \leq -0.5$, $p < 0.01$). The top 5 upregulated proteins were CHAF1B, CTAG1B/CTAG1A, DHFR, NCAPD2 and RAPGEF1 and downregulated were FAM241B, HSP90AA4P, PIQG, SMPD2 and TMEM19. High RNA expression of DHFR, CHAF1B and CTAG1A at diagnosis was associated with significantly shorter PFS and high expression of CHAF1B, CTAG1A and CTAG1B with significantly shorter OS in the CoMMpass dataset, suggesting a key role in MM resistance. Ex vivo samples from 19 patients (6 clinically sensitive/unexposed to IMiDs, 13 resistant, none exposed to CELMoDs) were analysed with ~7000 proteins identified. Degradation of Ikaros and/or Aiolos was demonstrated in all IMiD sensitive patients (6/6) but in resistant patients 8/13 (62%) degraded with Len and Mezi, 2/13 (15%) degraded with Mezi but not Len and 3/13 (23%) showed no degradation with either. This suggests loss of CRBN function led to resistance in a subset of patients, whilst in the remainder resistance arose through alternate mechanisms. To explore the full degradome in the primary sample context for the first time, the 16 patients demonstrating degradation were analysed. Degradation of Ikaros/Aiolos was confirmed with all IMiDs/CELMoDs and of ZFP91 with Pom, Iber and Mezi. The expected increase in magnitude of degradation of Ikaros/Aiolos was demonstrated with CELMoDs compared to IMiDs. Analysis of potential novel neosubstrates and differences in the degradome between clinically sensitive and resistant patients is ongoing. **Conclusions:** Exploring the whole proteome of primary patient samples enhances our understanding of mechanisms of resistance and has highlighted potential novel therapeutic targets in IMiD resistance such as CTAG1B/CTAG1A, for which TCR engineered T cells have been studied in solid tumours.

NURSING SYMPOSIUM ORAL PRESENTATIONS

NSO-01

Early Outcomes from a Nurse- and Pharmacist-Led Myeloma Survivorship Clinic: Living Better with Myeloma

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Introduction: Major advances in management have significantly improved overall survival in myeloma; increasing numbers of patients have complex survivorship needs related to ongoing treatment, comorbidities and aging, and to address elevated risks especially of infection, cardiovascular disease and secondary malignancy. Current models of care focus on disease surveillance and treatment; however, there is increasing recognition of the need for systematic structured survivorship care with a holistic focus to meet broader physical, psychosocial and preventive health needs. The Living Better with Myeloma (LBWM) clinic was established in 2023 as a nurse- and pharmacist-led survivorship model for patients in stable remission. A 12-month pilot phase was undertaken to establish the clinic and develop operational processes, tools and supporting structures to inform subsequent implementation. **Methods:** A retrospective analysis of the LBWM clinic was conducted of the pilot phase (November 2023– October 2024). Data were extracted from electronic medical records and analysed descriptively for care delivery and key outcome measures. **Results:** Over 12-months, of 67 patients, data for 34 consented patients was analysed; 44 nurse and 16 pharmacist consultations were delivered. Most nurse consultations were conducted in person (68%, 30/44). A total of 43 survivorship care plans were developed, 93% (40/43) were shared with the general practitioner (GP); the remainder did not have a GP on file. Non-adherence to population-based cancer screening programs was identified in 73% (32/44), with 56 recommendations made, commonly for skin (36%, 20/56), prostate (21%, 12/56) and bowel screening (20%, 11/56). Outstanding annual health screening

blood tests were identified in 73% (32/44) and recommended vaccinations in 48% (21/44). Common patient reported symptoms included fatigue (18%, 8/44), pain (18%, 8/44), diarrhoea (16%, 7/44), sexual dysfunction (14%, 6/44) and neuropathy (11%, 5/44). A total of 22 specialist referral recommendations were made. The most common internal referrals were for genitourinary (25%, 3/12), dental (17%, 2/12) and social work (17%, 2/12) related issues. Of the 16 pharmacist consultations, the commonest intervention was medication dose or timing adjustment (69% 11/16). **Conclusions:** Initial data from the LBWM clinic supports establishment of a nurse- and pharmacist-led survivorship clinic and development of operational processes and workflows, with high rates of survivorship care planning and GP communication indicating early integration of structured survivorship care. Frequent preventative care gaps, including cancer screening, routine health monitoring and vaccination, were identified alongside significant symptom burden. Findings highlight the breadth of survivorship care needs and inform ongoing development plans.

NSO-02

Estimating Post-Discharge Healthcare Resource Utilization for Cilta-cel Recipients

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Introduction: Data related to post discharge metrics after cilta-cel administration is limited. To potentially reduce healthcare utilization and patient visit burden, it is imperative to understand the post-discharge visit burden following discharge. We have evaluated the healthcare resource utilization among Cilta-cel recipients treated at Emory University. **Methods:** Cilta-cel recipients treated at Emory University from January 2, 2024 until December 10, 2025 were included in this analysis. A total of 173 patients that received Cilta-cel for the approved indication of relapsed/refractory multiple myeloma were eligible, after patients on clinical trials were excluded. Inpatient toxicity and supportive care metrics, post-discharge outcome variables of unplanned intermediate care center (ICC) visits, unplanned emergency department (ED) visits, and rehospitalizations were collected. **Results:** Of the 173 patients with a median age of 65.75 years (range: 38.5–85.1) 52.6% were male, 50.9% white and 47.4% were black. 3 patients (1.7%) received outpatient Cilta-cel. The median days of hospitalization among the inpatient group is 10 days (range, 7–93). Cytokine release syndrome (CRS) occurred in 57.8% patients (≥grade 2 in 9.9%). Tocilizumab was administered to 75.1% of patients (prophylactic toci in 25.4%). Neurotoxicity occurred in 15% of patients. At discharge, 96% of patients received antivirals, 90.5% received IVIG. 4 (2.3%) of patients had a stem cell boost. 58 (33.5%) patients had unplanned ICC visits [median 1 (range 1–5)]; the median time from discharge to ICC visit is 22.5 days (range, 1–489); 67 patients (38.7%) had unplanned ED visits [median 1 (range 1–7)]; the median time from discharge to ED visit is 85 days (range, 3–407) 56 patients (32.3%) had hospital readmissions [median 1 (range 1–5)]; the median time from discharge to readmission is 60 days (range, 1–408). Cumulative ICC visits were 89, which equals to 0.51 visit per patient that received Cilta-cel (most common reasons – infectious etiology - 39.3%; non-hematologic toxicity – 38.2%, hematologic toxicity – 14.6% and neurotoxicity – 7.9%). Cumulative ED visits were 116, which equals to 0.67 visit per patient that received Cilta-cel (most common reasons –non-hematologic toxicity – 73.3%, infectious etiology – 13.8%, hematologic toxicity – 6% and neurotoxicity – 6.9%). Cumulative readmission visits were 99, which equals to 0.57 readmission per patient that received Cilta-cel (most common reasons: non-hematologic toxicity – 50.6%, infectious etiology – 30.3%, neurotoxicity – 13.5%, immune effector cell enterocolitis 12.3%, hematologic toxicity – 3.8% and CRS 1.1%). **Conclusions:** About one-third of patients required ICC visits, ED evaluations, or readmissions within the first three months post cilta-cel administration. These data will allow us to make targeted interventions to mitigate unplanned intermediate care center visits (ICC), unplanned emergency department (ED) visits and rehospitalizations.

NSO-03

Physiological and Quality-of-Life Trajectories During Autologous Transplantation: Findings from the MY-TRAC Study

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Introduction: Passive wearable sensors offer a scalable method for capturing real-time physiology during myeloma treatment, but evidence for feasibility and acceptability in autologous stem cell transplantation (ASCT) is limited. MY-TRAC prospectively evaluated wearable-derived physiological and patient-reported outcomes across ambulatory and inpatient ASCT pathways. **Methods:** Adults undergoing ASCT were provided with a wrist-worn wearable (Fitbit Charge 6) from Day − 10 to +28. The primary endpoint was feasibility, defined as ≥70% waking-hour wear-time. Step count, heart rate (HR), and sleep duration were summarised across four windows: Pre-ASCT, Day0–5, Day+6–14, and Day+15–28. Patient-reported outcomes were assessed using the EORTC QLQ-C30 and myeloma-specific QLQ-MY20 at baseline and Day+28. PROM change was interpreted using a ≥5-point group-level MID threshold with exploratory paired testing and a ≥10-point individual-level responder threshold. Quantitative data were analysed descriptively.

Results: Thirty-two participants activated wearable monitoring (ambulatory n = 10; inpatient n = 22). Median age 61 years (43–71), 69% male. The study met its primary endpoint, 24 (75%) participants achieved ≥70% wear-time. Four-window datasets were available for 29/32 participants (91%) for step count, 28/32 (88%) for HR, and 23/32 (72%) for sleep duration. Median step count declined from 6,483 steps/day pre-ASCT to 2,205 Days0–5, reached nadir during Days+6–14 (1,299), and partially recovered by Days +15–28 (2,096). Median HR increased from 67 bpm pre-ASCT to 80 bpm during Days+6–14 and remained elevated during Days+15–28 (81 bpm). Median sleep duration increased from 380 min/night pre-ASCT to 487 during Days0–5 and remained elevated through Days+15–28. Sleep duration was similar between care settings at baseline, with ambulatory participants recording longer sleep during Days0–5 (533 vs 424 min/night), but broadly comparable sleep duration during later recovery. PROM completion was 97% (31/32), with analyses conducted in 31 paired observations. At group level, improvements meeting both MID and exploratory statistical criteria were observed in MY20 disease symptoms (−12.07; p = 0.000364) and insomnia (−17.86; p = 0.033), while deterioration meeting both criteria was observed for appetite loss (+15.48; p = 0.013) and body image (−16.67; p = 0.0014). Individual-level responder analysis using a ≥10-point threshold showed substantial heterogeneity, with body image deteriorating in 21/31 participants (68%), pain improving in 19/31 (61%) and MY20 disease symptoms improving in 15/31 (48%). **Conclusions:** Continuous wearable monitoring during ASCT generated objective physiological trajectories with marked activity suppression, sustained HR elevation, relatively preserved sleep duration, and partial recovery by Day+28. Integration with PROMs offers a novel approach to characterising multidimensional recovery and may inform digitally enabled supportive-care strategies in multiple myeloma.

NSO-04

Physiotherapist-led Exercise Prehabilitation Prior to Autologous Stem Cell Transplantation for Myeloma: Evaluation of Real-World Outcomes from Routine Delivery

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Introduction: Exercise prehabilitation before autologous stem cell transplantation (ASCT) can optimise function and quality of life (QoL). Our centre has implemented a program of prehabilitation before, and rehabilitation after, ASCT into routine clinical care. We aim to present real-world findings related to changes in function and QoL following prehabilitation prior to ASCT. **Methods:** An updated service evaluation was conducted at a single-centre tertiary referral hospital for haematopoetic stem cell transplantation in the United Kingdom. We deliver a hybrid service using face-to-face physiotherapy assessments and remote exercise training. Prehabilitation included weekly remotely supervised group exercise, via Zoom, in the phase between stem cell harvest and admission. Functional (6 min walk and timed sit-to-stand tests) and patient-reported outcome measures (QOL: EORTC-C30 and EQ5D-5L; physical activity (PA): PA vital signs) were assessed preharvest and repeated preadmission for ASCT. **Results:** Patients (n = 152) with a diagnosis of multiple myeloma referred for ASCT following induction chemotherapy were assessed over 18 months, of which follow-up outcomes were available for n = 124. Baseline assessments showed high prevalence of impaired function and lower limb strength with most patients not engaging in any PA at referral for ASCT. Improvements were evident following prehabilitation prior to admission. Mean changes in 6 min walk test (+55 m [95% CI 41.4, 69.9], p < .001) and timed sit-to-stand (+6 repetitions [95% CI 4.8,7.3], p < .001) were significant and beyond thresholds of clinical importance. Median levels of self-reported PA engagement increased. Improvements were also seen in the domains of QoL, including improved physical functioning, reduced fatigue and reduced pain. **Conclusions:** Implementation of physiotherapist-led assessments in the myeloma clinic and group exercise delivery under remote supervision are acceptable to patients undergoing ASCT. Outcomes from our centre demonstrate clinically important improvements in physical function, QoL and exercise engagement prior to admission for ASCT.

NSO-05

Typologies of Diagnostic Journeys in Multiple Myeloma

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Introduction: Multiple myeloma (MM), an incurable plasma cell malignancy, is one of the most challenging cancers to diagnose leading to frequent delays. Diagnostic delays are associated with increased complications and worse outcomes. Our understanding of diagnostic pathways in MM largely relies on secondary data explorations that fail to capture details of the MM patients' experience navigating their diagnostic journeys. The aim of this study was to describe patients' journeys and to categorize diagnostic journey types to facilitate future research and care improvement. **Methods:** This qualitative exploration used semi-structured interviews with adults diagnosed with

MM within the past 10 years to explore their diagnostic journeys. Interviews were conducted in English or Spanish. Two independent reviewers visually mapped diagnostic journeys which were then compared and reconciled through group discussion. Reconciled journey maps were categorized through several rounds of group discussion. This study was approved by the UNC IRB (#24-0018). **Results:** We interviewed a racially and ethnically diverse sample of 34 individuals living with MM (13 non-Hispanic (NH) Black, 12 NH White, 7 Hispanic, 2 NH Asian). We identified two primary entry points into the diagnostic journey; 1) Incidental/Asymptomatic (IA) and 2) Symptom Initiated (SI). The IA entry point included two major pathways. IA-1 Primary Care-Mediated; Journeys typically begin at a wellness visit (e.g., annual physical), where abnormal labs lead to a specialist referral and outpatient diagnosis. IA-2 Catastrophe-Mediated; An unrelated catastrophic event (e.g., car crash) leads to emergency department (ED) presentation and incidental diagnosis. The SI entry point included three major pathways. SI-1 Direct Outpatient; Symptoms prompt outpatient care-seeking, followed by testing and referrals that lead to an outpatient diagnosis. SI-2 Direct Emergency; Overwhelming symptoms prompt ED presentation as the initial care-seeking activity, leading directly to a MM diagnosis. SI-3 Indirect Prolonged; Multiple visits and several rounds of ineffective treatment resolve through: SI-3a Eventual Outpatient Diagnosis: eventual OP diagnosis; or SI-3b Catastrophic Emergency Diagnosis; Symptoms escalate prompting urgent ED presentation and diagnosis. **Conclusions:** This work represents the first ever typology of MM diagnostic journeys. We provide a framework for characterizing the complex and heterogenous diagnostic journeys experienced by MM patients. Our work expands on prior theory (Walter's Model of Pathways to Treatment) by highlighting the asymptomatic incidental pathway not previously represented and further exploring resolution settings (outpatient vs. emergency department). Our typology enables future investigations to explore drivers of distinct journey types, as well as their associations with key patient outcomes like symptom experience, end organ damage, care patterns and survival.

NSO-06

UK Expert Delphi Consensus on Managing Talquetamab-Associated Oral Side Effects and Weight Loss in Patients With Multiple Myeloma

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Introduction: Talquetamab (GPRC5D × CD3 bispecific antibody) is approved for adults with relapsed/refractory multiple myeloma after ≥3 prior therapies. Oral side effects (e.g., dysgeusia, xerostomia, stomatitis) are frequent and can impair quality of life, appetite and weight; evidence based practical guidance is limited. This Delphi study aimed to establish expert consensus on best practice diagnosis, monitoring, and management of talquetamab-associated oral side effects and weight loss. **Methods:** A Steering Committee of 2 haematologists, 1 dietitian and 1 pharmacist led a UK modified Delphi panel (Feb–Apr 2026), aligned with ACCORD guidance. An Expert Panel of 31 UK healthcare professionals (HCPs) (haematologists [11], clinical nurse specialists [8], pharmacists [3], dietitians [9]), meeting predefined eligibility requirements and prioritised using criteria to balance representation with expertise completed two online survey rounds. Surveys comprised 6-point Likert scale, multiple-choice and free text questions. Consensus was pre-defined as ≥75% agreement/disagreement. **Results:** Across both surveys, 29/31 HCPs participated; consensus was achieved for 29/41 statements in Round 1 (71%); in Round 2, 12/14 (86%) reached consensus. Across both rounds 41/55 (75%) reached consensus. Key agreements included baseline weight assessment to identify high-risk patients (96%); early (first 4 weeks; 100%) and ongoing monitoring for oral side effects (89%); use of patient-reported outcome tools (e.g., PRO-CTCAE [96%] and PROM tools [85%]) to support detection and monitoring of symptoms; and multidisciplinary management with pragmatic pathways, including upskilling the myeloma team to provide nutritional support where dietitian access is absent (79%). Patient/carer education was viewed as the most effective pre-emptive strategy (93%). Dietary advice should be patient-centred and informed by open discussion (100%), and may include small frequent meals (85%), avoid dry foods (96%), regular sips of liquid (78%). Supportive care for oral side effects includes oral hydration (79%) and saliva substitutes (93%). Dose delays are effective for patients not responding to supportive care for oral side effects (79%). Dietitian referral was recommended where possible for high-risk patients, significant weight loss (>5% since starting talquetamab or >10% from baseline), or BMI < 20 kg/m^2 (79%). Some uncertainty remains regarding use of formal grading for taste acuity (64%) and perception of evidence for emerging medical prophylactic interventions (71%). **Conclusions:** Given the limited evidence, this UK Delphi provides consensus recommendations to recognise, monitor and manage talquetamab-associated oral side effects and weight loss. Priorities include early risk assessment, patient-centered education, individualised dietary strategies and clear pathways for dietary support. The recommendations provide a framework for clinical practice, as talquetamab use expands in routine care.

NURSING SYMPOSIUM POSTER PRESENTATIONS

NSP-01

An Implementation Science Approach to Bispecific Antibody Education and Care Delivery for Multiple Myeloma in Rural and Frontier Oncology

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Introduction: Bispecific antibodies (BsAbs) are highly effective for relapsed/refractory multiple myeloma (MM), but early toxicity risks make administration resource-intensive, requiring frequent monitoring during ramp-up. Consequently, BsAb access in community, rural, and frontier settings remains limited. Preliminary work at our academic center identified these disparities and developed a multidisciplinary approach to BsAb education, yet many community practices still lack the necessary resources to operationalize these treatments. To drive durable system change beyond education, we expanded this work into an implementation science–guided model using the EPIS (Exploration, Preparation, Implementation, Sustainment) framework, bridging academic expertise and community oncology practices. **Methods:** Guided by the EPIS framework, the Exploration phase combined three needs-assessment activities: an online survey of community oncology providers across the regional catchment, site assessments characterizing determinants of readiness (staffing models, infrastructure capacity, equity-related challenges), and structured provider interviews. Consistent with EPIS principles, the assessment considered both external (geography, patient population) and internal (clinical workflows, resources) factors. The Implementation phase launched a monthly Project ECHO® telementoring program connecting community providers with subspecialty myeloma expertise through case-based discussion and didactics, with engagement tracked via attendance and credential composition. **Results:** In 2025, over 75% of MM clinic visits were with patients living more than 25 miles from our center, and 32% were from out of state. Preliminary survey responses (N = 10; 3 physicians, 7 advanced practice providers from five states in the regional catchment) identified top-priority education needs as high-risk disease (9/10), newly diagnosed MM (8/10), and T-cell engagers including BsAbs and CAR-T (7/10); 6/10 cited geographic distance and patient travel burden as the principal barrier to advanced-therapy referral. 9/10 sought improved management confidence, and 8/10 expressed interest in co-developing or presenting sessions. The Project ECHO® program engaged 51 interdisciplinary providers across 5 sessions year-to-date (mean 14.6/session; 73 attendance instances), with broad role representation (7 MD/DO, 8 APN, 17 RN, 5 PharmD, 3 PA, 11 other), delivering 6 case presentations and 5 didactics. **Conclusions:** Exploration-phase findings identified substantial geographic, educational, and systems-level barriers to implementing BsAb therapy in rural and frontier oncology, and early Implementation-phase engagement demonstrates rapid uptake of the model across diverse provider roles. Guided by EPIS, these results will inform a sustainable, replicable model for expanding specialty oncology care beyond academic centers and into community practice.

NSP-02

Building Specialty Capacity in Rural Health: Development and Outcomes of a Multiple Myeloma Project ECHO Program for Community Oncology Providers

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Introduction: Approximately 12 million people in the United States live more than three hours from an NCI-designated cancer center, disproportionately impacting rural and frontier populations. Community oncology providers in these regions increasingly manage medically complex patients in settings lacking subspecialty infrastructure. Meanwhile, oncology care is becoming increasingly complex, requiring providers to navigate rapidly evolving therapies such as bispecific antibodies (BsAbs) and CAR-T therapy, which are resource-intensive and strain existing infrastructure. To advance rural delivery of novel therapies and bridge academic centers to community clinics, our program launched a multiple myeloma (MM) focused Project ECHO® (Extension for Community Healthcare Outcomes), a collaborative tele-mentoring model that connects community providers with subspecialty expertise. **Methods:** The program used a hub-and-spoke tele-mentoring model connecting myeloma specialists with community providers through monthly virtual and in-person sessions. Educational content followed the multiple myeloma (MM) treatment trajectory, from diagnosis through transplant, relapse, relapsed/refractory disease, CAR-T therapy, and BsAbs. Sessions incorporated didactic presentations, case-based learning,. multidisciplinary discussion, and real-time problem-solving on toxicity management, care coordination, and implementation of novel therapies. Evaluation followed Moore's Outcomes Framework, assessing provider pre/post knowledge and workplace performance across its first five domains through attendance tracking, post-session surveys, and implementation barrier assessment. **Results:** Across 5 monthly sessions year-to-date, the program engaged 51 unique interdisciplinary providers (7 MD/DO, 8 APN, 17 RN, 5 PharmD, 3 PA, 11 other; mean 14.6/session, 73 total attendance instances), with 6 case presentations and 5 didactics delivered. Participants entered with mixed baseline knowledge of MM management. Post-session data showed 89–100% reported significant or moderate knowledge gains (Level 3). Application confidence (Level 4) reached 67–100%,

and intent to change clinical practice (Level 5) climbed from 67% to a unanimous 100%. Planned changes were clinically specific and evidence-based, including dexamethasone dose reduction, BsAb combinations, MRD-guided treatment decisions, and ramp-up BsAb protocols. Barriers to application were minimal. Qualitative responses reflected high satisfaction and enthusiasm. **Conclusions:** Across 2026 myeloma ECHO sessions to date, participant outcomes improved across each level of Moore's Framework. Participants left better equipped to apply evidence-based strategies, including quad-therapy sequencing, MRD-guided treatment decisions, and newer immunotherapy regimens. These findings indicate the ECHO model effectively translates specialized oncology knowledge into confident, actionable practice improvements, with particular value in reaching underserved communities.

NSP-03

Characteristics of Multiple Myeloma Patients with Central Nervous System Involvement

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Introduction: Despite advances in multiple myeloma (MM) treatment, systemic therapy alone for central nervous system MM (CNS MM) is often ineffective. While intrathecal (IT) chemotherapy with cytarabine, methotrexate, or topotecan, and/or radiation may result in transient responses, the median overall survival for patients with CNS involvement ranges between 2–10 months. **Methods:** This single center retrospective review identified patients (pts) with CNS MM (diagnosed as CSF plasma cells, parenchymal and/or leptomeningeal disease (LMD) on imaging) from 2016–2026 in the medical records. We assessed factors associated with development of CNS MM, overall survival (OS) from initial MM diagnosis (dx) and from onset of CNS MM, and progression free survival (PFS). Patients with extramedullary disease (EMD) were analyzed to identify factors associated with EMD, OS, and development of CNS disease. **Results:** 44 pts were identified who had clonal plasma cells in the CSF: 22 (50%) were White, 11 (25%) were Hispanic, 9 (20.5%) were Black, and 3 (6.8%) were Asian. 26 (59.1%) were males, and 52.3% were kappa predominant. Median age at diagnosis was 57 (range 25–78). Among 28 pts with R-ISS available, 4 (14.3%) had stage I disease, 14 (50%) had Stage II, and 10 (35.7%) had stage III. Of the pts with evaluable FISH panels (n = 24), we noted deletion 13q (15 pts), gain of CKS1B (13 pts), t(4;14) (7 pts), deletion of 17p (4 pts), and t (11;14) (2 pts). Of the 13 pts with gain of CKS1B, 12 also had deletion 13. Most common symptoms included weakness of the extremities and/or difficulty ambulating (26.6%), facial or extremity numbness (24.4%), altered mental status (24.4%), diplopia/vision disturbances (17%), headaches (15.5%), and seizure (6%). 26 pts (57.7%) presented with EMD prior to presenting with CNS disease (median time to CNS involvement after EMD was 6 months [range 1–40]). The most common sites for EMD included pleura/lung (7 patients), adenopathy (11 patients), pancreas (8 patients), soft tissues (5 patients), and intramuscular (2 patients) with all but one having multiple sites of disease. The median time from MM diagnosis to CNS disease was 38 months (range 1–99 months). **Conclusions:** In our analysis, pts with CNS MM had a poor prognosis with a median OS of 4 months from the time of CNS diagnosis, highlighting the need for more effective therapy. Additionally, 59.1% (26 pts) presented with EMD prior to CNS involvement. Further analysis of pts with EMD is warranted to determine whether CNS prophylaxis may benefit selected patients with EMD.

NSP-04

Chronic Illness Trajectory of Patients with Multiple Myeloma Derived from Health-Related Quality of Life Data: An Integrative Review

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Introduction: Multiple myeloma (MM) is increasingly recognized as a chronic malignancy due to substantial survival improvements associated with novel therapies. However, the disease course is still characterized by recurring treatment phases, symptoms, and progressive impairment of health-related quality of life (HRQoL). The chronic illness trajectory (CIT) model by Corbin and Strauss provides a conceptual framework for describing dynamic disease progression. No HRQoL-based CIT for MM has been synthesized previously. This integrative review aimed to develop a phase-specific CIT for MM patients based on published HRQoL data. **Methods:** An integrative literature review was conducted following the Whittemore and Knafl framework. Structured searches of MEDLINE, PubMed, Epistemonikos, the Cochrane Library, and CINAHL were performed in September 2023. Studies reporting quantitative HRQoL outcomes in MM at defined disease stages were included. Screening and selection were performed according to PRISMA recommendations. The methodological quality of the studies was assessed using the Mixed Methods Appraisal Tool (MMAT) 2018. HRQoL data were extracted, synthesized, and assigned to predefined disease stages based on the CIT model. **Results:** Twenty-three studies met the inclusion criteria and were included in the analysis. These studies comprised 13 randomized controlled trials, six non-randomized clinical trials, and four observational studies. Twenty-two of the studies used the EORTC QLQ-C30, and the Global Health Status (GHS) scale was identified as the most suitable parameter for trajectory mapping. Sixteen distinct disease stages could be assigned across the MM trajectory. HRQoL

was markedly impaired at diagnosis and deteriorated further during intensive treatment phases, particularly around autologous stem cell transplantation. Some recovery occurred during stable treatment phases. However, HRQoL progressively declined with each additional line of therapy. Functional domains demonstrated similar phase-dependent patterns. Fatigue, pain, sleep disturbance, and dyspnea were consistently associated with a high symptom burden. Evidence for advanced disease stages and terminal phases remained limited. **Conclusions:** In conclusion, this integrative review provides the first HRQoL-based chronic illness trajectory for patients with MM. The findings illustrate the dynamic burden experienced across disease and treatment phases, supporting the integration of longitudinal patient-reported outcomes into MM research and clinical care. A trajectory-oriented perspective may facilitate phase-specific supportive care interventions and contribute to more patient-centered management strategies in MM.

NSP-05

Closing the Gaps: Opportunities to Intervene in Post-Discharge Care Following Cilta-cel Administration

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Introduction: The objective of this study was to identify potential care gaps in among Cilta-cel recipients after discharging the patient from the hospital. We hypothesized that identification of care coordination strategies to optimize post-discharge outcomes will enhance patient safety. **Methods:** Cilta-cel recipients treated at Emory University from January 2, 2024 until December 10, 2025 were included in this analysis. A total of 173 patients that received Cilta-cel for the approved indication of relapsed/refractory multiple myeloma were eligible, after patients on clinical trials were excluded. We have evaluated patient and physician communication to understand the potential gaps in care during the post-discharge following Cilta-cel administration and their transition back to community oncology providers. **Results:** Of the 173 patients with a median age of 65.75 years (range: 38.5–85.1) 52.6% were male, 50.9% white and 47.4% were black. The median days of hospitalization is 10 days (range, 7–93). 93 (53.8%) have been successfully transitioned to local providers. The median time from the receipt of Cilta-cel to community transition is 28 days (range 13–398). 67 patients (38.7%) had unplanned ED visits [median 1 (range 1–7)]. The median time from discharge to ED visit is 85 days (range, 3–407). 56 patients (32.3%) had hospital readmissions [median 1 (range 1–5)]. The median time from discharge to readmission is 60 days (range, 1–408). Patient communication by phone or MyChart prior to ED1 visit happened in 34.3%, prior to ED2 visit in 19.2%, prior to ED3 visit in 20%, prior to ED4 visit in 25% and then 100% of the time for further ED visits. Patient communication by phone or MyChart prior to readmission-1 happened in 67.3%, prior to readmission-2 in 56%, prior to readmission-3 in 70%, prior to readmission-4 in 60%, prior to readmission-5 in 66.7%. **Conclusions:** The data suggests an opportunity to explore ways nursing could help improve communication, continuity of care, and the transition process between the academic center and community oncology teams. Transitions of care following CAR-T therapy remain a vulnerable period for multiple myeloma patients. Lower rates of communication prior to ED visits and acute care utilization following discharge highlights the need for improved communication, standardized transition-of-care process, a CART navigator aimed to proactively check on patients post discharge.

NSP-06

Consensus Recommendations for Delivering Bispecific Antibody Therapy (BsAB) in Multiple Myeloma (MM): An Evidence-Based Framework

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Introduction: Background: Bispecific antibodies (BsABs), including elranatamab, teclistamab and talquetamab, are increasingly used in the treatment of multiple myeloma (MM). Initial exposure during step-up dosing (SUD) is associated with cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infections and other adverse drug reactions. Current recommendations include hospitalisation during SUD to enable close monitoring and timely toxicity management. Emerging consensus guidance has identified factors that support safe ambulatory BsAB delivery models. Aim: The Myeloma Specialist Practice Network (M-SPN) identified the need for consensus recommendations to guide best practice in the delivery of BsAB to those with MM. The aim was to produce a practical, evidence-based resource to inform clinical practice, reduce variability of care, and support nurses and healthcare services in developing local models of care to guide safe patient management. **Methods:** A consensus-based expert review approach, in line with Accurate Consensus Reporting Document (ACCORD) check list was used in developing the guidelines. The working group included advanced practice MM nurses, including Clinical Nurse Consultants and Nurse Practitioners. Literature reviewed included licensing studies for elranatamab, teclistamab and talquetamab,

alongside evidence relating to CRS, ICANS, infection risk and ambulatory BsAB delivery. M-SPN members completed a survey identifying educational and practice needs relating to BsAB therapy. Findings from the literature review and survey informed document structure and section allocation according to clinical expertise. Draft recommendations were developed collaboratively and refined through regular consensus meetings. External review was undertaken by three international MM Nurse Practitioners and two Australian haematologists. **Results:** Consensus recommendations were developed across five domains to support safe and effective delivery: (1) stakeholder and service preparation, including treatment protocols, safety-netting strategies and education; (2) factors supporting ambulatory SUD delivery, including patient risk stratification, caregiver availability, distance from treatment centre, and supportive measures; (3) CRS mitigation strategies, including careful patient-selection, prophylactic tocilzumab as indicated, pocket dexamethasone, escalation of care pathways; (4) administration considerations including pre-medications, dosing and scheduling; and (5) nursing and supportive care considerations including care coordination, monitoring, communication pathways, documentation and patient education. **Conclusions:** These recommendations provide a practical resource to support implementation of BsAB therapy across diverse clinical settings.

NSP-07

Delivering a Patient Centered Myeloma Autograft Service

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Introduction: We provide myeloma (MM) autologous stem cell transplant (ASCT) services to a catchment population of ~4 million. Our MM patient group told us that they would like to spend less time in hospital during their ASCT. This corresponded with capacity challenges in our inpatient unit, leading to clinician and patient interest in developing alternative delivery models. **Methods:** To address the needs of our patients and service we introduced ambulatory (A-ASCT, admission only if required) and hybrid (H-ASCT, planned admission on day+7) models of ASCT delivery alongside our existing inpatient (I-ASCT) pathway. In parallel we developed a regular nurse led "Autograft Academy" patient and carer education session covering patient focused topics including nutrition, exercise and managing fatigue. Participants have the opportunity to hear the experience of patients who have recently completed H-ASCT or A-ASCT. Our MM patient group guided the focus of the work and participate in the Autograft Academy. We have assessed the safety, resource utilization and quality of life impact of these service improvements. **Results:** Since the introduction of H-ASCT and A-ASCT in December 2024, 65 patients have undergone ASCT (6 A-ASCT, 9 H-ASCT, 50 I-ASCT). There was no clinically significant difference in median neutrophil (A-ASCT 14 days; H-ASCT 13 days; I-ASCT 14 days) and platelet (A-ASCT 24 days; H-ASCT 28 days; I-ASCT 26 days) engraftment time between the 3 ASCT pathways. Median hospital length of stay was 6 days for A-ASCT, 10 days for H-ASCT and 20 days for I-ASCT. This equates to the creation of 174 days of additional inpatient bed capacity over a 15 month period. Interestingly median days of antibiotic use was lower for those on ambulatory/hybrid pathways (A-ASCT 3 days, H-ASCT 4 days, I-ASCT 10 days). There were no differences in ITU admissions and no safety concerns identified. We assessed patient reported symptoms at baseline, hospital discharge (where applicable), 1 and 3 months post ASCT. There was no detrimental impact on quality of life from A-ASCT or H-ASCT, with a suggestion that A-ASCT patient experienced less reduction in mobility and activity and recovered more quickly than those who had a planned admission during their treatment. Patients reported overall satisfaction with the ASCT service. **Conclusions:** We have demonstrated that a flexible approach to ASCT, with patient focused education and support can offer a safe and resource efficient ASCT programme, with no detrimental impact on engraftment, safety or patient quality of life, and a reduction in the use of antibiotic treatment. While only 25% of patients chose to have A-ASCT/H-ASCT, this still liberated 174 days of additional inpatient bed capacity, equivalent to the availability of an additional hospital bed for 2 weeks every month. Our ongoing drive to deliver patient focused care continues with the next phase of our work, focusing on exercise and functional activity.

NSP-08

Driving Improvement and Equity in Myeloma Care: A Patient-Focused Hospital Accreditation Initiative

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Introduction: Disparity in the management of myeloma can exist across the UK, leading to patients having varied experiences of care. The Clinical Service Excellence Programme (CSEP) is a Myeloma UK initiative designed to reduce inequities for myeloma patients by aligning hospital services with Myeloma UK Myeloma Best Practice Standards. These standards, developed in collaboration with patients, carers, and healthcare professionals, provide a framework for delivering high-quality, patient-centred care. **Methods:** Hospitals participating in CSEP complete a self-assessment covering ten themes that encompass myeloma management and care. Myeloma patients are also invited to complete a Patient Experience Survey (PES) which offers insights into their experience of care at their hospital. Following completion of the self-assessment and PES, results are analysed and Myeloma UK meet with the hospital team to discuss findings.

Hospitals receive an accreditation report or an action plan, highlighting strengths and offering recommendations for improvement. Exemplary practice is shared through articles published on the Myeloma UK HCP Hub. These articles foster knowledge sharing and professional networking, facilitating service development initiatives. Following accreditation, hospitals are invited to reaccredit every five years, and during this time healthcare professionals from CSEP hospitals receive regular updates. **Results:** Since its roll out in 2015, 95 hospitals have achieved CSEP accreditation, and 31 have gone on to achieve reaccreditation. Over 2,400 PES submissions have provided valuable feedback on patient care, helping to drive patient-centred service improvements. An analysis of reaccredited hospitals in 2024 showed that 50% of service improvement recommendations made through CSEP were fully or partially implemented. Feedback from HCPs indicated that 100% of hospitals taking part in CSEP found it useful for identifying areas of good practice and areas for improvement. Sharing practice is a key objective of CSEP and over 40 articles outlining innovative practice have been written by healthcare professionals and published online. Additionally, 10 new myeloma support groups have been set up following meetings with hospital teams, established through collaboration with Myeloma UK. CSEP has further amplified its impact by publicising hospital achievements through local and national media, raising awareness of myeloma among the public. **Conclusions:** Ongoing development of CSEP includes a refined data strategy to identify service gaps and prioritise high-need areas, particularly those areas of the UK with socioeconomic challenges and minoritised populations. This targeted effort aims to reduce healthcare disparities and improve myeloma care nationally. The achievements of the CSEP programme to date highlight the potential impact of collaboration between hospitals and the third sector to drive improvements and equity in myeloma care.

NSP-09

Examining the Role of Nurses in Multiple Myeloma (MM) Care: Insights from a European Survey

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Introduction: Nurses in Europe play a central and multifaceted role in MM care, contributing to clinical management, patient education, and psychosocial support. However, their roles and responsibilities across the patient journey remain inconsistently defined and often underrecognized. A structured survey-based mapping of MM nursing roles across Europe offers a pragmatic way to clarify responsibilities and identify challenges to inform actionable strategies for optimal care delivery. **Methods:** We conducted a 30-minute online survey between May and June 2025 among 60 nurses across hospitals and specialized clinics in France, Germany, Italy, Spain, and the UK. Eligible participants were MM nurses with >1 year of experience who spent ≥75% of their professional time in clinical practice and managed >10 patients with MM per year. The survey included closed and open-ended questions on nursing roles across the patient journey, availability of MM-specific training and guidelines, and key challenges in clinical practice, among other topics. Data were analyzed using descriptive statistics. All participants provided written informed consent. **Results:** All 60 nurses completed the survey: advanced nurse practitioners (28%), oncology nurses (28%), hematology nurses (27%), and clinical nurse specialists (17%). The mean MM care experience was 9.5 years. Most nurses identified themselves as key decision-makers across the MM patient journey. This involved counseling (72%), patient information and education (67%), and quality-of life assessment (65%) at diagnosis, and medication preparation (72%), medication administration (70%), and patient education (65%) during treatment and follow-up. Further, most nurses (95%) participate in multidisciplinary teams, with roles primarily focused on patient needs, such as home care (68%), symptom management (67%), and psychosocial support (56%). Over half (58%) were aware of guidelines defining the nursing role in MM, but 52% reported the guidelines to be nonspecific or locally developed. While 60% agreed that general nursing education covers some aspects of MM care, more than half reported insufficient MM-specific training for nurses in continuing medical education programs. Key challenges included nurse shortages (62%) and healthcare and hospital resource/capacity pressures (45%). Despite nearly all nurses (98%) believing their role in MM care should be better supported, owing to their proximity to patients (24%) and provision of holistic care (20%), existing challenges continue to limit their ability to provide optimal care. **Conclusions:** Although nurses play a central role across the MM patient journey, their ability to deliver optimal care is hindered by limited specialized training, lack of standardized guidelines, and broader systemic barriers. Addressing these gaps through clearer role definitions, improved MM-specific training, and stronger structural support could strengthen nursing practice, ultimately enhancing patient experience and outcomes in MM care.

NSP-10

Exploration of Symptom Burden and Functional Consequences of Myeloma-Related Spinal Disease Treated with a Spinal Brace: Observational Cohort Study

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Introduction: Multiple myeloma frequently affects the spine, causing pathological fractures, pain and reduced physical function. Despite widespread use of spinal bracing to manage spinal disease,

evidence for its safety, adherence and functional impact remains limited. The aim of this observational cohort study was to evaluate functional, symptom and quality of life (QoL) outcomes in myeloma patients treated with spinal bracing, alongside brace characteristics, adherence, adverse events, recruitment and attrition. **Methods:** Myeloma patients treated with a spinal brace at 2 London hospitals (October 2022–November 2024) completed baseline assessments (T0), with follow-up at brace removal (T1) and three months post-removal (T2). Sociodemographic, clinical and brace characteristics were collected. Primary outcomes included disability (Oswestry Disability Index), QoL (EORTC QLQ-C30), physical activity (International Physical Activity Questionnaire), fear-avoidance (Fear-Avoidance Components Scale; T1–T2 only) and functional exercise capacity (1-minute sit-to-stand (1MSTS), Thoracic Loaded Stand (TLS), balance). Outcomes were scored using validated manuals and established minimal clinically important difference (MCID) thresholds where available. Secondary outcomes included brace adherence, adverse events, recruitment and attrition. **Results:** Twenty participants (median age 60 years; 60% female) were included, predominantly fitted with Thoraco-Lumbar-Sacral Orthoses for spinal fractures, with a median of 2 fracture levels. QoL and symptom outcomes improved significantly and exceeded clinically meaningful reductions primarily between T0-T1, with gains maintained at T2. Disability improved significantly over time, with MCID reductions from T0-T1 that were maintained at T2, although participants remained moderately disability. Fear-avoidance showed minimal change between T1-T2. Physical activity, 1MSTS, TLS and balance improved from T0–T1 but remained below normative values at T2. Brace adherence was high, with discontinuation due to discomfort (n = 1). Seven adverse events were reported: fracture progression (n = 4), new fracture (n = 1), increased pain following brace removal (n = 1) and brace-related skin irritation (n = 1). **Conclusions:** Spinal bracing in myeloma patients with spinal disease was associated with clinically meaningful improvements in disability, symptoms, QoL and physical performance during the bracing period, with these gains largely maintained following brace removal. Despite high adherence and maintained improvements, participants continued to demonstrate moderate disability, functional impairment, fear-avoidance and low physical activity levels at 3 months post-removal. As an observational study, these improvements cannot be attributed solely to bracing and may reflect multiple factors including myeloma treatment and recovery over time. Larger experimental studies are needed to determine brace effectiveness and optimise recovery following brace removal.

NSP-11

From 'Frailty' to 'Treatment Compatibility': A Patient-Driven Rethinking of Risk Assessment in Multiple Myeloma

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Introduction: Frailty is a determinant of treatment decisions and outcomes in myeloma; yet its assessment remains challenging. Existing tools lack personalisation and fail to capture the multidimensional patient experience. In addition, the impact of the terminology used to describe frailty has not been explored. This study aimed to investigate patient perceptions of frailty, assessment and acceptability of the term itself. **Methods:** This single-centre study was conducted at a large UK haematology centre. 2 patient focus groups were undertaken, a total of 19 patients with myeloma and 1 carer, recruited via outpatient clinics and support groups. The first group explored perceptions of frailty and assessment tools. The second group examined perceptions of terminology and alternative language. Data collection included semi-structured discussions, questionnaires, and completion of IMWG frailty score and G8 tool. Data was analysed using thematic analysis. **Results:** No participants considered themselves frail pre diagnosis. However all participants felt they would be classified as frail using existing assessment tools, highlighting a clear disparity between self-perception and clinical categorisation. Perceptions of these tools were predominantly negative, with participants describing them as impersonal and not reflective of their lived experience. The second focus group demonstrated that the term "frailty" carries strong negative connotations. Participants associated it with vulnerability, fragility, weakness, and loss of positivity. Many felt being labelled as "frail" would negatively impact their mental health, reduce ability to maintain a positive outlook, and in turn impact on physical health. Exploration of alternative terminology proved challenging. The concept of "treatment compatibility" emerged as a more acceptable and constructive term. Participants supported the idea of a "treatment compatibility" scale, incorporating elements of existing frailty tools alongside factors they felt more accurately reflected their individual health status and ability to tolerate treatment. **Conclusions:** This study highlights a significant disconnect between patient perceptions of frailty and its clinical assessment in multiple myeloma. Importantly, the term "frailty" itself may have unintended negative psychological consequences, with potential implications for patient engagement, wellbeing, and treatment resilience.

NSP-12

Home Administration of Therapies for Hematologic Malignancies in Sweden: Insights from a Mixed-Methods Study of Registered Nurses

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Introduction: Frequent hospital visits are common for patients with haematological malignancies and may negatively affect quality of life while placing increasing demands on healthcare services, because of a higher prevalence of these diseases due to better survival. Providing treatment in the home setting has emerged as a potentially valuable approach to enhancing patient wellbeing and reducing system strain. Here, we explored how home administration of treatments for haematological malignancies is currently implemented in Sweden and to examine nurses' experiences, opportunities, and challenges associated with this model of care. **Methods:** A sequential explanatory mixed-methods design was employed, comprising a cross-sectional online survey followed by semi-structured interviews. Twenty-four registered nurses from six Swedish healthcare regions completed the survey, and data were analysed using descriptive and inferential statistics. Seven nurses subsequently participated in interviews, which were analysed using content analysis. Ethical approval was obtained from the Swedish Ethical Review Authority (Dnr.: 2025-06516-01). **Results:** Home administration of therapies for haematological malignancies was reported in 86.4% of the six healthcare regions, with approximately 25.0% of patients currently receiving treatment at home. Subcutaneous injections and infusions were the most frequently used administration routes, followed by intravenous therapy, and 68.0% responded that local protocols were in place. The most common conditions managed at home were acute myeloid leukemia and myelodysplastic syndrome, each reported by 89.5% of the respondents, followed by multiple myeloma which was reported by 78.9%. Medicine picked up by the patient was the most frequently applied method of delivery, reported by 78.9% of the respondents. Marked variation was identified in organisational structures and procedures across regions and hospitals. Key drivers for offering home administration included patient convenience, increased flexibility, and reduced pressure on hospital services. Content analysis yielded three themes: enhanced quality of life and wellbeing through home administration; person-centered and safe care in the home environment; organisational opportunities and challenges. Despite some organisational barriers, most nurses expressed strong support for home administration and valued being able to offer this option to patients. **Conclusions:** Home administration of treatments for haematological malignancies appears to be a feasible and advantageous model of care that may alleviate pressure on healthcare services while improving patients' quality of life. The development of standardised national guidelines is warranted to ensure equitable access to home-based cancer care across Sweden.

NSP-13

Home Immunoglobulin Services to Support Secondary Immunodeficiency in the Era of Bispecific Antibodies for Multiple Myeloma

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Introduction: Secondary Immunodeficiency (SID) is becoming increasingly common in haematology due to the expanding use of novel systemic anti-cancer therapies, including CAR-T cell therapy and bispecific antibodies. Resultant hypogammaglobulinaemia and recurrent infections are driving increased demand for long-term immunoglobulin replacement therapy. Traditional hospital-based intravenous (IVIG) delivery places significant pressure on day-case services and requires frequent patient attendance. As treatment complexity and service demand continue to rise, alternative models of care are required to maintain capacity whilst optimising patient experience. The aim of this service was to develop, implement, and evaluate a nurse-led home subcutaneous immunoglobulin (SCIg) service designed to support patients with SID, including those receiving novel myeloma therapies such as bispecific antibodies. **Methods:** A structured nurse-led home SCIG pathway was established incorporating governance approval, defined patient selection criteria, standardised patient training, competency assessment, and ongoing longitudinal monitoring. The service utilised manual push SCIG administration to facilitate safe, effective, and patient-centred home delivery. Eligibility was expanded to include selected patients receiving bispecific antibody therapy based on clinical and immunological risk assessment. **Results:** Implementation of home SCIG service has released approximately 1,100 day case chair hours annually whilst maintaining patient safety and treatment continuity. Patient-reported outcomes demonstrated high satisfaction (mean satisfaction score 9.52/10), with 80% of patients reporting reduced infection frequency and 62% reporting improved wellbeing (with the remainder remaining neutral). No patients have required discontinuation of home therapy or transitioning back to IVIG. **Conclusions:** Home SCIG represents a safe, sustainable, and patient-centred alternative to hospital-based IVIG for patients with SID in haematology. Nurse-led immunoglobulin services can reduce healthcare utilisation, improve patient experience, and support delivery of modern myeloma therapies within the evolving bispecific treatment landscape.

NSP-14

Hyperbaric Oxygen Therapy as Adjunctive Treatment for Steroid-Refractory IEC-Colitis After BCMA CAR T: A Two-Case Experience

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Introduction: Immune effector cell–associated enterocolitis (IEC-EC) is a recently described delayed complication of BCMA-directed CAR T-cell therapy in multiple myeloma, associated with significant morbidity and mortality. It is characterized by CAR T-cell infiltration of the gastrointestinal mucosa, leading to inflammatory epithelial injury, disruption of the mucosal barrier, and increased risk of severe, often fatal infections. To date, no standardized treatment exists, with limited response to TNF or α4β7 blockade (e.g., infliximab and vedolizumab) in steroid-refractory cases. Similarly, corticosteroids combined with T cell–directed therapies (e.g., cyclosporine, ruxolitinib) have demonstrated limited efficacy. Optimal management may therefore require both clone-directed therapy and strategies that promote mucosal repair. Hyperbaric oxygen therapy (HBOT) has demonstrated anti-inflammatory and tissue-restorative effects in inflammatory bowel disease but has not been explored in IEC-EC. **Methods:** We describe two patients with biopsy-confirmed IEC-EC following ciltacabtagene autoleucel (cilta-cel) treated with immunosuppressive therapy and adjunctive HBOT. Diagnostic evaluation excluded infectious etiologies; endoscopic biopsies demonstrated intramucosal CAR T-cell infiltration by anti-camelid VHH immunohistochemistry. HBOT was administered in 10-session blocks (60–90 minutes per session). Clinical response was assessed by stool frequency, corticosteroid use, hospital length of stay, and symptom resolution. **Results:** Patient 1, a 75-year-old male, presented on Day +90 post–cilta-cel with grade 3 non-bloody diarrhea refractory to corticosteroids and ruxolitinib. He progressed to grade 4 diarrhea with mesenteric volvulus requiring surgical resection around Day +180. HBOT was initiated and associated with marked clinical improvement, including reduction in stool frequency (5→1/day), discontinuation of corticosteroids, and cessation of parenteral nutrition. Symptoms recurred on Day +365 (biopsy confirmed) with pneumatosis on imaging. He responded to cyclosporine and repeat HBOT, with improvement in stool frequency (3→1/day). At the time of this report, repeat imaging is pending to evaluate pneumatosis. He remains in complete remission (CR) at Day +456. Patient 2, a 77-year-old male, presented on Day +72 with grade 3 non-bloody diarrhea refractory to corticosteroids and with only transient response to ruxolitinib and mesalamine. At recurrence, cyclosporine was initiated, and HBOT was added, resulting in sustained resolution of diarrhea and discontinuation of parenteral nutrition. He remains in CR at Day +264. **Conclusions:** To our knowledge, this is the first report of HBOT use in IEC-EC. Adjunctive HBOT was feasible, well tolerated, and associated with clinical improvement in both patients. While causality cannot be established due to other concurrent therapies, these findings support the need for prospective evaluation of HBOT as a non-immunosuppressive, mucosal-protective adjunct in IEC-EC.

NSP-15

Impact of Premedication De-Escalation on the Incidence of Infusion-Related Reactions with Isatuximab

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Introduction: Isatuximab (Isa) is an anti-CD38 monoclonal antibody (mAb) used in the treatment of multiple myeloma (MM). Incidence of infusion related reactions (IRRs) is reported in 38–46% of patients with those reactions primarily occurring in the first cycle (Lancet. 2019;394(10214):2096, Lancet. 2021;397(10292):2361). A 2024 retrospective review showed premedications can be omitted after the first cycle in patients receiving daratumumab, another anti-CD38 mAb (JCO Oncol Pract. 2024:OP2300470). Mayo Clinic began omitting premedications for patients receiving Isa after completion of cycle 1 (C1) in April 2024. **Methods:** Retrospective cohort study at the Mayo Clinic to assess rates of IRRs pre- and post-implementation of premedication de-escalation in patients with MM receiving Isa based therapies. Secondary objectives were to evaluate premedication related adverse events (ADEs) and impact on infusion center chair time. The study included patients aged ≥18 who received at least 5 consecutive doses of Isa at a Mayo Clinic site between 3/2/2020 and 4/1/2026. They were excluded if treated on a clinical trial or Isa doses administered >1 month apart. **Results:** 78 patients were included. The pre-intervention group included 50 patients with mean age of 68 years, 50% were female, and 90% were white. The post-intervention group included 28 patients with a mean age of 70.4 years, 42.9% were female and 82.1% were white. Premedications were administered to all patients during C1 in the pre-intervention group and 85.7% of patients in the post-intervention group. All patients in the pre-intervention group continued premedications during C2, whereas only 6 patients continued to receive premedications in the post-intervention group. IRRs were seen in 18% of patients in the pre-intervention group and 25% of patients in the post-intervention group during the first cycle of therapy prior to de-escalation. One patient in the pre-intervention group and no patients in the post-intervention group experienced an IRR during C2. A total of 12 patients in the pre-intervention group and 9 patients in the post-intervention group experienced at least one premedication related ADE. Commonly reported ADEs included insomnia, edema, headache, and hypertension. These were mainly attributed to

steroid use. Mean time from infusion center check-in to check-out was 5.47 hr for C1 and 4.28 hr for C2 in the pre-intervention group compared to 5.4 hr and 3.8 hr in the post-intervention group. **Conclusions:** Premedication de-escalation following completion of C1 of Isa is safe and can reduce incidence of ADEs and infusion center chair times. Limitations of this study include the retrospective design and reliance on documentation of ADEs that may occur outside of the infusion center. Practice variation across sites may impact documentation and chair time. Future directions include evaluation of patient satisfaction and impacts on cost savings.

NSP-16

Implementation of a Nurse-Led Myeloma Clinic to Improve Service Efficiency and Patient-Centred Care

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Introduction: The increasing prevalence of Multiple Myeloma, alongside advances in treatment leading to longer patient survival, has placed sustained pressure on Haematology outpatient services. Traditional consultant-led clinic models are often associated with high patient volumes, prolonged waiting times, and limited flexibility to address the holistic needs of patients. In response a nurse-led Myeloma clinic was developed to improve service efficiency, reduce consultant clinic burden, and enhance patient centred care within a tertiary centre. **Methods:** The service redesign involved the establishment of a specialist nurse-led clinic for clinically stable Myeloma patients receiving ongoing systemic anti-cancer therapy (SACT) or under long-term monitoring. Clinical Nurse Specialists, with expertise in Myeloma management, conduct patient assessments, review laboratory results, manage treatment toxicities, and make prescribing decisions within agreed protocols. Clear eligibility criteria and escalation pathways have been implemented to ensure patient safety with appropriate medical oversight. Challenges have included the need for robust training, competency assessment, and ongoing professional development to support autonomous nursing practice. Governance structures, including defined protocols, prescribing frameworks and clear documentation standards, have been essential to ensure clinical safety and accountability. Medical clinic numbers pre and post implementation have been analysed to determine if there has been a measurable improvement to service efficiency. **Results:** The introduction of the nurse-led clinic has resulted in a measurable reduction in consultant clinic workload, allowing medical staff to prioritise newly diagnosed patients, complex cases, and those requiring treatment changes. Clinic capacity has been optimised through flexible scheduling and improved patient flow, contributing to shorter waiting times and increased appointment availability. The model has supported a more efficient use of multidisciplinary team resources. A key benefit of the nurse-led model was the enhancement of patient centred care. Patients have reported high levels of satisfaction with the accessibility and continuity provided by the nursing team. Consultations are often longer and more holistic, allowing for comprehensive discussions around symptom management, treatment adherence, psychological support and quality of life. **Conclusions:** In conclusion, the implementation of the nurse-led Myeloma clinic represents an effective strategy to reduce clinic burden, improve service efficiency, and deliver high-quality patient-centred care. This model aligns with with current healthcare priorities of workforce optimisation and sustainable service delivery, while maintaining strong clinical governance and patient safety.

NSP-17

Initial Experiences of Outpatient Bispecific Antibody Administration at a Large Academic Center

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Introduction: Bispecific antibodies (BsAbs) have advanced treatment for multiple myeloma. Four BsAbs (teclistamab, talquetamab, elranatamab, and linvoseltamab) are approved in the United States and in some other countries. Expanding outpatient (OP) administration of BsAb to local communities is essential to meet rising demand and address limited inpatient capacity. Administering tocilizumab before BsAbs reduces the incidence and severity of cytokine release syndrome (CRS), supporting OP and community-based care. This report describes our initial experiences in developing an OP BsAb protocol and evaluating safety outcomes in a cohort receiving OP BsAbs with prophylactic tocilizumab. **Methods:** A multidisciplinary team developed patient(pt) selection criteria and protocols for OP BsAb therapy. This includes structured education for pts/caregivers, provision of supportive medications, and monitoring protocols. Eligibility required residing < 30 minutes of the center, a 24-hour caregiver, good performance status, no rapidly progressive disease or significant comorbidities, and willingness to participate in OP monitoring. Data from all pts were collected to assess safety, efficacy, and opportunities for process improvement. **Results:** Between March 1 and May 15, 2026, 27 pts received BsAbs at our center. Four pts (15%) met criteria for OP, while 23(85%) required IP admission. Reasons for IP admission were distance >30 mins (17/23, 74%), rapidly progressive disease (5/23, 22%), and insufficient caregiver support (1/23, 4%). Prior to OP BsAb, pts received dexamethasone and acetaminophen, and a single dose of tocilizumab (8 mg/kg IV), followed by BsAb therapy with step-up dosing (dose 1,

Monday; dose 2, Wednesday; dose 3, the following Monday) to minimize CRS risk over the weekend. Providers evaluated pts before each dose, and the nurse coordinator conducted daily telephone calls to review medications, vital signs (checked every 6 hours) and side effects. At the first sign of CRS or ICANS, pts were instructed to self-administer dexamethasone 12 mg and acetaminophen 650 mg, then contact the provider. None of the OP pts developed a fever >38 °C or showed symptoms of ICANS. No hospitalizations occurred during step-up dosing. **Conclusions:** This initial single-center experience shows that OP BsAb administration with prophylactic tocilizumab is feasible in selected pts (4/27, 15%) without observed CRS, ICANS, or unplanned hospitalization. These results are consistent with larger studies, indicating that BsAb administration in OP and community settings is feasible when supported by rigorous patient selection and preparedness to manage adverse events. Distances >30 mins from the center represented the primary limitation to OP BsAb and underscores the need to expand community access. A team approach supports pt and caregiver understanding and adherence to protocols, thereby ensuring the safe delivery of these therapies. Future analyses will assess the financial impact of OP versus IP dose escalation of BsAb.

NSP-18

Insights from a Nurse-Led Care Programme: A Qualitative Audit in a Resource-Constrained Oncology Setting

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Introduction: Patients with multiple myeloma in low-resource settings often face barriers to timely diagnosis, treatment access, symptom management, and continuity of care. These challenges may include limited understanding of the disease and treatment, transport difficulties, financial strain, stigma, and inadequate psychosocial support. A nurse-led care programme was implemented to address these gaps through patient navigation, supportive care, psychosocial counselling, and patient and caregiver education. **Methods:** This qualitative study examined patient navigation and supportive care pathways within an ongoing multiple myeloma care programme in a low-resource setting. Participants were patients with multiple myeloma and caregivers attending a tertiary academic hospital and care centre. Data comprised structured observations recorded by nurses and social workers during clinical and supportive care interactions, using standardized forms. Observation records collected over a period of 9 months (September 2025 to April 2026) were analysed using thematic analysis. All data were anonymised to protect patient confidentiality. **Results:** 337 observation records from 104 patients were analysed. Nurse-led contacts improved engagement and enabled timely identification of clinical and psychosocial needs. Theme 1: System barriers disrupted continuity of care; ongoing education and counselling were essential. Theme 2: Social and spiritual support shaped coping and engagement; family hardship and transport challenges limited access, while faith practices fostered resilience. Counselling on lifestyle, caregiver involvement, and practical support (assistive devices, accommodation) reduced barriers. Integrated clinical and psychosocial support improved understanding, adherence, and wellbeing. **Conclusions:** In this low-resource setting, patient navigation and integrated supportive care were associated with better continuity of care, improved patient understanding, and enhanced coping with disease-related and treatment-related challenges. These findings support continued investment in nurse-led navigation and holistic supportive care models, particularly within resource-constrained oncology settings. Future evaluations should employ mixed-methods designs with patient-reported outcome measures to strengthen the evidence base.

NSP-19

Maintaining Continuity of Multiple Myeloma Care During a Major Nursing Labor Disruption Through Multidisciplinary Workforce Redeployment

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Introduction: Healthcare labor disruptions present significant challenges to maintaining continuity of care for patients with multiple myeloma (MM), many of whom require ongoing infusion therapy, supportive care, and close clinical monitoring. In January 2026, a nursing labor strike across Mount Sinai Hospital (MSH), Mount Sinai West (MSW), and Mount Sinai Morningside (MSM) in New York City required rapid operational restructuring to preserve outpatient oncology and research services. **Methods:** A multidisciplinary contingency staffing model was implemented across three Mount Sinai campuses from January 12 to February 11, 2026. Operational strategies included redeploying Icahn School of Medicine nursing staff to outpatient clinics, utilizing research nurses to support investigational infusion visits, and deploying travel nurses to inpatient and outpatient standard-of-care infusion areas. Physician scheduling templates were temporarily modified during the first week of disruption, with a gradual return to baseline clinic volumes thereafter. Operational metrics evaluated included completed chemotherapy-related visits (chemotherapy infusions, chemotherapy injections, and vascular access device visits), office practice visits (new and established), transferred treatments, and research-related encounters. Volumes were compared with the average 2025 baseline activity levels. **Results:** Across MSH, MSW, and MSM, 77% of baseline chemotherapy-related treatment volume and 94% of baseline office practice visits were maintained during the labor disruption period. A total of 275 chemotherapy treatments were successfully transferred to non-striking affiliated facilities to preserve continuity of care. Research operations were also maintained throughout the disruption. During

the 5-week period, 263 research infusion visits were completed, representing 71% of the planned research infusion volume. Additional research activity included 104 inpatient visits and 336 other research-related visits. Research infusion completion rates improved progressively during the disruption period, rising from 44% in week 1 to 92% in week 5. **Conclusions:** Rapid implementation of a multidisciplinary staffing and operational contingency model allowed preservation of substantial outpatient MM treatment and clinical research activity during a major nursing labor disruption. Strategic redeployment of institutional nursing resources, integration of research nursing staff into clinical operations, utilization of travel nurses, and transfer of treatments to affiliated sites were critical to maintaining continuity of care for patients with MM. These findings may help inform future operational preparedness strategies for oncology programs facing workforce disruptions.

NSP-20

Making Sense of Dollars Available for Cancer Patients With History of Toxic Environmental Exposure

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Introduction: The Radiation Exposure Compensation Act (RECA), enacted in 1990, was substantially expanded in 2025 to improve compensation for individuals with cancer exposed to ionizing radiation from U.S. nuclear weapons testing during and after WWII. The geographic area was increased from 21 specific counties to all of Utah, Idaho, and New Mexico and parts of Arizona and Nevada. Compensation for qualifying malignancies increased from $50k to $100k. Multiple myeloma (MM), a recognized compensable malignancy under RECA, is prevalent in the eligible area with 15–20k people living with myeloma in the region. The expansion of RECA has immense implications for the financial health of MM patients in the U.S. Mountain West and care sites have an obligation to dedicate resources to enrolling patients in such programs. **Methods:** A single center electronic health record (EHR) review identified 2,173 patients with MM. Patients potentially eligible for RECA benefits were identified using expanded program birth year criteria (born between September 24, 1944 and November 6, 1962). Final eligibility determination was made by MM program licensed clinical social worker (LCSW) in person or over the phone at the time of clinic visits. Clinical providers discussed the RECA program with all patients born on or before Nov 4, 1962. Application resources obtained from a grant funded RECA assistance clinic were distributed to potentially eligible patients. Upon filing of application with the federal government our clinic provided a physician signed diagnosis certification letter. **Results:** Among 2,173 patients with multiple myeloma 1,312 (60.4%) met age-based RECA eligibility criteria. According to methodology above, 58 patients were screened by LCSW and 19 patients (32.8% of LCSW screened patients) formally met eligibility criteria for RECA application and two have received compensation. **Conclusions:** Implementing a RECA screening initiative at a single academic center in the U.S. Mountain West identified a large number of MM patients eligible for financial compensation. Extrapolating the observed final eligibility rate (32.8%) to the 1,312 age-eligible patients suggests that ~ 430 patients at this center may qualify for compensation, representing $43 million in benefits from RECA. The potential financial impact across the mountain west is immense. Considering that the RECA geographical region has tens of thousands of MM patients the uncompensated financial impact could reach nearly $400 million. As financial toxicities of MM diagnosis increase enrolling patients in compensation programs such as RECA should be supported by LCSWs, nurse navigators and APPs in the form of screening and application assistance. Future initiatives should integrate toxic exposure compensation program application assistance into supportive oncology infrastructure at major academic cancer centers.

NSP-21

M-FIT: An EHR-Integrated Myeloma Frailty Assessment Tool for Real Time Clinical Decision Support

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Introduction: Multiple myeloma (MM) predominantly affects older adults, with most cases diagnosed and deaths occurring in patients over 65 years of age. The elderly MM population is highly heterogeneous; chronological age and performance status alone are insufficient to guide treatment decisions. The NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma recommends considering frailty assessment in older MM patients using the International Myeloma Working Group (IMWG) Myeloma Frailty Score Calculator, which can help inform prognosis and treatment intensity decisions. However, routine frailty assessment is inconsistently performed in clinical practice because the underlying tools are time-consuming and not natively integrated into electronic health record (EHR) workflows. Our team sought to demonstrate the feasibility of operationalizing the IMWG frailty score with our institutional EHR as a first step towards point of care risk stratification, guideline-concordant decision making, and consistent tracking of frailty status in patients with MM. **Methods:** Using an EHR-based implementation framework, our team built an integrated M-FIT (Myeloma Frailty Integrated Tool) consisting of a structured clinical document capturing the four IMWG components: (1) Patient age stratification (≤75, 76–80, and >80 years); (2) the Charlson

Comorbidity Index (CCI) scored across 19 weighted comorbid conditions; (3) the six-item Activity of Daily Living (ADL) scale; and (4) the eight-item Instrumental Activity of Daily Living (IADL) scale. Feasibility was assessed by conducting frailty assessments on 10 patients using the M-FIT following go-live. Evaluation metrics included time to score completion and clinical integration. Clinical integration is defined as the incorporation of the frailty assessment into the clinical note during routine visits. **Results:** Since our go-live for the M-FIT within our EHR, we completed frailty scores on 10 patients. We found the median time to calculate the score was 140 seconds (range 40–180 seconds). Additionally, rules comparing documented findings against discrete data in the patient's medical history enabled the identification of discrepancies. This helped to update the patients' medical history when needed, thereby improving the accuracy of the data entered into the calculator. **Conclusions:** We present the first implementation of an automated myeloma frailty score calculation embedded within an EHR (M-FIT) at our institution, and report pilot feasibility and clinician usability. This work addresses a critical gap between clinical tool validation and real-world deployment, with the potential to facilitate earlier and easier identification of frail patients and guide appropriate clinical intervention.

NSP-22

Nurse Led Care in AL Amyloidosis: Impact of a Nurse Led Clinic on Enhancing Patient Experience, Improving Outcomes and Service Evaluation

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Introduction: Systemic AL amyloidosis is a rare condition, most patients present with heart failure and historically have poor outcomes. Contemporary treatment requires intensive monitoring, frequent medication adjustments, and supportive care. An outpatient nurse-led clinic was established in our specialist centre 2019 aimed to provide proactive monitoring, supportive care, timely escalation to medical teams to reduce unnecessary hospital admissions. A weekly Friday clinic, two days post-treatment when side effects at the highest, allowing intervention before the weekend. Assessment of hypotension, fluid management oedema, treatment-related toxicities, treatment optimisation, psychological social needs, as well as end-of-life planning. This study evaluated patient experience. **Methods:** An anonymous patient satisfaction survey September 2025-April 2026 three months after diagnosis. The questionnaire assessed confidence in the nurse-led clinic, satisfaction with care, communication, symptom management, and access to support. Responses were recorded using 4-point Likert scale (strongly agree-disagree) free-text comments were collected and analysed. **Results:** Thirty-four patients (18 male, 16 female; median age 61 years [range 38–84]) were invited. Disease characteristics Mayo stage III 44%, Mayo stage I-II 35%, renal involvement 53%. Seven patients were not included as died within three months of diagnosis. Eighteen patients (53%) responded. 84% patient feedback was highly positive, noting strongly agree (57% all domains) agree (27% all domains). 89% felt their concerns were escalated appropriately to the consultant team, 89% received advise regarding symptoms, 89% given treatment side effects management, 89% knew how to contact the Clinical Nurse Specialist (CNS). 83% reported test results were clearly explained, 83% had confidence and satisfied in the nurse-led clinic, 83% were listened to and emotionally supported. 72% reported continuity of care with the same nurse. Areas of disagreement accounted for only 6%-11% related to: continuity of care, explanation of results and overall satisfaction. Nine patients provided free-text feedback 56% positive themes included high levels of satisfaction, support, excellent communication, and reassurance from the CNS team. Areas of improvement included: chemotherapy scheduling 22%, administration communication 22%, timing of clinic calls 11%, phlebotomy 11%. **Conclusions:** The nurse-led clinic for AL amyloidosis delivers high patient satisfaction, support, and confidence in care delivery. This service provides early clinical intervention, timely optimisation of blood pressure, diuretic, antiemetic, laxative medication doses, contributing to reducing out of hours calls and unplanned hospital admissions. Patient driven feedback highlights improvement in cross-service coordination and operational processes. Ongoing evaluation will continue additionally including evaluation of interventions delivered to patients, survivorship and impact of quality of life.

NSP-23

Optimising Elranatamab Treatment Delivery in Relapsed Refractory Multiple Myeloma: A Nurse Practitioner-Led Delivery Model at a Single Tertiary Centre

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Introduction: Elranatamab, a B-cell maturation antigen bispecific antibody is approved for relapsed/refractory multiple myeloma (RRMM) patients who have received at least three prior lines of therapy including a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody. We describe the implementation and patient outcomes of elranatamab at a single tertiary centre highlighting the essential role of a Multiple Myeloma Nurse Practitioner (MMNP)-led supportive care delivery program. **Methods:** Drug access was via an early access program or Pharmaceutical Benefits Scheme listing. Patients received elranatamab step-up dosing during a 5-day inpatient admission or as an outpatient (n = 3) with prophylactic tocilizumab. A REDCap (Research Electronic Data Capture) database was utilised for standardised data

entry, including patient demographics, prior lines of therapy, adverse events, and treatment response. Descriptive statistics were used to describe the clinical outcomes and adverse events. **Results:** To date 25 patients have received elranatamab treatment. The median age was 67 (range 49–78) years. Patients received a median of 5 (range 3–10) prior lines of therapy with a median of 5 (range 1–22) years since diagnosis. 68% of patients achieved a very good partial response or better with an 84% overall response rate. PET scans were performed in 10 patients and 4 achieved complete metabolic response at 6 months post-treatment. Adverse events included cytokine release syndrome (56%, all grade 1–2); multiple infections including cytomegalovirus with 24% requiring antiviral therapy; grade 4 neutropenia (56%) requiring regular filgrastim; skin toxicities including desquamation (11%) and injection site reactions (24%); and fatigue (68%). **Conclusions:** A MMNP-led elranatamab delivery model is feasible, safe, and effective in the management of RRMM patients. Elranatamab achieves high response rates in heavily pre-treated patients, and an MMNP-led model enables rapid identification and management of adverse events. This model supports high-quality, coordinated care for both inpatient and outpatient step-up dosing with reduced healthcare resource use and cost burden for outpatient delivery. Further evaluation of patient outcomes is planned as outpatient delivery participation increases.

NSP-24

Optimising Patient Experience in CAR T Therapy for Multiple Myeloma: Insights into Patient Motivations and Barriers

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Introduction: Multiple myeloma (MM) and amyloidosis (AL) represent treatable plasma cell cancers lacking a definitive cure. The introduction of a breakthrough therapeutic approach, largely confined to clinical trial settings in the UK, brings both anticipation and challenges in managing treatment-related toxicities and patient expectations. Chimeric antigen receptor (CAR)-T cell therapy is a novel immunotherapy strategy for MM with encouraging outcomes in clinical trials. This study aimed to evaluate patient knowledge and perceptions of CAR-T therapy, with a focus on understanding key concerns, motivations, and educational needs. **Methods:** A cross-sectional anonymised questionnaire was distributed via Microsoft Forms to MM/AL patients at a private tertiary centre and is still ongoing at time of abstract submission. The survey assessed demographics, treatment history, awareness and knowledge of CAR-T, willingness to undergo treatment, perceived benefits, concerns, and support needs. **Results:** A total of 68 patients responded, representing a broad range of ages and treatment histories, with two thirds having received two or more prior lines of therapy. Awareness of CAR-T therapy was high (>87%), with 75% feeling they had a moderate or greater knowledge of the treatment. The majority of patients (95%) were open to CAR-T, and 50% of them had discussed being a candidate with their consultant. Primary drivers were long-term survival and treatment-free interval, followed by clinical team guidance and patient-reported experiences. Key clinical concerns included longer term neurotoxicity (parkinsonism), cytokine release syndrome, infection risk, and long-term complications such as secondary cancers. Psychosocial barriers included cost/access to treatment, effect on partners, carers and family. Compromises patients were willing to take included frequent outpatient visits, extended sick leave from work and cosmetic side effects; however, most were less willing to accept cognitive issues (short and long term) and the need to isolate/shield. Approximately 20% of respondents reported lack of insurance approval as a major barrier. Some UK private insurers are still not routinely funding CAR-T, creating inequity of access. Patients identified important unmet needs, including improved education on CAR-T and its side effects, access to real-world patient experiences, and enhanced clinical support, particularly through one-to-one discussions and structured education. **Conclusions:** Patients with MM demonstrate high awareness and strong willingness to consider CAR-T, driven primarily by the potential for prolonged survival and treatment-free intervals. However, knowledge gaps, concerns regarding toxicity, and significant access barriers remain. Targeted patient education, improved communication, and structured supportive care interventions are essential to optimise patient experience and support informed decision-making, while addressing disparities in access to this emerging therapy.

NSP-25

Patient Reported Outcomes and Toxicities with Quadruplet Regimen Isa-VRd in Transplant Ineligible Newly Diagnosed Multiple Myeloma: A Single Centre Study

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Introduction: The addition of Isatuximab to Bortezomib–Lenalidomide–Dexamethasone (IsaVRd) improves responses in transplant-ineligible newly diagnosed multiple myeloma (TI-NDMM) patients as per IMROZ outcomes, but real-world patient

experience and toxicity during prolonged therapy remain incompletely characterised. Aims: To evaluate real world patient-reported quality of life (QoL), functional impact, and toxicities during the first year of IsaVRd treatment. **Methods:** Single-centre, cross-sectional survey of TI-NDMM patients within 12 months of starting Isa-VRd. A structured instrument based on EORTC QLQ-C30 captured global health/ QoL, symptom burden, functional impact on activities of daily living (ADLs) including social/ work/ leisure, financial concerns, infections/ hospitalisations, infusion reactions, side effects and administration preferences. Anonymous responses were summarised descriptively. **Results:** Fourteen patients initiated Isa-VRd (median age 75 years [61–86]; 43% male). Patients were early in therapy (median 4 cycles [1–8]). At time of data cut-off, all had responded; ORR 86% (12/14), ≥VGPR 29% (4/14). Dose reductions were common (~80% for lenalidomide/ dexamethasone). Five of fourteen had inpatient care during induction. 10 of 14 (71%) responses were received. Among respondents common symptoms were fatigue 90% (9/10), steroid-related sleep disturbance 50% (5/10), peripheral neuropathy 30% (3/10), and gastrointestinal toxicity 40% (4/10). Steroid-related mood/anxiety symptoms occurred in 60% (6/10). Patients commonly described practical coping strategies such as planning for steroid-related insomnia. Infusion-related reactions occurred predominantly in early cycles and were manageable (classical IV reactions 40% [4/10]; broader administration-linked symptoms 60% [6/10]). Infections were infrequent (10–20%; 1–2/10, with one pre-treatment). QoL was generally preserved with a median overall health and QoL rating of 5 out of 7. Most patients maintained independent ADLs (70% [7/10]). Sixty percent (6/10) reported no negative impact on overall QoL, and 70% (7/10) felt toxicities were manageable with supportive care and dose modification. Eighty percent (8/10) felt reassured by treatment efficacy and clinical support. Preferences for administration were varied. Some favoured simplified or home-based/oral approaches, others preferred in-hospital infusions for reassurance and routine. **Conclusions:** In this real-world TI-NDMM cohort, administration of Isa-VRd was feasible and produced impressive early response rates. Toxicities, especially fatigue, steroid-related insomnia/mood change, and mild neuropathy were common but manageable, with most patients reporting preserved QoL and functional independence. Embedding patient-reported outcomes into care pathways can prompt earlier mitigation (e.g., steroid/lenalidomide optimisation, infusion-rate adjustments, neuropathy and sleep management) and support personalised delivery to improve QoL during prolonged quadruplet therapy.

NSP-26

Prescribing and Use of Corticosteroids in UK Myeloma Patients

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Introduction: Corticosteroids are an integral component of treatment for patients with multiple myeloma (MM). Despite well-established therapeutic benefits, they are associated with well-known adverse effects. Commonly reported side effects include insomnia, mood disturbance, increased appetite, hyperglycaemia, increased risk of infection, and gastrointestinal irritation. With prolonged exposure, osteoporosis, fluid retention, and ocular complications such as cataracts may occur. Regular review and appropriate monitoring are therefore essential to minimise treatment-related morbidity. The primary objective of this work was to review current corticosteroid prescribing practices across UK myeloma centres and assess whether the development of UK-wide guidance would be beneficial. A secondary objective was to explore patients' knowledge and understanding of corticosteroid therapy. **Methods:** A survey was distributed to allied healthcare professionals involved in the care of MM patients across the UK. The survey focused on prescribing practices, review processes, and approaches to dose reductions. In addition, a patient feedback questionnaire was given to patients attending the Beatson West of Scotland Cancer Centre to assess their experiences of steroid treatment and their understanding of the rationale for its use. **Results:** Corticosteroid review and dose-reduction practices varied considerably among the 22 respondents. 32% reported there was no routine practice for reviewing or reducing corticosteroid therapy. Among respondents who undertook regular review, there was substantial variation in both timing and approach. The majority of respondents (82%) reported that disease response influenced decisions to reduce or discontinue corticosteroids. Only 55% of respondents reported routinely measuring HbA1c in patients receiving corticosteroids. Patient feedback from 33 participants indicated that most frequently reported side effects were insomnia, weight gain, and mood changes, experienced by 54% of respondents. Notably, 71% of respondents reported that they did not understand the role of corticosteroids in their treatment. Despite this, only one patient reported being completely averse to taking corticosteroids, and the majority expressed trust in their clinician's decision to continue therapy despite experiencing side effects. **Conclusions:** This survey highlights significant variation in corticosteroid prescribing, review, and monitoring practices across UK myeloma centres. Given the well-documented adverse effect profile, the development of UK-wide guidance outlining recommendations for routine review and dose reduction may be beneficial. Patient feedback demonstrates that many patients have a limited understanding of the purpose of corticosteroid therapy and associated side effects. This underscores the importance of consistent and reinforced counselling on corticosteroids, alongside education on novel anti-myeloma treatments, to support informed patient engagement and optimise treatment outcomes.

NSP-27

Reducing Workflow Burden and Improving Care Delivery in Multiple Myeloma: The Role of On-Body Injectors for Oncology Nursing Practice

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Introduction: The increasing use of biologic therapies in multiple myeloma (MM) has intensified operational and workforce pressures across oncology care settings. Conventional subcutaneous (SC) syringe administration requires labour-intensive preparation, manual injection, and sustained healthcare professional (HCP) involvement, contributing to workflow inefficiencies, occupational strain, and growing nursing burden. Workforce shortages and increasing treatment complexity further challenge oncology nursing and pharmacy services. On-body injectors (OBIs) are novel drug delivery devices that enable hands-free SC administration. In this study, we explore whether and how OBI implementation can alleviate health system challenges and workforce pressures while enhancing care efficiency. **Methods:** A targeted literature review was conducted using Embase, Ovid MEDLINE, and Ovid Nursing Database to identify evidence relating to SC administration challenges and the impact of OBIs in oncology care. Grey literature and nursing-focused publications were also reviewed. Evidence was synthesised thematically across HCP and health-system domains, focusing on nursing experience, workflow efficiency, occupational hazards, and care delivery implications. **Results:** Conventional SC administration pathways involve multiple resource-intensive steps, including biologic preparation under aseptic conditions, syringe priming, cold-chain handling, and manual administration. These processes contribute to substantial pharmacy and nursing workload and require specialised training and sustained clinical oversight. Evidence suggests that OBIs may simplify administration workflows by reducing manual preparation and injection requirements. Pharmacists and nurses reported strong preferences for OBI systems due to ease of use, simplified preparation processes, and reduced physical burden during administration. Compared with manual SC injections, OBIs are likely to reduce repetitive strain associated with prolonged manual injection force and decrease the risk of occupational injuries, including needlestick injuries. Closed-system OBI designs may additionally reduce HCP exposure to hazardous agents during drug preparation and handling. Reduced patient anxiety associated with hidden needle designs also lessens counselling requirements and improves clinic workflow efficiency. Literature also suggests that hands-free administration may further allow greater flexibility for nursing staff to optimise treatment throughput within busy oncology settings and support future decentralised care models in oncology practice. **Conclusions:** OBIs offer a promising strategy to reduce HCP workload burden associated with SC biologic administration in MM care. As SC biologics become increasingly integrated into MM treatment pathways, wider adoption of administration innovations is likely to help address workforce pressures while supporting more sustainable oncology service delivery.

NSP-28

Restructuring an Integrated Pharmacist-Led Ambulatory Haematology Service at a Tertiary Cancer Centre

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Introduction: The treatment landscape in malignant haematology is rapidly evolving toward complex ambulatory delivered therapies requiring coordinated multidisciplinary care across the continuum. Pharmacists are medication experts who improve optimisation and safety within multidisciplinary teams. While inpatient pharmacy services are well established, dedicated ambulatory pharmacist-led models remain less well defined. At our tertiary cancer centre, pharmacy services are primarily delivered through a rotational workforce within operational units. This service redesign aimed to establish an integrated pharmacist-led ambulatory model with senior pharmacy leadership to strengthen medication management across transitions of care and longitudinal follow-up. To our knowledge, this is among the first Australian descriptions of a dedicated pharmacist-led ambulatory haematology clinic. **Methods:** A pre-existing ambulatory pharmacist clinic was redesigned into a structured haematology-focused clinic with defined referral criteria and longitudinal follow-up of high-risk patients. Initial focus was myeloma, expanding to broader high-risk haematology populations. Standardised review points were implemented across key transitions including treatment initiation, post-discharge, pre-transplant and pre–CAR-T. Core activities included comprehensive medication reviews, toxicity/supportive care management, adherence assessment, education and coordination across care settings. The pharmacist was embedded within the haematology multidisciplinary team, contributing to clinical decision-making, protocol optimisation and governance including nurse-led clinics. **Results:** Service activity increased from an average of 50 patient reviews annually, to an average of 40 patients per month, with sustained growth in clinician-initiated referrals for direct and indirect patient care. The model enabled rapid implementation of pharmacist-led pathways, including an immunomodulatory drug desensitisation protocol and outpatient bispecific antibody step-up dosing pathway. It contributed to our myeloma survivorship clinic, where 75% of patients required medication changes, demonstrating medication complexity and value of longitudinal pharmacist review. **Conclusions:** An integrated pharmacist-led ambulatory haematology model enabled specialist pharmacist expertise to be embedded across the continuum of multidisciplinary malignant haematology care. The model supported safe delivery of novel outpatient therapies, complex medication decisions and governance in evolving haematology practice. Further evaluation

will assess clinical impact, clinician experience and patient reported outcomes.

NSP-29

Review of Nurse and Pharmacist Survey Evidence on an On-Body Injector and Implications for Isatuximab Subcutaneous via the On-Body Injector in Patients With Multiple Myeloma

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Introduction: Subcutaneous (SC) delivery of isatuximab (Isa), an anti-CD38 monoclonal antibody, has been investigated in clinical trials using a novel wearable on-body injector (OBI). The OBI was designed for hands-free administration, may reduce healthcare professional (HCP) burden by potentially reducing repetitive strain and needlestick injuries, and has the potential to allow at-home administration via HCP. Given the key role of nurses and pharmacists in preparing and administering SC biologics, understanding their preferences regarding OBI administration is crucial. Here, we summarize studies on nurse and pharmacist preferences for the administration and preparation of SC OBI vs manual SC injection. **Methods:** Data were synthesized from 5 published or presented industry-sponsored studies using surveys or questionnaires. In 3 studies, participants had experience with large-volume SC manual injection and were introduced to the OBI via a 1-minute short demo video and a 4-minute presentation before the survey began. In the remaining 2 studies, participants had experience with SC OBI and SC manual injection. Across studies, surveys assessed HCP preferences and perceptions regarding SC OBI vs manual SC injection. **Results:** Across the 5 studies, a total of 154 nurses and 111 pharmacists were surveyed. These studies consistently showed high preference for SC OBI administration and preparation over manual SC injection. Nurse preference (from 3 studies, including 1 with 3 physicians and 16 nurses) ranged from 78.9% to 100% for SC OBI. A combined study of 81 nurses and 81 pharmacists reported 93.8% preference for SC OBI preparation, and a dedicated pharmacist study showed 100% preferred SC OBI vs manual SC injection preparation. Participants identified ease of learning and use as key drivers of preference, with highly valued attributes including hands-free administration and single-step, needleless preparation. Additional perceived benefits included improved workflow efficiency, time savings, reduced physical and mental burden for HCPs, lower risk of needlestick injuries due to lack of needle exposure, decreased patient pain associated with thinner needles, increased patient mobility, and greater flexibility in preparation and administration settings. **Conclusions:** Nurses and pharmacists consistently expressed a preference for the preparation and administration of SC OBI vs SC manual injection. Preference was driven by the OBI's potential for improved efficiency, time savings, a simpler preparation process, flexibility in the preparation location and a reduced risk of needlestick injuries. Limitations of this review include the differences in participant experience with the OBI across studies. Evidence from the studies summarized supports the potential of Isa SC OBI to enhance the clinical care landscape for both nurses and pharmacists.

NSP-30

Specialized Nurse-Led Infrastructure Supporting Advanced Immunotherapy Clinical Trials in Multiple Myeloma

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Introduction: The rapid evolution of immunotherapeutic strategies in Multiple Myeloma (MM), particularly chimeric antigen receptor T-cell (CAR-T) and T-cell engager (TCE) therapies, has transformed treatment while introducing substantial complexity in clinical trial execution. At our academic institution, a dedicated nurse-led MM research program has emerged as a model for integrating advanced clinical practice. This program, comprising six advanced practice providers and three registered nurses, serves as a specialized clinical research unit and sub-investigator team under the supervision of an MM physician. **Methods:** In 2025, the team managed over 40 active cellular therapy protocols, including 16 CAR-T trials (8 first-in-human or novel agents and 8 FDA-approved constructs), 22 TCE protocols evaluating both investigational and commercially available therapies (10 novel TCE therapies and 12 FDA-approved TCEs), and two antibody-drug conjugate studies. The program treated over 189 patients. The nursing team plays a central role in protocol feasibility and operational planning, utilizing a Feasibility and Financial Risk (FFR) acuity tool to assess trial complexity, resource allocation, and patient safety considerations prior to activation. They conduct independent clinical assessments, confirm eligibility and safety criteria, execute protocol-directed therapies, document adverse events (AEs), and implement real-time toxicity mitigation strategies. **Results:** This nurse-led model effectively manages the operational complexity and safety demands of early- and late-phase MM trials. The nursing team contributes to protocol selection and activation by stratifying study acuity and feasibility using the FFR framework, enabling efficient resource

utilization and safe trial implementation. They provide continuous patient monitoring across both inpatient and outpatient settings, including hybrid care models for step-up dosing of TCE therapies that optimize safety while reducing inpatient utilization. Rigorous adherence to protocols, detailed documentation, and proactive AE surveillance ensure continuity and quality of care. Implementation of multimodal adaptive operational systems has improved workflow efficiency, strengthened dynamic risk monitoring, and enhanced interdisciplinary coordination across pharmacy, laboratory, and data management teams. **Conclusions:** A nurse-led clinical research program can successfully support a large, complex portfolio of advanced immunotherapy trials in a high-acuity academic setting. By serving as sub-investigators, nurses enhance trial quality, ensure patient safety, and expand physicians' research capacity. Their leadership in protocol feasibility assessment, AE management, hybrid care delivery models, and translational application highlights the expanding role of specialized nursing in hematologic malignancy research. This model supports broader adoption of nurse-led cellular therapy programs to safely and efficiently deliver innovative therapies.

NSP-31

Symptom Burden, Unmet Information Needs, and the Role of a Patient-Led Support Group in POEMS Syndrome: A Mixed-Methods Survey of 21 Patients

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Introduction: POEMS syndrome is a rare plasma cell disorder (estimated prevalence 0.3 per 100,000) that remains unfamiliar to many clinicians outside specialist centres. The rarity of POEMS means most patients never encounter another person with their diagnosis through clinical channels, leaving peer connection absent from their care by default. Disease-directed therapy is increasingly effective, yet high residual symptom burden and unmet supportive care needs persist. This nurse-led service evaluation was undertaken to characterise those needs and to evaluate a virtual peer support group specifically established for people living with POEMS. **Methods:** An anonymous online questionnaire combining structured (Likert and multi-select) and free-text items was distributed to members of a virtual POEMS support group during October 2025. Items covered demographics, symptom burden, treatments received, perceived disease control, information sources and unmet learning needs, and the perceived impact of the support group on knowledge, healthcare interactions, connectedness, and wellbeing. Responses were summarised descriptively; free-text responses were reviewed thematically. Respondents provided informed consent for anonymous use of their responses. **Results:** 21 patients responded; 57% had been diagnosed >5 years previously and 95% had received disease-directed treatment (stem cell transplant 57%, chemotherapy/plasma cell-directed therapy 57%, radiotherapy 43%, corticosteroids/immunotherapy 33%). Despite 95% rating their disease as "very well" or "somewhat" controlled, residual symptom burden was high: mobility difficulty (90%), nerve pain or weakness (62%), and fatigue (43%). Diagnosis had required multiple opinions (52%) or specialist neurology input (43%). Unmet information needs were substantial: 76% wanted more on latest research/treatments, 62% on nutrition and exercise, 57% on symptom management. Among 12 support group attenders, 8/12 reported improved understanding of POEMS, 6/12 improved wellbeing, and 6/12 greater connection with others; 8/12 reported no change in confidence discussing their condition with clinicians. Most-valued aspects were meeting other patients and learning from guest speakers (each 6/21). Free-text responses described profound impacts on independence, work, and identity, and identified geographical access and lack of structured content as barriers. **Conclusions:** A virtual peer support group delivered measurable benefits in understanding, wellbeing, and connection for most attenders in this rare-disease cohort, despite less effect on patient–clinician communication confidence. These findings are contextualised by high residual symptom burden and substantial unmet information needs persisting despite good disease control underscoring the opportunity for nurse-led supportive care and structured integration of peer support into POEMS clinical pathways.

NSP-32

The Disclosure Gap in Myeloma Care: A Pilot Identifying Barriers to Symptom Reporting and the Value of Patient-Led Support Tools

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Introduction: Effective symptom reporting is crucial for managing treatment-related toxicity in patients receiving myeloma therapy. This allows for timely dose modifications, treatment delays, and supportive care to reduce avoidable morbidity. Under-reporting is well-recognised and multi-factorial. This pilot study aimed to identify patient-perceived barriers to communication and evaluate the acceptability of a patient-led support tool intended to empower symptom disclosure and standardise pre-clinic preparation. **Methods:** Participants (N = 9) were recruited from a single-centre myeloma clinic. A mixed-methods approach was used, consisting of a semi-structured patient focus group (analysed via thematic analysis) followed by a qualitative and quantitative questionnaire. This approach allowed for an in-depth exploration of the patient experience regarding the ease of symptom reporting, reasons for non-disclosure, and the perceived value of a patient-led pre-clinic prompting tool. **Results:** Most patients (89%; 8/9) found symptom reporting "straightforward" or "manageable," yet 78% (7/9) had forgotten to mention concerns during consultations. One-third (33%; 3/9) intentionally withheld symptoms due to perceived time constraints, clinician burden, treatment implications, or emotional avoidance.

Primary barriers: lack of clinician continuity (67%; 6/9), complex medical language (44%; 4/9), and rushed clinic environments (33%; 3/9). Facilitators: pre-appointment notes (78%; 7/9) and clinician continuity (67%; 6/9). All (100%) preferred a communication style mixing open and closed questions. Sensitive topics that the group found hardest to discuss included anxiety/low mood (67%; 6/9), end-of-life concerns (56%; 5/9) and finances (22%; 2/9). Omissions were driven by pressure to "stay positive" (33%) or avoiding distress (22%). While 89% previously used symptom questionnaires, they did so "rarely." The bulk (89%; 8/9) suggested a prompt tool would improve disclosure and supported patient-led co-design. **Conclusions:** There is a clear discrepancy between patient-perceived ease of communication and the actual frequency of symptom omission, driven by memory failure and the cognitive burden of the consultation. The fact that 78% of patients "forget" to mention concerns suggests that reliance on spontaneous patient reporting is an insufficient strategy. Addressing this "disclosure gap" is a clinical safety priority. Future interventions should move beyond simply encouraging patients to speak up and instead provide structured, patient-designed tools. By systematically identifying concerns, clinicians can mitigate the effects of disease, comorbidities and therapy on memory, ensuring patient-prioritised themes are consistently heard. This pilot provides a scalable framework to standardise symptom reporting across international myeloma centres, facilitating enhanced communication within the multidisciplinary team.

NSP-33

Tocilizumab for Prevention of Cytokine Release Syndrome Associated with Ciltacabtagene Autoleucel

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Introduction: Ciltacabtagene autoleucel (Cilta-cel) is a CAR T-cell that targets BCMA expressed on myeloma cells and is FDA approved for RRMM after >1 prior line of therapy and who are lenalidomide refractory. In CARTITUDE-1 and CARTITUDE-4, cytokine release syndrome (CRS) occurred in 95% and 76.1%, respectively, with a median onset of 7–8 days. Though most CRS events are grade 1–2, patients are standardly monitored inpatient for 7–10 days to ensure prompt management of CRS and ICANS. Tocilizumab (toci), an IL-6 inhibitor approved for CRS treatment, has reduced CRS incidence with bispecific antibodies when given as prophylaxis. To reduce rates of CRS and facilitate outpatient administration of cilta-cel, we instituted a protocol change and administered prophylactic toci on day +5. Timing was based on the drug's half-life of approximately 12 days and the median time to CRS observed in clinical trials and institutional experience. Here, we present the methodology and the impact of prophylactic toci on the rates of CRS and ICANS with cilta-cel. **Methods:** Patients receiving cilta-cel at Winship Cancer Institute of Emory University between June 2025 and May 2026 and scheduled to receive prophylactic toci 8 mg/kg (max 800 mg) on day +5 were included. Patients who developed early CRS and received toci before day +5 did not receive the prophylactic dose. Per institutional standard of practice, all patients who experienced any grade CRS were treated with toci, and dexamethasone was administered for persistent or grade 3–4 CRS. ICANS was treated with corticosteroids. CRS and ICANS were graded using ASTCT criteria. **Results:** 68 patients received cilta-cel with the intent to receive prophylactic toci. Median age was 65 (range 42–81) with a median of 3 prior lines of therapy (range 1–8). The per protocol (PP) cohort included 57 (84%) patients who received prophylactic toci on day +5. 11 (16%) patients developed early CRS and received therapeutic toci before day +5. In the intent-to-treat cohort, CRS incidence was 29.4%, including 5 grade 2 (7.4%) and 1 grade 3 (1.5%) events. In the PP cohort, CRS occurred in 9/57 patients (15.8%), including 3 grade 2 events (5.3%). Median CRS onset was 8 days (range 5–10), and median duration was 1 day (range 1–4). ICANS occurred in 7 patients (10.3%), including 1 grade 4 and 1 grade 2 event, both in patients with early CRS who did not receive prophylactic toci. Only 1 grade 1 ICANS event occurred in the PP cohort. **Conclusions:** Prophylactic toci on day +5 decreased the incidence and severity of CRS in RRMM patients receiving cilta-cel markedly from 76 to 95% in clinical trials to 16% in our treated population. This strategy improved tolerability, reduced steroid and immunosuppressant use, shortened hospitalization, and supported outpatient cilta-cel administration potentially improving access and patient satisfaction. Longer follow-up is needed to evaluate long-term safety, efficacy, and rates of other immune effector cell-associated toxicities, including MNTs and colitis.

NSP-34

Using a Needs-Based Assessment to Develop a Multimodal Toolkit Supporting Care Partners of Myeloma Patients

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Introduction: Care partners (CPs) play a critical role in supporting patients living with multiple myeloma (MM). Myeloma patients often rely on CPs to assist with navigating treatment,

monitoring symptoms, and coordinating care throughout the disease trajectory. Although resources exist, they are often fragmented and may not fully address CP needs. Both patients and CPs frequently seek information through digital platforms, and understanding differences in their information needs can inform more targeted education and support. The International Myeloma Foundation (IMF) Nurse Leadership Board (NLB) aimed to develop a comprehensive, multimodal toolkit for CPs by improving access to support resources and educational content throughout the care continuum. **Methods:** To ensure the toolkit adequately addressed CPs needs, we analyzed the questions submitted to Myelo, a conversational artificial intelligence (AI) application developed by the IMF within its Myeloma Knowledge Platform to characterize linguistic patterns and identify CP–specific concerns. All questions were deduplicated, normalized, and stemmed using a standardized text processing pipeline. CP questions were identified using 50+ explicit relationship terms. Log-odds differences were computed for the full corpus and the CP subset. In addition, a survey consisting of a 10-item questionnaire was sent to CPs through a support group to assess challenges, needs and knowledge gaps. **Results:** Among a total of >30,000 questions submitted to Myelo January 1 to October 30, 2025, over 500 (1.6%) inquiries were from CPs. The overall corpus emphasized clinical and laboratory concepts, whereas CP queries focused more on support and logistical concerns. CPs more often asked about legal, financial, insurance, emotional effects and education, whereas the full corpus inquired about trials, treatments, testing and staging of myeloma. The survey was sent to 130 CPs, with 24 respondents (18%). Most CPs were spouses or significant others (92%), aged ≥61 years (67%), had served in the CP role for 1–10 years (79%), and lived with the patient (92%). Reported challenges included disease and treatment complexity, physical sequelae of MM, information overload, and limited access to early palliative care. Findings from the CP survey highlighted a strong need for CP-specific resources to reduce burnout and isolation. CPs reported benefits from educational organizations, spiritual or faith-based care, support groups and practical assistance. **Conclusions:** The Myelo analysis revealed differentiated educational needs of CPs on practical, emotional, legal and financial guidance and support. The findings from the survey helped the IMF NLB to develop care partner resources to meet their learning needs. The toolkit would include both a physical component and links/QR codes to curated educational resources on the IMF website. This initiative highlights the role of oncology nurses in developing practical resources that address both clinical and psychosocial aspects of care.

LATE BREAKING ABSTRACTS

LBA-01

CERVINO: Phase (Ph) 3 Results of Etentamig vs Investigator's Choice of Standard Available Therapies (SAT) in Patients (Pts) With Triple-Class Exposed Relapsed or Refractory Multiple Myeloma (RRMM)

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Introduction: Etentamig (Etenta) is a second-generation BCMA × CD3 bispecific T-cell engager composed of a low-affinity CD3 binding domain, potentially reducing cytokine release syndrome (CRS) and infections, a high avidity bivalent BCMA-binding domain, and retained FcRn binding enabling monthly (Q4W) dosing after a single step-up dose (SUD). CERVINO (NCT06158841) is a global, randomized Ph 3 study evaluating Etenta vs investigator's choice of SAT in RRMM. We report primary results from the prespecified interim analysis of CERVINO. **Methods:** Eligible pts with triple-class (proteasome inhibitor, immunomodulatory drug, and anti-CD38 mAb) exposed RRMM had ≥2 prior lines of therapy (pLoT) and were anti-BCMA treatment (tx) naïve. Pts were randomized 1:1 to Etenta Q4W or SAT (carfilzomib + dexamethasone [Kd], elotuzumab + pomalidomide + d [EloPd], or selinexor + bortezomib + d [SVd]). Dual primary endpoints were overall response rate (ORR) and progression-free survival (PFS); key secondary endpoints included overall survival (OS) and depth of response. **Results:** At cutoff, 393 pts (Etenta: N = 196; SAT: N = 197) were randomized (median [med] follow-up: 11.4 months [mo]; med age: 70 yrs; 68.2% ≥ 65 yrs; 14.5% US pts). Of US pts on Etenta, 41.7% received tx in community settings and 45.8% initiated tx in an outpatient setting. Med time from MM diagnosis was 5.2 yrs, and pts had a med 3 (range: 1–10) pLoT (≥3: 55.2%). Disease was triple-class refractory in 51.9%, and refractory to last pLoT in 90.1% and anti-CD38 mAb in 86.0%; 23.4% had high-risk cytogenetics. For Etenta vs SAT, ORR [95% CI] was significantly higher (74.0% [67.25–79.97] vs 45.7% [38.59–52.91]; $P < 0.0001$), and PFS was significantly improved (HR: 0.40; 95% CI: 0.29–0.54; $P < 0.0001$) with benefit maintained across all prespecified subgroups; med PFS (95% CI) was not reached (14.55–not estimable) vs 6.2 (4.63–7.26) mo. For Etenta vs SAT, 12-mo OS was 87.9% vs 72.0% (HR: 0.48; 95% CI: 0.29–0.77; nominal $P = 0.0012$); prespecified efficacy boundary for OS was not crossed at cutoff. For safety analysis set pts (Etenta: N = 195; SAT: N = 193), TEAEs occurred in 97.9% vs 95.3%, Grade (G) 3/4 TEAEs in 73.3% vs 64.2%, and serious TEAEs in 51.8% vs 40.4%. Fewer Etenta pts vs SAT had TEAE-related discontinuations (3.6% vs 9.6%) or fatal TEAEs (2.6% vs 5.7%). For Etenta vs SAT, G3/4 infections were 27.7% vs 19.2% (G5: 1.5% vs 3.1%). Of Etenta pts, CRS was 39.5% and ICANS was 3.6%, both primarily G1/2 with G3 ≤ 1% and no G4/5. Of pts who received a single SUD, CRS was 28.3% (G1: 23.9%; G2: 4.4%; no ≥ G3); ICANS was 0.9% (1 pt; G1). **Conclusion:** In heavily pretreated pts with triple-class exposed RRMM, Etenta significantly improved ORR and PFS vs SAT, with an early positive OS signal. A single SUD and Q4W dosing from initiation were associated with very low rates of CRS, ICANS, and ≥ G3 infections, reinforcing Etenta's best-in-class safety potential. Data support Etenta monotherapy as a new standard of care with convenient dosing suitable for global outpatient and community use.

LBA-02

Early Indian Real-World Experience With Imported Talquetamab in Heavily Pretreated Plasma Cell Neoplasms: A Single-Centre Case Series

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Introduction: Talquetamab access and India-specific real-world data remain limited. We describe response and safety at a tertiary Indian centre using talquetamab obtained through import rather than routine domestic commercial supply, since it is not commerically available. This is the largest data set available in India of Talqeutamab. **Methods:** Following institutional ethics approval, we retrospectively reviewed 10 adults receiving talquetamab at Fortis Memorial Research Institute, Gurugram, India. Treatment records spanned January 19, 2025, to July 29, 2026. Response and adverse events were analysed as recorded. Categorical outcomes are reported as n/N and response with a two-sided Clopper-Pearson exact 95% confidence interval. **Results:** Median age was 62 years (range, 46–78), six patients were male, nine had multiple myeloma, one had plasma cell leukaemia, and three had extramedullary disease. Patients had received a median of five prior lines (range, 4–6). Seven patients had prior BCMA-directed exposure. Recorded response was at least partial response in 8/10 patients (80.0%; exact 95% CI, 44.4%-97.5%): six complete responses, one very good partial response, and one partial response. Cytokine release syndrome occurred in 7/10, all grade 1; six received prophylactic tocilizumab. No ICANS was recorded. Infection occurred in 7/10 and was grade 3 or higher in 5/10; CMV reactivation and bacterial infection each occurred in 4/10, and tuberculosis in 1/10. Grade 3 cytopenia occurred in 6/10. Taste/oral, skin, and nail changes occurred in 9/10, 6/10, and 6/10, respectively. All patients received monthly intravenous immunoglobulin. No deaths were recorded. Two patients developed talquetmab-induced dizziness-ataxia syndrome. **Conclusions:** In this small descriptive series, talquetamab was associated with an 80% recorded response proportion and expected CRS and mucocutaneous signals, alongside a substantial burden of infection and cytopenia. The data support careful infection surveillance, standardized response confirmation, and structured documentation of oral, skin, nail, and neurologic effects in larger prospective real-world cohorts.

LBA-03

48-Month Survival Analysis of the BENEFIT Trial, Isatuximab Plus Bortezomib, Lenalidomide, and Dexamethasone for Transplant-Ineligible Newly Diagnosed Multiple Myeloma Patients

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Introduction: The quadruplet-based regimens Isatuximab+VRd (bortezomib, lenalidomide and dexamethasone) has become a new standard of care (SOC) for transplant-ineligible newly diagnosed multiple myeloma (TI NDMM) over IsaRd based on the BENEFIT trial.The 18-month measurable residual disease (MRD) negativity rate at a threshold of 10-5, the primary end point, was achieved in Isa-VRd 53% versus IsaRd 26% (OR 3.16, 95%CI 1.89–5.28, $p < 0.0001$). The 24-month MRD and 12-month sustained MRD demonstrated similar patterns at 10-5 and 10-6. Yet, no survival differences were observed. We analyzed both 48-month consolidated early data on Progression-Free Survival (PFS) and extrapolation of long term PFS of BENEFIT. **Methods:** BENEFIT is a phase 3 trial that randomly assigned TI NDMM, aged of 65 to 79 years, to Isa-VRd or IsaRd until progression. MRD was centrally assessed by next generation sequencing with a 10-6 threshold. The sustained MRD negativity rate was defined as MRD-negative 10–5 results during 12 months. The high-risk (HRMM) definition was based on the international genomic consensus staging. Treatment effect on the first 4 years is estimated using difference in restricted mean survival time (RMST) between arms and PFS projections are generated using classical parametric models following NICE Health Technology Assessment guidance. **Results:** After a median follow-up of 48.9 months, 65 (24%) patients had progressed, 26 (19%) in Isa-VRd and 39 (29%) in IsaRd, and 21 and 20 patients had died, respectively. The PFS estimation was 87.2% and 85.5% at 18 months, 78% and 72.3% at 36 months, and 74% (95%CI: 67;82) and 65.7% (58;74.5) at 48 months, respectively. The 48-month PFS RMST was 40.5 (38;43) and 38.6 (36;41) months across arms, resulting in a difference in RMST of 1.9 (−1.6 to 5.4) months ($p = 0.29$).

We studied the same survival times in the HRMM. A progression was observed in 24% and 50% of HRMM, and 17% and 23% in non-HRMM across Isa-VRd and IsaRd, respectively. The 48-month PFS rate was 63.1% (50;80) and 40.2% (26;63) in HRMM across arms, and 79% (71;88) and 73.1% (65;82) in non-HRMM, respectively. The 48-month PFS RMST, 36.4 (31;41.5) versus 32.3 (26;38) months across arms in HRMM, and 42.4 (40;45) versus 40.4 (38;43) months in non-HRMM. When modelling long-term PFS, 10-year PFS rate ranged from 34 to 44% in IsaRd arm and from 47 to 66% in IsaVRd arm. These PFS results, which should be interpreted with caution due to uncertainty surrounding extrapolation methods suggest that the majority of patients receiving Isa-VRd could potentially remain progression free at 96 months. **Conclusions:** The PFS remains not statistically different when restricting analysis to the first 48 months in BENEFIT, but long term PFS modeling suggests that difference is to be expected. These results support the clinically meaningful benefit of the Isa-VRd regimen compared to IsaRd in TI NDMM patients, including HRMM. This data supports Isa-VRd as a new SOC for TI NDMM patients aged of 65 to 79 years. NCT04751877.

LBA-04

Comparison Between Daratumumab- and Isatuximab-Based Therapies in Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: CD38-targeting monoclonal antibodies have become foundational components of frontline therapy for newly diagnosed multiple myeloma (NDMM). Daratumumab was the first in class agent and demonstrated substantial improvements in depth of response, progression-free survival (PFS), and rates of minimal residual disease (MRD) negativity. Isatuximab, although binding a distinct CD38 epitope and exhibiting unique mechanistic properties, has shown comparable clinical activity in early-phase and in randomized trials. Despite these advances, the relative performance of daratumumab- and isatuximab-based regimens in NDMM remains uncertain, as head-to-head trials are lacking. To address this gap, we performed a systematic review and meta-analysis of randomized controlled trials evaluating these two CD38-directed antibodies. **Methods:** A PRISMA-compliant systematic search identified 15 randomized trials published between November 2015 and April 30, 2026 which met the eligibility criteria. Extracted outcomes included overall response rate (ORR), ≥very good partial response (≥VGPR), MRD negativity, PFS, overall survival (OS), and adverse events (AEs). Random-effects models were applied for pooled analyses. To explore sources of heterogeneity, meta-regression incorporated study-level covariates such as control arm performance, transplant eligibility, cytogenetic risk distribution, and duration of follow-up. **Results:** Pooled ORR was 94.3% for daratumumab-based regimens and 91.5% for isatuximab-based regimens, with no significant subgroup differences ($p = 0.258$). Rates of ≥VGPR (84.9% vs. 84.4%) and MRD negativity (44.0% vs. 61.9%) were comparable, and PFS hazard ratios showed no meaningful difference (0.56 vs. 0.64). OS data for isatuximab were limited to two studies (HR 0.81, 95% CI 0.35–1.83), whereas daratumumab-based regimens demonstrated a significant OS benefit (HR 0.67, 95% CI 0.58–0.77). Considerable heterogeneity was observed across end-points. Meta-regression adjusting for control arm outcomes reduced

heterogeneity and revealed a significantly higher ORR with daratumumab (OR 0.54, p = 0.003), while ≥VGPR, MRD negativity, PFS, OS, adjusted safety outcomes remained similar. Grade ≥3 AEs were more frequent with daratumumab (93.3% vs. 78.6%, p = 0.018), though heterogeneity was substantial (I^2 = 96.1%). After adjustment for control arm, this difference was no longer significant (p = 0.849). Rates of grade ≥3 infections were similar (30.5% vs. 24.0%, p = 0.478; I^2 = 93.7%). Following control arm correction, overall serious AEs remained comparable, but grade ≥3 infections were significantly lower with isatuximab (OR 0.72, p = 0.007). **Conclusions:** Daratumumab and isatuximab exhibit broadly similar efficacy and safety profiles in NDMM. After adjustment for control arm performance, daratumumab shows a higher ORR, whereas isatuximab is associated with fewer grade ≥3 infections.

LBA-05

Five Year Survival Outcomes Among Patients With Multiple Myeloma in Tanzania, A Multicenter Retrospective Study

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy that remains a major cause of cancer-related morbidity and mortality worldwide. Although substantial improvements in survival have been achieved in high-income countries through the introduction of novel therapeutic agents and stem cell transplantation, survival outcomes in sub-Saharan Africa remain poorly documented. In Tanzania, evidence on long-term survival and factors influencing mortality among patients with MM is limited. **Methods:** A multicenter retrospective cohort study approved by MUHAS IRB No. MUHAS-REC-05-2025-2853 was conducted among adult patients diagnosed with MM between 2012 and 2025 at four tertiary referral hospitals in Tanzania: Muhimbili National Hospital, Ocean Road Cancer Institute, Benjamin Mkapa Hospital, and Kilimanjaro Christian Medical Centre. Eligible patients met the International Myeloma Working Group diagnostic criteria. Overall survival was estimated using the Kaplan–Meier method, while factors associated with mortality were assessed using Cox proportional hazards regression models. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were calculated to identify independent predictors of mortality. Analysis was performed by SPSS version 27 and Significance was set at a p < 0.05. **Results:** A total of 504 patients were included in the analysis, with a median age of 58 years (IQR: 51–65), and 55.2% were male. The estimated five-year overall survival rate was 20%, with a median overall survival of 13.9 months. Survival was significantly higher among patients receiving bortezomib-based therapy and those completing eight or more chemotherapy cycles. In multivariable analysis, male sex (aHR = 1.56, 95% CI: 1.12–2.17), low hemoglobin level (<10 g/dL) (aHR = 2.09, 95% CI: 1.40–3.12), and lower educational attainment were independently associated with increased mortality. Conversely, antiviral therapy was associated with reduced mortality risk (aHR = 0.45, 95% CI: 0.23–0.92). Although lack of health insurance was associated with poorer survival in unadjusted analyses, this association was not statistically significant after adjustment for confounding factors. **Conclusions:** This study demonstrates that five year survival among patients with multiple myeloma in Tanzania remains low against global benchmarks and is influenced by a combination of demographic, clinical, laboratory, and treatment-related factors. Severe anemia, male sex, and lower educational attainment were independently associated with increased mortality, while use of bortezomib, 8 cycles or more of chemotherapy and antiviral therapy was associated with improved survival. The study strengthened the importance of prognostic disease markers and highlighted the role of healthcare access to novel agents, continuity of care and supportive care in determining survival. This study shows important evidence to improve myeloma management in Tanzania and paves the way for future research to reduce the burden of multiple myeloma across Africa.

LBA-06

Functional Recovery With First-Line Daratumumab-Based Therapy in Multiple Myeloma: A Multicentre Observational Study

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Introduction: The treatment of patients with newly diagnosed multiple myeloma who are not eligible for transplantation is undergoing significant changes. Real-world evidence is crucial to understanding treatment patterns and management of these patients, who are often underrepresented in clinical trials. Our study aims to improve decision-making about the treatment strategy of these patients in the first-line setting. **Methods:** We conducted a multicenter retrospective study involving 10 Slovak hematology departments to evaluate the demographic, clinical, and treatment characteristics of patients with transplant ineligible newly diagnosed multiple myeloma, focusing on changes in functional status during

treatment assessed by the Karnofsky Performance Status score. Data were collected by physicians at participating centers. We analyzed an observational multicentre cohort of 154 patients with multiple myeloma treated with first-line daratumumab-based therapy, comparing Dara-VMP (n = 75) and Dara-Rd (n = 79). The analysis focused on treatment response, Karnofsky performance status (KPS), adverse events and progression- free survival (PFS). Treatment allocation was non-randomized and clinically imbalanced: patients receiving Dara-VMP were frailer and had more renal impairment, more amyloidosis, lower creatinine clearance and lower baseline KPS than those receiving Dara-Rd. **Results:** Despite differences in baseline patient characteristics across regimens, responses were high and similar between regimens, with an overall response rate of 98.6%. Functional status improved in 64.7% of evaluable patients, with a median KPS gain of 10 percentage points. Improvement was more frequent among patients achieving CR or VGPR than among those with PR, supporting and association between response depth and functional benefit. Dara-VMP patients started from a lower functional level, yet their best-response KPS approached that od Dara-Rd patients, suggesting functional recovery in a clinically frailer subgroup. Median PFS was not reached and did not differ significantly between regimens. Overall hematological and non-hematological toxicity rates were similar, although dose reductions were more frequent with Dara-VMP. **Conclusions:** Our results highlight high response rates and frequent functional improvement after first-line daratumumab- based treatment in this multicentre real-world cohort.

LBA-07

Long-Term Outcomes With Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone (DVRd) Versus VRd in Transplant-Eligible Newly Diagnosed Multiple Myeloma (TE-NDMM) in the Phase 3 PERSEUS Study

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Introduction: In the primary analysis of the intent-to-treat (ITT) population from phase 3 PERSEUS (median follow-up [mFU] 47.5 mo), DVRd induction/consolidation plus DR maintenance (DVRd-DR) showed superior efficacy vs VRd-R in patients (pts) with TE-NDMM in progression-free survival (PFS; hazard ratio [HR] 0.42; $P < 0.001$), overall minimal residual disease negativity (MRDneg; 10^{-5}: 75.2% vs 47.5%; $P < 0.001$) and sustained (≥12 mo) MRDneg (10^{-5}: 64.8% vs 29.7%). This long-term PFS analysis reports outcomes in the ITT population at a 6.8-y mFU. **Methods:** The primary endpoint was PFS; secondary endpoints were overall and sustained MRDneg, overall survival (OS), PFS on next line of therapy (PFS2), and safety. MRDneg was assessed in the ITT population using next-generation sequencing (clonoSEQ; 10^{-5} and 10^{-6}) and was defined as achievement of both ≥CR and MRDneg. Sustained MRDneg was assessed for ≥12(±1), 24(±3), and 36(±3) mo without MRD positivity in between. Nominal 2-sided P-values reported are not adjusted for multiplicity. **Results:** 709 pts were randomized 1:1 (DVRd-DR, n = 355; VRd-R, n = 354). With an additional 34 mo FU since the primary analysis, and mFU of 81.3 mo (0.03–88.3), PFS continued to improve with DVRd-DR vs VRd-R (HR 0.35; 95% CI, 0.26–0.46; $P < 0.0001$). Median PFS was not reached for DVRd-DR vs 81.5 mo for VRd-R (95% CI, 73.8–NE). The 6y PFS rate was 81.1% vs 56.1%, respectively. Overall MRDneg favored DVRd-DR vs VRd-R at 10^{-5} (77.2% vs 50.3%, [OR 3.41; $P < 0.0001$]) and 10^{-6} (68.7% vs 36.7% [OR, 3.88; $P < 0.0001$]). Sustained MRDneg rates were higher with DVRd-DR vs VRd-R at 10^{-5} (12 mo: 70.4% vs 36.2%; 24 mo: 65.9% vs 31.4%; 36 mo: 60.0% vs 26.8%) and 10^{-6} (12 mo: 59.4% vs 25.4%; 24 mo: 55.5% vs 21.5%; 36 mo: 47.6% vs 17.2%). Of 322 DVRd-DR pts who received maintenance, 236 (73.3%) stopped Dara following per-protocol MRD-guided discontinuation after ≥24 mo of maintenance, ≥CR, and sustained MRDneg for ≥12 mo. 175 (74.2%) remained off Dara without restarting Dara maintenance at the time of

analysis; the median duration from Dara discontinuation to the last clinical cutoff was 44.1 mo. PFS2 continued to favor DVRd-DR vs VRd-R (HR 0.50; 95% CI, 0.37–0.69; P < 0.0001) despite most VRd-R pts receiving an anti-CD38 as second-line (2L) treatment (99/136 [72.8%]). Overall, fewer DVRd-DR pts (14.2%) received 2L therapy vs VRd-R (39.2%). OS is immature with 51 DVRd-DR and 84 VRd-R deaths reported; OS trends in favor of DVRd-DR vs VRd-R (HR 0.57; 95% CI, 0.40–0.81; P = 0.0014). No new safety signals were observed with additional FU. **Conclusions:** After 6.8 y mFU, PERSEUS showed that pts treated with DVRd induction/consolidation and DR maintenance achieved among the deepest and most durable responses seen in phase 3 NDMM studies. Improved overall and sustained MRDneg rates seen since the primary analysis translated into improved PFS and PFS2, with an emerging OS benefit, even after per-protocol MRD-guided discontinuation of Dara maintenance. These findings reinforce DVRd-DR as the standard of care in TE-NDMM.

LBA-08

MRD-Guided Frontline T-Cell Redirection Therapy for Newly Diagnosed High-Risk Multiple Myeloma Using Teclistamab-Daratumumab Intensification and Talquetamab-Daratumumab Early Rescue Intervention

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Introduction: Despite optimized frontline therapy, patients with newly diagnosed high-risk multiple myeloma (ND-HRMM) remain at high risk of treatment failure. As persistent MRD predicts outcome, GEM-TECTAL investigates whether early incorporation of bispecific antibodies within an MRD-guided approach can increase the depth and durability of MRD negativity. To evaluate the safety and preliminary efficacy of teclistamab-daratumumab (Tec-D) intensification following daratumumab-bortezomib-lenalidomide-dexamethasone (D-VRd) induction in ND-HRMM. **Methods:** GEM-TECTAL is an ongoing multicenter, phase 2 study enrolling 30 ND-HRMM patients fit for quadruplet induction regardless of transplant eligibility (NCT05849610). High-risk disease was defined by high-risk cytogenetic abnormalities (HRCA; del(17p), t(4;14), t(14;16), amp(1q)), R-ISS III and/or extramedullary/paramedullary disease (EMD/PMD). Approximately 50% of patients were planned to have ultra-HR disease (R-ISS III, ≥2 HR-CA, or HR-CA+EMD). Patients received 4 cycles of D-VRd followed by 6 cycles of Tec-D intensification. Thereafter, MRD-negative patients received Tec-D maintenance for 2 years, whereas MRD-positive patients received early rescue with talquetamab-daratumumab. The primary endpoint was MRD-negative complete response (MRD-CR; next-generation flow, 10^-6) after Tec-D intensification. The study is sponsored by PETHEMA Foundation and Janssen Pharmaceutica NV. **Results:** At data cutoff (May 7, 2026), all 30 patients enrolled between November 2023 and March 2025 had started treatment and 28 completed Tec-D intensification. Median age was 70 years (48–77), 50% were male, 21 had HR-CA, 10 had ≥2 HR-CA, and 21 (70%) met ultra-HR criteria. After D-VRd, ORR was 76.7% (≥CR 20%; MRD-CR in ITT 13.3%). Two patients discontinued during induction (1 progressive disease, 1 COVID pneumonia). After Tec-D intensification, ORR increased to 93.3%, with ≥CR in 80%. The primary endpoint of MRD-CR was 73% (22/30) in ITT. Complete metabolic response by PET-CT was 75% of evaluable patients. TEAEs occurred in 96.4% of patients. During induction safety was consistent with D-VRd. During Tec-D intensification, infections occurred in 78.6% (grade 3, 14.3%), with no grade 4/5 events. CRS occurred in 7 patients (25%), all grade 1; only one required tocilizumab. One patient developed grade 2 ICANS, resolving with steroids. Teclistamab was discontinued due to TEAEs in 2 patients (rash, peripheral neuropathy) and 1 patient died (unrelated to study treatment). 2 patients stopped treatment after intensification (1 withdrew consent and 1 other). Twenty-two patients remain on Tec-D maintenance. One patient switched to talquetamab-daratumumab because of persistent MRD positivity. Median follow-up was 9.8 months. **Conclusions:** Early MRD-guided incorporation of Tec-D intensification induced deep responses and high MRD-CR in ND-HRMM, supporting the evaluation of a full-immune based bispecific antibody-based, transplant-free approach in difficult to treat high-risk disease.

LBA-09

Real-World Outcomes of First-Line Bortezomib, Thalidomide, and Dexamethasone for Multiple Myeloma in a Resource-Limited Setting

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Introduction: The current standard treatment of multiple myeloma (MM) is based on triple or quadruple therapy. The goal of first-line therapy is to achieve the best possible response and

proceed to autologous stem cell transplantation (ASCT) in eligible patients. Bortezomib, thalidomide, and dexamethasone (VTd) is the standard regimen at our institution. Our objective was to determine outcomes with VTd in transplanted and non-transplanted patients. **Methods:** Medical records of patients with newly diagnosed MM treated at the National Cancer Institute of Peru from 2017 to 2023 were retrospectively reviewed. Patients received VTd as first-line therapy. Smoldering MM and plasma cell leukemia were excluded. Baseline characteristics were assessed, and overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to identify prognostic factors. Variables significant in univariate analysis (UA) were included in multivariable analysis (MA). **Results:** A total of 126 patients were included, the median age was 59 years (30–83). The majority were male (64%). The IgG subtype was seen in 60% of the cases, followed by IgA (27%) and light chains (12%). According to the ISS classification, ISS I, ISS II and ISS III were 36%, 30% and 28%, respectively. 26% (33) had plasmacytoma. The median number of treatment cycles was 6 (1–8). 76% of the total cohort (96 patients) were eligible for ASCT, finally 46% (44 patients) of all eligible patients underwent transplantation, 82 beingthe non-transplanted group. The PR in 15%. overall response rate was 79.6%, with complete response (CR) + stringent CR in 36%, followed by very good partial response (PR) in 28% and Cytogenetic risk stratification was not available due to lack of FISH. The median follow-up was 21 months (1–85). The median OS for the entire cohort was 80 months (IQR 29-NR) with a 5-year OS of 74.37% (95% CI, 47.3–82.3). The UA showed a significant difference for the group that underwent ASCT (5-year OS 86% vs 68.2%, p = 0.008) and for female sex (85.5% vs 33.9%, p = 0.03). The MA only showed a significant difference for the transplant group (HR = 0.24, 95% CI = 0.08–0.72, p = 0.01). The PFS for the entire cohort was not reached. The median PFS for the transplanted cohort was not reached and for the non-transplanted cohort was 29 months (IQR 11-NR). The 5-year PFS for those undergoing ASCT was 89.74 vs 38% for those not undergoing ASCT (p = <0.001). The MA showed statistical significance for the transplant group (HR = 0.13, 95% CI = 0.04–0.38). **Conclusions:** ASCT was associated with significantly improved overall and progression-free survival and remained the only independent prognostic factor for overall survival in multivariable analysis. Despite most patients being transplant-eligible, fewer than half ultimately underwent ASCT, highlighting a substantial gap between transplant eligibility and access in this resource-limited setting.

LBA-10

Plasma Cell Leukemia in a North African Cohort: A 27-Year Single-Center Experience Bridging Clinical Reality and the Novel-Agent Era

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Introduction: Plasma cell leukemia (PCL) is the most aggressive plasma cell neoplasm, characterized by the presence of circulating plasma cells (CPCs) in peripheral blood. Divided into primary (pPCL) and secondary (sPCL) forms, PCL carries a dismal prognosis even in the modern therapeutic era. Data from North Africa remain extremely sparse. **Methods:** We conducted a retrospective, descriptive, single-center study at the Department of Clinical Hematology, Farhat Hached University Hospital, Sousse, Tunisia, spanning 27 years (January 1999–December 2025). Eighteen patients fulfilling either Kyle 1974 criteria or revised IMWG 2021 criteria (≥5% CPCs) were included. **Results:** Six patients had pPCL and 12 had sPCL (male predominance; M:F = 2:1; mean age 65 years). Anaemia was universal (100%); thrombocytopenia occurred in 89% and renal failure in 61% of patients. In sPCL, the median interval from multiple myeloma (MM) diagnosis to leukemic transformation was 11.5 months (1–96 months). Cytogenetic evaluation revealed universally high-risk profiles, with sequential analysis in three sPCL patients documenting clonal evolution at transformation. Therapy evolved from conventional polychemotherapy toward proteasome inhibitor-based triplets (VTD, VRd) from 2017 onwards; no patient received anti-CD38 monoclonal antibodies or haematopoietic stem cell transplantation (HSCT) after PCL diagnosis. Median overall survival (OS) was 3 months for pPCL and 1.5 months for sPCL from PCL diagnosis. The sole objective response in the cohort was achieved with second-line carfilzomib-lenalidomide-dexamethasone (KRd) in one sPCL patient, yielding a very good partial response (VGPR) and the longest OS in the series (26 months from MM diagnosis, 22 months from PCL). **Conclusions:** PCL in our North African cohort carries uniformly dismal outcomes, largely attributable to limited access to modern anti-CD38 quadruplet regimens and consolidative HSCT. The striking salvage response achieved with KRd underscores the transformative potential of second-generation novel agents. Our findings call for the urgent integration of daratumumab-based protocols into national Tunisian guidelines and for the establishment of a regional PCL registry to drive evidence-based progress in resource-constrained settings.

LBA-11

First-in-Human Clinical Proof-of-Concept of IASO206, an Intravenously Administered In Vivo BCMA CAR-T Therapy for Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: Although BCMA-directed CAR-T therapies produce deep responses in RRMM, individualized ex vivo manufacturing requires leukapheresis, complex manufacturing, lymphodepleting chemotherapy, and prolonged vein-to-vein time, limiting broad patient access. IASO206 is an intravenously administered lentiviral vector designed to generate functional BCMA-directed CAR-T cells directly in vivo after a single intravenous infusion. We report the initial clinical proof-of-concept from an ongoing first-in-human Phase I study. **Methods:** Patients with RRMM who had received at least two prior lines of therapy and relapsed or refractory after exposure to proteasome inhibitor, immunomodulator and/or anti-CD38 antibody were enrolled, which is administered as a single intravenous infusion without leukapheresis, ex vivo manufacturing, or lymphodepleting chemotherapy. Dose levels evaluated to date include 1×10^8, 3×10^8, and 9×10^8 transduction units (TU). Primary objectives were characterization of the safety profile and determination of the recommended Phase 2 dose (RP2D). **Results:** As of July 23, 2026, eight patients had received IASO206: three at 1×10^8 TU, three at 3×10^8 TU, and two at 9×10^8 TU. Seven patients had complete safety and efficacy evaluation. The median number of prior lines was 3.5 (range, 2–8); 5/8 (62.5%) were triple-class refractory; and 7/8 (87.5%) had high/ultra-high-risk cytogenetic features.

Among seven patients with cellular-kinetic data, the Cmax of flow-cytometric CAR-positive cell occurred on Days 17–23 and ranged from 7.67 to 5,692.3 cells/μL (median, 658.2). The peak VCN occurred on Days 14–21 and ranged from 500.615 to 105,312.5 copies/μg DNA. The safety analysis set comprised the first seven treated patients. No DLT, death, or ICANS was reported. Grade 1–2 infusion-related reactions occurred in 6/7 patients on the infusion day and resolved quickly. Grade 1 CRS occurred in 6/7 patients, with a median recorded duration of 2 days. Grade ≥3 hematologic adverse events following were observed in 6/7 patients exhibiting transient neutropenia and leukopenia, and 3/7 patients exhibiting transient thrombocytopenia. Grade ≥3 infections only occurred in 1 of 7 patients on Day 63. Among seven efficacy-evaluable patients, six patients achieved partial response or better (ORR, 85.7%), four patients (57.1%) achieved VGPR or better. Responses continued to deepen over time. All evaluable patients except one in the 1×10^8 TU cohort achieved MRD negativity (10^{-5}). Because the follow-up duration remains relatively short, the efficacy data are still immature.

Conclusions: IASO206 demonstrated the first clinical proof-of-concept that functional BCMA-directed CAR-T cells can be generated directly in vivo following a single intravenous administration. The favorable safety profile and encouraging anti-myeloma activity support further clinical development. Updated clinical data will be presented at the IMS Annual Meeting.

LBA-12

Iberdomide, Daratumumab, Dexamethasone (IberDd) vs Daratumumab, Bortezomib, Dexamethasone (DVd) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM): Results From EXCALIBER-RRMM Phase 3 Study

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Introduction: IBER is a CELMoD with enhanced antimyeloma cytotoxicity and immune stimulation vs IMiDs. IBER has shown synergistic effects with anti-CD38 monoclonal antibodies (mAbs) and clinical activity in heavily pretreated RRMM patients (pts). Minimal residual disease (MRD) negativity is recognized as an early indicator of long-term benefit. We report the first MRD results from EXCALIBER-RRMM (NCT04975997), a 2-stage, phase 3 randomized trial comparing IberDd vs DVd, and the first study in RRMM to use MRD and PFS as dual primary endpoints. **Methods:** Eligible pts had 1–2 prior lines of therapy (LOTs); pts refractory to anti-CD38 mAbs or bortezomib (BORT) were excluded. Pts were randomized to oral IBER on days 1–21 of each 28-d cycle plus Dd or to DVd per established schedules. Dual primary endpoints were MRD-negative (threshold 10^{-5} by flow cytometry) complete response (CR) and PFS. MRD-negative CR at any time was assessed in a prespecified interim analysis of 420 pts randomized to IberDd (1.0 mg IBER, selected dose from stage 1, n = 207) or DVd (n = 213) with ≥12 months of follow-up. PFS event accrual, based on a larger cohort of 800 pts, is ongoing. **Results:** In the prespecified MRD analysis group, median age was 68 y (range, 35–87), 18.1% were ≥75 y, 67.1% had 1 prior LOT, 90.2% had prior IMiDs (48.1% IMiD refractory), and 94.5% had prior proteasome inhibitors. Median follow-up was 15.7 mo, and 62.3% (IberDd) and 46.0% (DVd) of pts remained on treatment (tx). Significantly more pts achieved MRD-negative CR with IberDd vs DVd (41.1% vs 20.7%; proportion difference 20.1% [95% CI, 11.5%–28.6%], $P < 0.0001$; odds ratio 2.75). This benefit was consistent across prespecified subgroups, including pts refractory to lenalidomide (LEN) in last LOT, pts with renal impairment, and ≥75 y of age. MRD-negative CR was sustained for ≥6 mo in 34/36 (94.4%) evaluable pts with IberDd and 16/18 (88.9%) with DVd. Median time to MRD-negative CR was 9.2 mo (IberDd) and 10.2 mo (DVd). Higher ORR (88.9% vs 76.1%) and CR/stringent CR (45.9% vs 24.9%) were observed with IberDd vs DVd. Grade (Gr) 3/4 adverse events (AEs) occurred in 97.1% vs 72.1% of pts, neutropenia in 84.3% vs 11.3% (mainly in the first 2 cycles), and infection in 39.2% vs 21.6% with IberDd and DVd, respectively. Gr 3/4 neutropenia was manageable with growth factor support and dose interruptions/reductions. Peripheral neuropathy was less common with IberDd vs DVd (any Gr, 12.3% vs 42.6%; Gr 3/4, 2.9% vs 5.4%). AEs led to discontinuation of IBER or BORT in 7.8% of pts in each group. Gr 5 infections were uncommon (2.0% [IberDd] vs 1.5% [DVd]). Deaths were reported in 11.1% (IberDd) vs 15.5% (DVd) of pts, mostly due to progressive disease. **Conclusions:** IberDd led to a statistically significant and clinically meaningful improvement in MRD-negative CR vs DVd, with a manageable safety profile. IberDd represents an effective tx option for pts with RRMM as early as first relapse, that can be easily administered across diverse care settings.

LBA-13

Real-World Efficacy of Anti-CD38 (Daratumumab)-Based Regimens and Long-Term Outcomes in Transplant-Eligible Multiple Myeloma: A 10-Year Tunisian Cohort Study

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Introduction: Daratumumab-based quadruplets are now standard-of-care frontline therapy in transplant-eligible multiple myeloma (MM) in high-resource countries, but real-world data on daratumumab access and outcomes from low- and middle-income settings remain scarce. We report a 10-year single-center experience characterizing how daratumumab is actually used, and with what outcomes, in a North African transplant-eligible MM cohort where reimbursement restricts access to later treatment lines. **Methods:** Retrospective study of 140 newly diagnosed transplant-eligible MM patients (2016–2025; 128 induced, VTD in 83.6%). Daratumumab was unavailable in first-line induction due to reimbursement policy and was used only as salvage therapy (post-induction failure, relapse) or maintenance. Regimens included D-RD, D-VD, D-VRD, DPD, DKPD, and DVMP. Response and 5-year relapse-free survival (RFS) were assessed by treatment line and by daratumumab exposure. **Results:** No patient received daratumumab at induction. As post-induction salvage (n = 4), daratumumab-based regimens achieved 100% objective response (2 VGPR, 2 CR). At first relapse, daratumumab-based regimens (7/28, DRD n = 5, DVD n = 2) contributed to an overall relapse response rate of 76.9%, versus 19 patients on non-daratumumab salvage. At second relapse, 8/13 rescued patients received daratumumab-containing regimens, with an overall response rate of 61.6% (4 CR, 1 VGPR, 3 PR). Only 1/30 patients (3.3%) received daratumumab-dexamethasone maintenance. Despite superior response rates, 5-year RFS was lower with daratumumab exposure at first relapse than without (6.2% vs 40.8%, p = 0.001), a pattern consistent with confounding by indication, since daratumumab was preferentially allocated to higher-risk, more heavily pretreated relapses in this access-restricted setting rather than reflecting an adverse treatment effect. **Conclusions:** This is, to our knowledge, the first real-

world characterization of daratumumab utilization patterns across a full transplant-eligible MM treatment course from North Africa. Daratumumab access was confined almost entirely to salvage and relapse lines, with negligible frontline or maintenance use — a stark contrast to pivotal-trial positioning — yet still produced high response rates even in adverse-risk relapses. These data provide concrete evidence to support policy advocacy for earlier daratumumab reimbursement in resource-limited settings.

LBA-14

Functional and Lipidomic Cargo Characterization of Mesenchymal Stromal Ce1ll-Derived Extracellular Vesicles in Multiple Myeloma

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Introduction: The bone marrow microenvironment plays a critical role in multiple myeloma (MM) survival, progression, and therapeutic resistance. Mesenchymal stromal cells (MSCs) communicate with malignant plasma cells through extracellular vesicles (EVs), which can transfer biologically active molecules and modulate tumor-cell behavior. However, the functional properties and lipid cargo of MSC-derived EVs in MM remain poorly understood. **Methods:** MSCs were isolated from non-MM controls (Ctr-MSC), patients with active MM (MM-Act-MSC), and patients in remission (MM-Rm-MSC). EVs were isolated by size exclosuion chromatography and characterized by flow cytometry using EV-associated markers CD9, CD63, and CD81 and MSC-associated markers CD73 and CD90. EV uptake by MM cell lines was assessed using fluorescence-based assays. We assessed functional effects using viability and proliferation assays and performed quantitative lipidomic profiling of EVs from three donors per group to characterize lipid-class composition, fatty-acid ratios, and lipid-module enrichment. **Results:** MSC-derived EVs were efficiently internalized by MM cells, with uptake of MM-Act-MSC-EVs showing a 1.2-fold increase versus control EVs ($p = 0.05$). MM-Act-MSC-EVs significantly increased MM-cell viability and proliferation compared with Ctr-MSC-EVs (2.0-fold, $p = 0.001$), indicating a tumor-supportive phenotype associated with active disease. Lipidomic profiling showed substantial inter-donor heterogeneity and incomplete separation of active MM, remission, and control samples by principal component analysis, suggesting selective rather than global lipidome remodeling. When active MM and remission samples were pooled, MM-associated MSC-EVs showed a lower total polyunsaturated-to-saturated fatty-acid ratio than controls (0.83-fold, $p = 0.047$) and a reduced non-membrane 18:1/18:0 ratio ($p = 0.048$). Free fatty-acid species were significantly overrepresented among MM-associated lipid alterations ($p = 0.001$; BH $q = 0.013$), with relative depletion of cholesteryl ester species. Lysophosphatidylcholine (LPC) species showed the strongest active-disease-associated pattern ($p = 0.022$); LPC 22:1 represented a 3.16-fold higher proportion of total LPC in active MM versus controls ($p = 0.024$). **Conclusions:** MSC-derived EVs from patients with MM exhibit tumor-supportive functional activity and selective disease-associated lipid remodeling. The lipidomic phenotype includes a shared MM-associated shift in fatty-acid and neutral-lipid composition, together with more pronounced active-disease-associated lysophospholipid remodeling. These findings support a potential role for altered MSC-EV lipid cargo in microenvironment-mediated MM support and identify lipid-remodeling and lysophospholipid-signaling pathways for further mechanistic investigation.

LBA-15

Myeloma Bone Disease: What Does a Deteriorating Osteocyte Lacuno-Canalicular Network Mean for Bone Recovery?

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Introduction: Myeloma bone disease (MBD) remains a devastating complication of myeloma, causing pain and reduced quality of life, even in patients achieving extended disease remission. Debate over whether osteolytic lesions can or cannot repair is ongoing. Recent clinical studies have presented evidence of partial lesion repair in patients receiving myeloma treatment, but the extent and bone quality following repair is unclear. Osteocytes are the most abundant bone cell, and along with their lacuno-canalicular network (LCN), are crucial to maintain appropriate bone homeostasis. However, osteocytes have been historically under investigated, particularly in the context of myeloma. Understanding how the osteocyte LCN is affected in myeloma may hold the key to optimising MBD management. Here we present data from an observation clinical study demonstrating microscopic and macroscopic changes in bone, including the osteocyte LCN, in response to myeloma treatment. **Methods:** This pilot study assessed bone recovery in newly diagnosed myeloma patients receiving first-line therapy. Patients underwent whole-body low-dose CT imaging and bone marrow biopsy at baseline and 3 months post-induction ± autograft (and zoledronic acid), alongside monthly fasting serum bone turnover markers. Trephines sections were stained for tartrate resistant acid phosphatase activity (TRAP) and haematoxylin to assess osteoblast and osteoclast numbers. The osteocyte LCN was analysed using silver nitrite staining and immunohistochemistry for sclerostin expression. **Results:** All patients ($n = 10$) at post treatment follow-up demonstrated radiological evidence of at least partial osteolytic lesion repair.

Response varied between lesions at different radiological sites. In addition, increased trabecular bone volume ($p = 0.003$) and osteoblast number ($p < 0.05$) were evident on trephine analysis. Osteocyte lacunar density was not significantly different at baseline and follow-up. However, osteocyte canalicular coverage was significantly reduced ($p < 0.01$), due to a combination of fewer canaliculae per osteocyte ($p = 0.0272$) and reduced average length of canaliculae ($p = 0.0063$). There was no significant change in sclerostin expression from baseline to follow-up on trephine sections. Serum CTX-I was suppressed from 2 months ($p < 0.0001$), and sclerostin from 3 months ($p = 0.011$). **Conclusions:** This pilot confirms that osteolytic lesions have the potential for repair, likely supported by myeloma-targeted therapies such as proteasome inhibitors. However, the bone quality when repair occurs is currently unknown. Our findings demonstrate that osteocyte LCN connectivity is significantly reduced following myeloma treatment, which is likely detrimental to bone repair. These data highlight the ongoing need for novel, bone-targeted therapies to support MBD recovery.

LBA-16

Relationships Between Quality of Life, Bone Pain, Fatigue and Disease Symptoms, and Physical Activity, Neuromuscular Strength and Fitness, in People With Multiple Myeloma

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Introduction: People with multiple myeloma (MM) experience the lowest quality of life (QoL) of all cancer populations. Whilst physical activity (PA) and exercise have been shown to improve outcomes in other cancers, there is limited research about their relationship with treatment-related side effects, patient-reported outcomes (PRO), and QoL in people with MM, and how that might inform the design of exercise interventions. This cross-sectional study aimed to explore the associations between PA levels, neuromuscular strength and fitness and QoL, disease symptoms, bone pain and fatigue in people with MM. **Methods:** Baseline characteristics were collected for people at any stage of MM who had consented to participate in one of two randomised controlled trials of an exercise intervention. Baseline measures were collected using validated surveys (EORTC QLQ-C30 with MY20 module, FACT-MM, FACT-BP, FACIT-F, Godin LTPA), neuromuscular fitness (five-times (5STS) and 30-second sit-to-stand test (30STS)) and dynamometry. Clinical fatigue was classified by FACIT-F score <34. Self-reported completion of ≥150 min moderate-to-vigorous physical activity (MVPA) was considered sufficiently active. **Results:** Participants with MM (n = 120; mean age 64 ± 9 years, range 33–79; 68% male) predominantly presented with lytic lesions (78%) and other skeletal complications (13%; back pain, osteoporosis, osteoarthritis). Most participants were insufficiently active (66%) with almost half (47%) experiencing clinical fatigue (FACIT-F: mean 30.9; 95%CI 28.6, 33.3). The presence of bone pain was reported by 84% of participants (FACT-BP: mean 47.8; 95%CI 45.6,49.9). Mean neuromuscular fitness was 14.8 sec (5STS: 95%CI 13.1,16.5; n = 53) and 10.6 reps (30STS: 95%CI 9.9,11.3; n = 58), reflecting poorer scores than healthy older adults. Overall QoL (EORTC QLQ-C30: mean 79.5; 95%CI 77.1,81.8) was marginally higher than typically observed at diagnosis. Symptoms of disease (EORTC QLQ-MY20: mean 21.7; 95%CI 18.6,24.8) were at the lower limit generally measured at baseline in clinical trials for MM. Mean grip strength was 40.5 kg (males: 95%CI 38.7,42.3) and 24.6 kg (females: 95%CI 22.8,26.4), reflective of normative values in healthy older adults. Physically active participants (34%) reported better QoL ($p = 0.009$), with lower levels of fatigue ($p = 0.02$), bone pain ($p = 0.002$) and symptom burden ($p = 0.002$), compared to those who were insufficiently active. Associations (r 0.23–0.54; $p < 0.05$) were observed between neuromuscular fitness and improved PROs, though no associations ($p > 0.05$) were observed with upper body strength. **Conclusions:** Participants experience high levels of clinical fatigue and bone pain but report low levels of PA. Those with higher levels of PA had improved QoL and disease symptoms. These findings highlight a significant need for targeted interventions to increase physical activity and neuromuscular fitness to optimise QoL and disease symptoms in people with MM.

LBA-17

Cevostamab Consolidation Following BCMA CAR T Cell Therapy: Primary Analysis of the Phase 2 "STEM" (Sequential T Cell-Engagement for Myeloma) Trial

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Introduction: BCMA-targeted CAR T cells have great efficacy in relapsed/refractory multiple myeloma (RRMM), but most patients (pts) relapse. FcRH5 is a MM antigen expressed independently of

BCMA. Cevostamab (cevo) is an FcRH5-targeted T cell-engaging bispecific antibody with activity in RRMM. We hypothesized that fixed-duration cevo following CAR T cells would be feasible, tolerable, and improve sustained MRD-negative (neg) complete response (CR) rates. **Methods:** In this single-institution, investigator-initiated study (NCT05801939), RRMM pts with ≥stable disease after standard-of-care CAR T cells (ide-cel or cilta-cel) received cevo starting 10–12 weeks (wks) post-CART at a step-up dose of 3.6 mg IV on Cycle 1 Day 1 (C1D1), followed by 132 mg on C1D8, then q3wks for 8 cycles. Pts with MRD-neg CR after C8 (Adaptive Clonoseq, at 10^{-5} sensitivity) stopped therapy; MRD+ or non-CR pts received another 8 cycles. Primary endpoint was rate of MRD-neg CR at 1 year post-CAR T cells. Data cut-off was 6/26/26. **Results:** 27 pts (20M, 7F; median age 64; 21 White, 6 Black) enrolled, with median 4 (range 2–10) prior lines, 74% triple-class refractory, 11% prior BCMA therapy, and 11% prior talquetamab. 74% had any high-risk cytogenetics, 41% ≥2 high risk features; 19% extramedullary disease. 93% received cilta-cel and 7% ide-cel. Reponses at enrollment (post-CAR T cells) were 63% CR/sCR, 15% VGPR, 18% PR, 4% SD; all 25 evaluable for MRD were MRD-neg. No DLTs occurred, including no ICANS or HLH; CRS developed in 4 pts (15%, 3 G1, 1 G2) and infusion reactions in 22% (all G1/2). Median number of cycles was 8 (range 1–16); 7 (26%) pts held ≥1 dose of cevo due to toxicity and 6 (22%) were dose-reduced to 90 mg. Only 3 pts required the 2nd 8 cycles of cevo. Common TEAEs were neutropenia (78%, G3/4 48%), lymphopenia (74%, G3/4 67%), cough (63%, G3/4 0%), rash 48% (G3/4 0%), upper respiratory infection (44%, G3/4 0%), thrombocytopenia (41%, G3/4 22%), nasal congestion (37%, G3/4 0%), and AST increase (33%, G3/4 7%). Infections occurred in 70% (G3/4 in 15%), and serious AE's in 44%; no new immune-related AEs occurred since the prior interim analysis. At 1 year post-CAR T cells, 89% of pts (24/27) had sCR, 7% (2/27) VGPR; 25/26 (96%) were MRD-neg at 10-5, and 23/26 (88%) at 10-6. One sCR pt unevaluable by Clonoseq was MRD-neg by flow cytometry (10-5 sensitivity). The 1-year MRD-negative CR rate (primary endpoint) was 89% (24/27). With median follow-up of 24 months (mos, range 15–37) post-CAR T cells, 2 patients have progressed (at 5 and 15 mos), and estimated 24-mo PFS and OS are 93% and 96%, respectively. Based on CAR transgene qPCR (n = 25), 10 pts (40%) had transient CAR increase after starting cevo, primarily during C1. At 12 mos post-CART, 11 pts (44%) had persistent transgene levels >10 copies/μg. **Conclusions:** Cevo consolidation post-CAR T cells is feasible and well-tolerated in late-line RRMM, with 89% of pts showing sustained MRD-neg sCR at 1 year and promising 2-year PFS.

LBA-18

First-in-Human In Vivo Generation of CD19/BCMA Dual-Targeting CAR-T Cells in Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: The individualized manufacturing largely limits the accessibility of ex vivo CAR-T. QI-019A is an in vivo lentiviral vector built on the ClariT platform, which uses Macroi-293 cells to reduce vector clearance and incorporates a CAR-less strategy to avoid premature expression during packaging. With its bispecific CD19/BCMA CAR design, QI-019A targets both myeloma cells and their precursors for deeper and longer-lasting responses. We report the initial results from a phase 1, open-label study of QI-019A in 9 R/R MM patients (NCT07429721). **Methods:** Eligible adults with measurable disease after ≥2 prior lines of therapy and an ECOG performance status of 0–2 were enrolled. Prior BCMA-targeted therapy was permitted. QI-019A was administered as a single intravenous infusion without lymphodepletion, and dose escalation followed an accelerated-titration design. **Results:** By August 2026, 9 R/R MM patients had been treated with QI-019A across two dose levels (DL1 and DL2, 2.0–9.0 × 108 TUs). The median age was 59 years (48–79), and the median prior treatment line was 3 (2–6). At baseline, 5 individuals presented with triple-class refractory disease, and 5 had paraosseous plasmacytomas. Furthermore, 3 patients had been exposed to BCMA-targeted therapies, including 1 relapsed two years post-BCMA CAR-T and 2 progressed following an anti-CD3/BCMA/GPRC5D trispecific T-cell engager.No dose-limiting toxicities occurred. Vector-related reactions (primarily fever and chills) were observed in 44.4% (4/9) of patients, resolving within two days. Grade 1 CRS occured in 77.8% (7/9) of patients, with no instances of ICANS or IEC-HS. Grade 3–4 cytopenias included leukopenia, lymphocytopenia, and neutropenia (66.7% each), thrombocytopenia (33.3%), and anemia (11.1%). CAR-T kinetics demonstrated a dose-dependent pattern. Compared with DL1, DL2 reached peak expansion earlier (median day 11 vs. day 14) and had a higher median Cmax (41,401 vs. 13,422 copies/μg DNA). Remarkably, 2 of the 3 patients with prior BCMA-targeted therapy still achieved robust CAR-T expansion. Flow cytometry revealed that peak-expanded CAR-T cells primarily exhibited central and effector memory phenotypes. Additionally, while the CAR transgene was present in bone marrow BCMA+ cells, the absence of CAR protein expression further confirmed the T-cell specificity.During a median follow-up of 2.0 months (1.0–4.5), 7/8 evaluable patients demonstrated clinical responses (4 sCR, 1 VGPR, 1 PR, and 1 MR). All responding patients achieved MRD negativity (10-5) in bone marrow. Notably, in patients previously exposed to BCMA-targeted therapies, 2 attained

sCR. **Conclusions:** These first-in-human data confirm the feasibility of in vivo CD19/BCMA dual-targeting CAR-T without lymphodepletion in R/R MM. QI-019A enables a rapid 8-day screening-to-infusion turnaround and demonstrates favorable early safety, robust expansion, and promising efficacy. Long-term follow-up is ongoing to assess response durability and clinical outcomes.

LBA-19

REM Prognostic Model in Real-World Chinses RRMM Patients With BCMA CART Treatment

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Introduction: BCMA-targeted CAR-T cell therapy has ushered in a new era of immunotherapy for patients with relapsed/refractory multiple myeloma (R/R MM). Current evidence is based on registrational trials and commercial data of standardized single-target CAR-T products, and the derived MyCARe model only predicts prognosis for rigorously selected patients. However, due to geographic disparities, insurance policies and limited clinical trial access, real-world R/R MM patients receive heterogeneous CAR-T regimens. To date, no real-world head-to-head comparative analyses have been reported, and the MyCARe model requires further optimization to boost its predictive performance in unselected patient cohorts. **Methods:** This retrospective study enrolled 109 R/R MM patients who received Academic BCMA CAR-T therapy at the First Affiliated Hospital of Soochow University and Suzhou Hongci Hematology Hospital from September 30, 2015, to September 30, 2025. The primary endpoint was PFS. Secondary endpoints included ORR, OS, NGF-MRD negativity rate (10^{-5}), and AEs. **Results:** 109 R/R MM patients were 70% male and at a median age of 57 years. Median time from diagnosis was 33 months, with a median of 2 prior treatment lines(1-9). 50% patients had prior ASCT, 50% were double-refractory, 19% >= triple-refractory, while 2% had prior BCMA-targeted therapy. 64% patients were re-classified as R-ISS stage II–III at CART treatment, and 26% patients had CGS-defined high-risk cytogenetic abnormalities. EMD was present in 43% of cases, including 32% EME and 10% EMB. 5% had plasma cell leukemia, 10% had >= 2% circulating tumor burden, and 28% had >= 50% bone marrow infiltration. Overall, 52% of patients received bridging therapy and 47% achieved ≥PR after bridging. ORR and CRR were 80.2% and 59.4%, and 33.3% of patients achieving 10-5 NGF-MRD negativity. With a median follow-up of 23 months (1–109 months), the median PFS and OS were 20 and 41 months. PFS was significantly inferior in patients with EME versus EMB (HR = 2.25, P = 0.029), while cytogenetic risk did not impact PFS (HR = 1.21, P = 0.525). Multivariate analysis identified R-ISS II–III (HR = 2.42, p = 0.002), EME or PCL presence (HR = 1.65, p = 0.036), and multiple refractory(> = triple-refractory) (HR = 2.18, p = 0.009) as independent PFS risk factors. The REM model exhibited effective prognostic stratification, with median PFS of 44, 15, and 4.5 months for low-, intermediate-, and high-risk groups. **Conclusions:** This study shows that Academic BCMA-targeted CAR-T cell therapy significantly prolongs survival and yields a favorable, manageable safety profile in Chinese patients with relapsed/refractory multiple myeloma. It achieves effective disease control even in patients with high-risk cytogenetic abnormalities and EMB. R-ISS II- III stage at CART treatment, soft-tissue extramedullary disease, plasma cell leukemia, and multiple refractoriness represent independent risk factors for poor prognosis after CAR-T treatment.

LBA-20

Second CAR T-Cell Infusion After Prior CAR T-Cell Failure in Multiple Myeloma

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Introduction: Relapse or progression after CAR T-cell therapy remains a major challenge in relapsed/refractory multiple myeloma (RRMM), and evidence guiding a second infusion is limited. We evaluated efficacy, safety, and in vivo expansion after a second CAR T-cell infusion following prior CAR T-cell failure. **Methods:** This retrospective study included 23 patients with RRMM who received a second CAR T-cell infusion from January 2018 to April 2026. Products targeted BCMA, GPRC5D, or both. Responses were assessed using International Myeloma Working Group criteria. Progression-free survival after the second infusion (PFS2), overall survival (OS), and duration of response (DOR) were estimated using Kaplan-Meier methods. Expansion was evaluated by peak transgene copy number (Cmax), time to peak (Tmax), and area under the curve from days 0-28 (AUC0-28). Comparative analyses were exploratory. **Results:** Median age was 54.6 years, median prior lines of therapy was 5, and 9 patients (39.1%) had extramedullary disease. The median interval between infusions was 16.2 months. Twelve patients received same-target retreatment, 8 switched targets, and target status was unavailable in 3. At the July 1, 2026 cutoff, median follow-up was 46.4 months. Among 20 response-evaluable patients, the overall response rate was 80.0%, including complete or stringent complete response (CR/sCR) in 6 (30.0%), very good partial response in 3 (15.0%), and partial response in 7 (35.0%). Median DOR was 9.3 months (95% CI, 7.81-10.79), median PFS2 was 7.2 months (95% CI, 3.4-28.8), and median OS was 32.5 months (95% CI, 12.4-not reached). Among 16 patients evaluable after both infusions, 7 (43.8%) achieved an equal or deeper response after the second infusion. CR/sCR occurred in 5 of 12 patients receiving same-target retreatment and none of 8 who switched targets (P = 0.029); target strategy was not associated with PFS2 or OS. Cmax and AUC0-28 were higher in responders than nonresponders (P = 0.036 and P = 0.044). Higher Cmax was associated with early grade 3 or higher thrombocytopenia and anemia (both P = 0.025). Cmax and AUC0-28 were not associated with PFS2 or OS, whereas later Tmax

was associated with a lower risk of progression or death (HR per day, 0.893; 95% CI, 0.808-0.988; P = 0.028). Cytokine release syndrome (CRS) occurred in 21 patients (91.3%), including grade 3 or higher CRS in 3 (13.0%); no immune effector cell-associated neurotoxicity syndrome or treatment-related deaths occurred. Grade ≥3 neutropenia, thrombocytopenia, and anemia occurred in 95.7%, 82.6%, and 82.6%, respectively. Infections occurred in 17 patients (73.9%). **Conclusions:** A second CAR T-cell infusion produced meaningful responses in selected patients after prior CAR T-cell failure. Same-target retreatment was associated with deeper responses but not longer PFS2 or OS. Greater early expansion was associated with response and severe cytopenias, while later peak expansion was associated with longer PFS2. Larger prospective studies are needed.

LBA-21

Second-Week Onset and High Mortality of IEC-HS After CAR T-Cell Therapy in 1,931 Recipients

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Introduction: Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) is an uncommon, potentially fatal delayed toxicity after CAR T-cell therapy. Recognition is difficult because its clinical and laboratory features overlap with cytokine release syndrome (CRS), immune effector cell-associated hematotoxicity (ICAHT), infection, disease progression, and lymphodepletion-related cytopenias. We characterised IEC-HS incidence, timing, clinical course, management, and outcomes in a large single-centre cohort. **Methods:** We retrospectively screened 1,931 consecutive patients with haematologic malignancies who received CAR T-cell therapy at a single centre from January 2016 through June 2026. Suspected cases were adjudicated using 2023 ASTCT consensus criteria; CRS and IEC-HS were graded by ASTCT criteria. We collected event timing, serial laboratory values, ICAHT, documented infections, treatments, organ support, survival, and recorded primary causes of death. Incidence was reported with an exact binomial 95% confidence interval (CI). **Results:** Twenty patients met ASTCT criteria, for a clinically recognised incidence of 1.04% (95% CI, 0.63%–1.60%). Median age was 44 years; 10 (50%) were male. CRS occurred in all patients at a median of 3 days after infusion, and 18 (90%) had grade 3–4 CRS. IEC-HS began at a median of 12 days after infusion, with a median interval of 9 days from CRS onset; 17 (85%) had grade ≥3 IEC-HS. All patients developed fever and ICAHT. Infection was documented in 15 (75%), and 11 (55%) required vasopressors. Median recorded peak ferritin reached the assay upper limit of 50,000 ng/mL at a median of 16 days, versus 1,717.8 ng/mL at baseline. Median IL-6, IL-10, and soluble IL-2 receptor levels increased from 5.2 to 1,397.5 pg/mL, 6.3 to 305.4 pg/mL, and 747.0 to 3,615.5 U/mL, respectively. Median platelet count and fibrinogen fell from 50 to 16 × 10^9/L and from 3.40 to 1.19 g/L, while D-dimer rose from 0.53 to 4.42 µg/mL FEU. All patients received glucocorticoids, antibacterial therapy, and transfusion support. Tocilizumab was used in 13 (65%), ruxolitinib in 4 (20%), plasma exchange in 15 (75%), and continuous renal replacement therapy or other blood purification in 9 (45%).All 20 patients died during follow-up. Median overall survival from CAR T-cell infusion was 44 days, and median survival from IEC-HS onset was 26 days. By 30 and 60 days after IEC-HS onset, 10 (50%) and 13 (65%) patients had died. Recorded primary causes of death were infection (n = 11), disease progression or relapse (n = 6), IEC-HS (n = 2), and multiorgan failure (n = 1). **Conclusions:** IEC-HS was uncommon but carried a heavy treatment burden and poor survival. Onset clustered in the second postinfusion week, shortly after severe CRS, identifying a critical period for surveillance. Infection was the leading recorded cause of death, underscoring the need to evaluate and treat infection in parallel with control of hyperinflammation and timely transfusion and organ support.

LBA-22

Assessment of Disease Activity by a First-in-Human CD38-Targeting Cyclic Peptide PET Tracer in Multiple Myeloma

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Introduction: CD38 is a major therapeutic target and biomarker in multiple myeloma (MM), but its expression is primarily assessed by localized bone marrow biopsy, which may not fully reflect the spatial heterogeneity of systemic disease. A CD38-targeted radiotracer may enable noninvasive whole-body visualization of CD38-positive lesions and support disease assessment and treatment evaluation. **Methods:** We developed and optimized the CD38-targeting cyclic peptide radiotracer [68Ga]Ga-SCH001 and conducted systematic preclinical and prospective clinical translational studies. Binding affinity, target specificity, pharmacokinetics, and imaging performance were evaluated using cellular assays, xenograft models, biodistribution and blocking studies, and dynamic PET/CT in cynomolgus monkeys. Clinical PET/CT was subsequently performed in 12 subjects, including 11 patients with MM and 1 patient with POEMS syndrome, to evaluate safety, biodistribution, lesion visualization, and treatment-related imaging changes. **Results:** SCH001 exhibited high affinity for CD38, with an equilibrium dissociation constant of 45 nM. [68Ga]Ga-SCH001 showed specific uptake in CD38-positive cells and tumors, high tumor-to-background contrast, and markedly reduced uptake after competitive blocking. Dynamic imaging demonstrated rapid blood clearance, predominant renal excretion, and low nonspecific uptake in most normal tissues. Clinically, [68Ga]Ga-SCH001 was well tolerated and clearly visualized diffuse bone marrow involvement, focal osteolytic lesions, nodal disease, visceral

involvement, and extramedullary soft-tissue masses. Treatment-naïve patients showed extensive axial and appendicular skeletal uptake, with maximum lesion SUVmax values of 14.82 and 33.92. Patients evaluated after systemic therapy generally showed lower overall skeletal uptake but persistent focal or extramedullary disease, with representative maximum SUVmax values ranging from 8.54 to 13.72. Marked interpatient and interlesional heterogeneity was observed, with lesion SUVmax values of up to 30.58. PET findings were concordant with available CD38 immunohistochemistry and histopathology. Additionally, compared with other CD38-targeted radiotracers, [^{68}Ga]Ga-SCH001 achieves superior performance for PET imaging of MM. **Conclusions:** [68Ga]Ga-SCH001 demonstrated favorable affinity, specificity, pharmacokinetics, and clinical safety. CD38-targeted PET enabled noninvasive whole-body visualization of MM lesions and revealed spatially heterogeneous disease and discordant treatment responses. This tracer may provide a complementary approach to bone marrow biopsy for assessing CD38 expression, disease distribution, and treatment-related changes in MM.

LBA-23

From Clinical Observation to Precision Medicine: Six Decades of Research Evolution in Primary Plasma Cell Leukemia

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Introduction: Primary plasma cell leukemia (pPCL) is a rare and highly aggressive plasma cell neoplasm characterized by adverse cytogenetic features, extramedullary dissemination, and poor survival despite recent therapeutic advances. Although numerous clinical and translational studies have been published, the global evolution and intellectual structure of pPCL research have not been systematically evaluated. We performed a comprehensive bibliometric analysis to characterize publication trends, scientific influence, collaborative networks, and emerging research directions in pPCL. **Methods:** Publications related to pPCL were retrieved from the Scopus database using the search term "primary plasma cell leukemia." English-language original articles published between 1961 and 2026 were included. Bibliometric analyses were performed using the Bibliometrix package in R through the Biblioshiny interface. Publication growth, citation performance, leading journals, authors, institutions, international collaborations, keyword co-occurrence, conceptual structure, thematic evolution, and trend topics were analyzed. **Results:** A total of 1,426 publications from 587 scientific sources, involving 10,607 authors, were identified. Scientific production demonstrated a sustained annual growth rate of 4.8%, with a marked acceleration after the early 2000s. The mean citation count per publication was 41.9. Blood emerged as the leading journal in both productivity and scientific influence, while the United States dominated global research output and served as the principal hub of international collaboration. Bibliometric network analyses demonstrated a clear evolution from early descriptive clinical reports toward translational and precision medicine–oriented research. Recent thematic and conceptual analyses identified high-risk cytogenetics, stem cell transplantation, molecular profiling, targeted therapies, and immunotherapeutic strategies as the major contemporary research priorities, highlighting a progressive shift toward biologically driven and personalized therapeutic approaches. **Conclusions:** This study provides the first comprehensive bibliometric roadmap of pPCL research spanning more than six decades. The field has evolved from predominantly descriptive clinical observations to collaborative, molecularly driven investigations focused on precision medicine. By identifying influential contributors, major research themes, and emerging priorities, these findings offer a framework for future international collaboration and may help accelerate translational research aimed at improving outcomes in this highly aggressive plasma cell malignancy.

LBA-24

Patient Understanding of Multiple Myeloma: Findings of an Online Survey of Patient Perspectives on Communication, Information and Support

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Introduction: Multiple myeloma (MM) is a complex haematological malignancy requiring increasingly specialised and evolving treatment, making effective communication essential for informed decision-making and patient-centred care. Patients' understanding of MM, their prognosis and management plan is influenced by the information provided by healthcare professionals (HCPs) and how this information is communicated. A survey was designed to explore patient understanding and experiences of communication, information and support. **Methods:** The UK-wide online survey for adults living with MM was conducted between January and April 2025. Content was developed following a literature review and consultation with HCPs and patient representatives to identify examples of gaps in communication or information that was challenging to discuss or understand. Patient understanding and experiences were explored in six sections with both fixed-choice and free-text response formats, allowing respondents to identify terminology and phrases that enhanced or hindered their understanding of diagnosis, treatment and disease management. The survey was shared with myeloma charities, support groups, via social media and by word of mouth. Quantitative and qualitative data were analysed using descriptive statistics and thematic analysis respectively. **Results:** 138 people living

with MM completed the survey in full. Most participants (76%) had been living with MM for 1-10 years, and 75% reported they had never heard of MM prior to their diagnosis. Important communication gaps were identified. Only 46.6% had discussed their prognosis with a HCP, and three-quarters of these conversations were initiated by patients. Only 3% had received recordings of consultations despite evidence that these can support patient understanding. Free-text responses were organised into six overarching themes: making sense of MM; gaps in understanding MM; communicating MM to family & friends; family & friends' behaviours; HCP interactions; and healthcare systems and pathways. Many felt confused by the complex terminology and had unanswered questions about their disease, treatments and prognosis. Limited understanding often led to family & friends exhibiting unhelpful behaviours. However, positive communication and supportive behaviours were reported as helping respondents navigate day-to-day life. **Conclusions:** Patients identified persistent communication challenges surrounding diagnosis, prognosis and complex treatment information. This survey demonstrated how complex language used routinely by HCPs can contribute to distress and misunderstandings, while also identifying opportunities to enhance communication throughout the patient journey. These findings will inform the development of educational resources to support more effective communication between patients, their families and HCPs.

LBA-25

Analytical Validation of a High-Sensitivity Soluble BCMA Assay on the Fully Automated Immunoassay System

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Introduction: B-cell maturation antigen (BCMA) is an established therapeutic target in multiple myeloma (MM), and circulating soluble BCMA (sBCMA) has emerged as a promising biomarker for monitoring treatment response, risk stratification, and tumour burden. Because sBCMA concentrations can vary widely in disease, clinical assays require a broad dynamic range, high sensitivity, and resistance to high-dose hook effects. To address these needs, we adapted and validated a highly sensitive sBCMA assay on the Sysmex HISCL™-5000 Automated Immunoassay System (HISCL). We evaluated assay performance, including calibration curve robustness, lower limit of quantitation (LLoQ), high-dose hook-effect resistance, and endogenous dilution linearity, and assessed its ability to distinguish healthy individuals from MM patients. We also demonstrated strong agreement with a commercially available BCMA ELISA kit. **Methods:** The analytical performance of the sBCMA immunoassay was evaluated on the HISCL platform. A calibration curve with a dynamic range up to 480 ng/mL was established. Analytical sensitivity was assessed by determining the LLoQ, defined as the lowest concentration achieving a coefficient of variation (%CV) < 15%. Resistance to the high-dose hook effect was evaluated using recombinant human BCMA concentrations up to 10,000 ng/mL. Endogenous assay performance, dilution linearity, and parallelism were assessed by two-fold serial dilutions (1×-16×) of plasma samples from healthy donors and patients with MM. **Results:** The HISCL sBCMA assay demonstrated a reliable calibration range up to 480 ng/mL and a LLoQ of 0.01 ng/mL with excellent precision (%CV = 6.9%). The assay showed complete resistance to the high-dose hook effect up to 10,000 ng/mL and excellent endogenous linear parallelism up to a 16-fold dilution. The assay clearly differentiated MM patients from healthy donors, with significantly elevated sBCMA levels in the MM cohort. Comparison with a commercially available BCMA ELISA kit demonstrated strong correlation (Pearson $r = 0.975$, Spearman $\rho = 0.964$) and good agreement across the tested concentration range ($R^2 = 0.951$). **Conclusions:** The developed sBCMA immunoassay using HISCL exhibits robust analytical performance characterized by high sensitivity, precision, and reproducibility. Endogenous sBCMA in both healthy individuals and MM patients demonstrated excellent linear parallelism up to a 16-fold dilution, indicating accurate measurement with minimal matrix interference. All healthy plasma samples quantified well above the assay LLoQ (0.01 ng/mL), with the lowest measured endogenous concentration (2.44 ng/mL) more than 240-fold above this limit. Strong agreement with a commercial BCMA ELISA kit further supports the assay's analytical validity. By clearly differentiating MM patients from healthy donors through significantly elevated sBCMA levels, this automated high-throughput platform shows strong potential for monitoring tumour burden and therapeutic response in patients with multiple myeloma.

LBA-26

High-Sensitivity Longitudinal Circulating Plasma Cells Monitoring After T-Cell-Redirecting Therapies: The Impact of Early Clearance on Response and Survival Outcomes

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Introduction: Bone marrow (BM)-based measurable residual disease (MRD) is the current standard for response assessment in multiple myeloma (MM), but its invasive nature limits frequent longitudinal monitoring during T-cell–redirecting immunotherapies, where rapid treatment responses and early disease progression require close serial assessment. We investigated whether high-sensitivity monitoring of circulating plasma cells (CPCs) in peripheral blood (PB) could provide an early, minimally invasive biomarker of treatment efficacy. Thus, the aim was to evaluate the prognostic

value of baseline CPCs burden and longitudinal CPCs kinetics in patients with relapsed/refractory (RR) MM treated with CAR-T cells or bispecific antibodies (bsAbs). **Methods:** We prospectively monitored CPCs by next-generation flow cytometry (NGF) in 73 RRMM receiving CAR-T cells or bsAbs. Overall, 343 serial PB samples were collected from pre-treatment through 12 months according to a predefined monitoring schedule. Baseline CPCs burden and longitudinal CPCs kinetics were correlated with response, progression-free survival (PFS) and overall survival. Multivariable Cox and Firth logistic regression models were adjusted for age, treatment modality, previous treatment lines and baseline CPCs burden. **Results:** Baseline CPCs were detected in 46/73 (63%) RRMM patients. Higher baseline CPCs burden (≥0.002%) was associated with inferior PFS and remained independently associated with shorter PFS when analyzed as a continuous variable (HR 1.42, 95%CI 1.07–1.88; p = 0.015). In contrast, early CPCs kinetics provided substantially greater prognostic information. Among 32 evaluable baseline CPCs-positive patients, complete CPCs clearance at Day +7 was associated with significantly higher complete response (CR) rates than persistent CPCs detection (70.6% vs 13.3%; p = 0.0016) and showed superior discrimination for CR compared with baseline CPCs burden (AUC 0.79 vs 0.61). In multivariable analyses, persistent Day +7 CPCs detection independently predicted shorter PFS (HR 10.58, 95% CI 1.31–85.51, p = 0.027) and a markedly lower probability of achieving CR (OR 0.00053, 95% CI 0.00000048–0.59, p = 0.035), independently of treatment modality, previous treatment lines and baseline CPCs burden. Landmark analysis further identified four distinct CPCs clearance trajectories (i.e., sustained undetectable, early clearance, delayed clearance, and persistent CPCs) which were associated with progressively shorter PFS (p = 0.00085). **Conclusions:** Peripheral CPCs clearance within the first week of T-cell–redirecting therapy is an early and independent biomarker of treatment efficacy. Longitudinal CPCs kinetics further refine risk stratification beyond baseline disease burden and independently of treatment modality, supporting prospective validation of PB NGF monitoring as a practical complement to BM-based MRD for real-time response assessment in RRMM. ACK: Bologna AIL, PNRR-TR1-2023-12378246, RC26000969

LBA-27

The Evolving Landscape of MRD in Myeloma: A 1-Year Single-Center Study

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Introduction: Approximately 1.19% of all cancer in India is multiple myeloma; the incidence rate is rather low when compared to Western nations. In both newly diagnosed and recurrent contexts, MRD negative has become one of the most potent indicators of long-term prognosis in multiple myeloma. Here we present an assessment of MRD by multicolor flow cytometry and its impact on prognosis and correlation with cytogenetic abnormalities in our center. **Methods:** A prospective longitudinal study, including the newly diagnosed multiple myeloma presenting to our centers in 1 year. They were given different therapy based on their biochemical parameters like RVd, VTd, Cybord, and Dara RVd. MRD assessment was done by multicolor flowcytometry. A cutoff of 10^{-3} was considered MRD negative. MRD was assessed at the end of induction, day +100 post-ASCT, and at the end of 1 year. **Results:** In this study, MRD assessment was done in 30 cases; 20 cases were in sCR, out of which 18 (47.3%) were MRD negative (following RVd/VTd, ASCT, and Dara Vd) and 2 (15.7%) were MRD positive while in sCR, and 10 were in VGPR; those 10 (38.4%) cases were MRD positive. Out of the 30 patients who achieved MRD negativity, 10 cases (55.56%) belong to RISS stage II, and 6 cases (33.33%) belong to RISS stage III. Even RISS staging also doesn't affect the MRD achievement with a p-value > 0.005. Over 36 months of follow-up, events occurred in 57.1% of MRD-positive patients compared to 5.0% of MRD-negative patients. The mean event-free survival was significantly shorter in the MRD-positive group (25.1 months; 95% CI 19.6–30.6) compared to the MRD-negative group (46.6 months; 95% CI 43.8–49.3). MRD positivity was independently associated with inferior event-free survival, conferring a 16-fold higher risk of relapse or death (HR: 16.33, 95% CI: 2.03–131.26; P = 0.009). MRD negative was achieved in 18 cases, of which 4 cases had del13q and 1 case had gain 1q and t(4:14) (p = 0.06). It means that achieving MRD negativity is not affected by the cytogenetic abnormalities but rather by the aggressive therapy to achieve MRD negativity. It is the aggressive therapy with which MRD negative status can be achieved even with high-risk cytogenetics/RISS stage III or relapsed MM. **Conclusions:** The study contributes to the growing body of evidence underscoring the importance of MRD monitoring in improving patient outcomes and guiding therapeutic decisions. The findings corroborate the emerging role of MRD negativity as a powerful prognostic marker, linking it to better treatment responses and longer progression-free survival. The study also explored that there is no influence of baseline characteristics on MRD status when treated aggressively. Newer therapies are effective and better tolerated, reaching a deeper response. It should be incorporated to escalate and de-escalate the therapy. Achieving MRD negative and sustained MRD negativity should be the primary endpoint in MM treatment, reinforcing its role as a validated surrogate of clinical benefit.

LBA-28

Circulating Plasma Cells in Newly Diagnosed Multiple Myeloma: Prognostic Validation and Single-Cell Multi-Omics Profiling

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Introduction: Circulating plasma cells (CPCs) represent a liquid biopsy marker reflecting tumor dissemination in multiple myeloma

(MM). Although CPCs are associated with adverse outcomes, their clinical utility in treatment selection and the biological basis underlying therapeutic vulnerability of CPCs remain poorly understood. **Methods:** We retrospectively analyzed 502 newly diagnosed MM (NDMM) patients treated at Jiangsu Province Hospital. CPCs were quantified by standardized 8-color multiparameter flow cytometry at diagnosis. The optimal CPC threshold for progression-free survival (PFS) was determined using maximally selected rank statistics. Paired bone marrow (BM) and peripheral blood (PB) plasma cells from four NDMM patients were analyzed by single-cell RNA sequencing (scRNA-seq), with validation by mass cytometry (CyTOF) in ten additional patients. Prognostic relevance of molecular signatures was assessed using the MMRF CoMMpass dataset. **Results:** CPCs were detected in 375 (74.7%) patients. A cutoff of 0.017% was identified as the optimal threshold for PFS discrimination. Patients with CPC-high status (≥0.017%, n = 281) showed significantly inferior PFS compared with CPC-low patients (< 0.017%, n = 221) (median PFS: 33.7 vs. 52.6 months; HR = 1.92, 95% CI 1.48–2.50; p< 0.001). Multivariate analysis confirmed CPC-high status as an independent adverse prognostic factor beyond established clinical and cytogenetic risk factors. Importantly, daratumumab-based induction therapy significantly improved outcomes compared with non-daratumumab regimens (median PFS: not reached vs. 36.7 months; HR = 0.56; p = 0.044). Following propensity score matching, CPC-high status remained strongly associated with inferior PFS in patients receiving non-daratumumab therapy, whereas this adverse prognostic impact was markedly attenuated in patients treated with daratumumab-based induction. Single-cell transcriptomic profiling identified a proliferative high-risk malignant plasma cell population enriched in CPCs, characterized by increased KDM6A expression and a distinct molecular phenotype. This CPC-associated clone was captured by a novel gene module, termed Module Prime, including SPP1, STMN1, PTTG1, HMGB1, and CDC20, which was associated with cell-cycle activation and aggressive disease biology. High expression of Module Prime genes predicted inferior overall survival in the MMRF cohort. CyTOF validation confirmed enrichment of this high-risk plasma cell population in CPC-high patients at the protein level. **Conclusions:** CPC burden provides independent prognostic information in NDMM and identifies a biologically aggressive disease compartment. CPC-high patients appear to derive particular benefit from daratumumab-based therapy, suggesting CPCs may serve as a predictive biomarker for treatment selection. Integrated single-cell and proteomic profiling reveals a CPC-associated high-risk clone, providing mechanistic insight into circulating myeloma cell vulnerability and supporting CPC-guided precision therapy.

LBA-29

Gut Microbiome-Driven Metabolic and Innate Immune Changes Drive Progression from MGUS to Multiple Myeloma

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Introduction: Current risk stratification for MGUS and smouldering myeloma (SM) remains limited at the individual patient level leading to lifelong monitoring for most patients and significant associated burden on healthcare services. Identifying more specific biomarkers would not only help to improve risk stratification but could also direct us to new targets for disease prevention in the future. Age and obesity are the two most established risk factors for progression of MGUS to myeloma (MM). Both have also been associated with significant gut dysbiosis and a pro-inflammatory state, providing potential insight into the mechanistic drivers of disease progression. A growing body of work implicates the interaction between the gut microbiome, the immune system and the bone marrow, in age-related inflammatory diseases and haematological malignancies. Changes in the microbiome have already been reported in myeloma patients, with most attention to date focused on their role in treatment response and resistance. In addition, immune dysregulation is well described in MM and even patients with MGUS are known to have an increased risk of infection. What has not been addressed is the mechanistic interplay between gut metagenomics, metabolomics and innate immune function across MGUS, SM and myeloma progression. **Methods:** Matched stool and serum samples were collected from patients with MGUS, SM and MM. Stool and serum metabolomics were performed by NMR on 42 stool and 67 serum samples. Shotgun metagenomic sequencing was performed on patient stool samples. PBMCs were analysed by flow cytometry for monocyte frequency, and phagocytic activity was assessed by stimulation with E. coli bioparticles. **Results:** Metabolic disturbance in both stool and serum was greatest in SM relative to MGUS, identifying SM as the key transitional phase for metabolic reprogramming. Phenylalanine and tryptophan metabolism and biosynthesis were shown to be significantly and consistently dysregulated. Both of these metabolic pathways have previously been linked to gut dysbiosis, inflammation and myeloma cell survival. Three of the MGUS patients progressed to MM within one year. Metabolomic analysis of their stool samples revealed a number of metabolites, including serine and butyrate, that differ in the patients who progressed compared to other MGUS patients. In addition, flow cytometry analysis of peripheral blood samples showed reduced monocyte numbers and phagocytic activity in myeloma patients compared to MGUS patients. This provides the first direct evidence of innate immune changes in the peripheral blood during disease progression. **Conclusions:** These data provide the first evidence

linking gut microbial metabolic dysregulation and changes in monocytes with progression of MGUS to MM.

LBA-30

Ferroptosis Resistance Mediates Selinexor Resistance in Multiple Myeloma via MTCH1-Dependent Disruption of Mitochondria-Associated Endoplasmic Reticulum Membranes

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Introduction: Selinexor, a first-in-class selective inhibitor of nuclear export targeting XPO1, has demonstrated clinical activity in relapsed/refractory multiple myeloma (MM). However, acquired resistance significantly limits its therapeutic efficacy. We previously identified ferroptosis suppression as a critical determinant of selinexor resistance, yet the upstream regulatory mechanisms linking cellular stress adaptation to ferroptotic vulnerability remain largely unknown. **Methods:** Selinexor-resistant (DR) MM cell models were established, followed by single-cell transcriptomic profiling to identify resistance-associated molecular alterations. Ferroptosis sensitivity, mitochondrial function, and mitochondria-associated endoplasmic reticulum membrane (MAM) dynamics were evaluated using pharmacological and genetic approaches. Protein interaction mechanisms were investigated by co-immunoprecipitation. **Results:** Pharmacological induction of ferroptosis markedly enhanced selinexor sensitivity in DR MM cells, indicating ferroptotic resistance as a key mechanism of drug adaptation. MTCH1 was significantly upregulated in selinexor-resistant cells and MM clinical samples and was associated with inferior clinical outcomes. Mechanistically, MTCH1 directly interacted with the mitochondrial fusion protein MFN2, preventing its mitochondrial recruitment and impairing MFN2-mediated ER–mitochondria tethering. Disruption of the MTCH1–MFN2 axis resulted in abnormal MAM remodeling, impaired mitochondrial homeostasis, reduced mitochondrial oxidative stress, and decreased lipid peroxidation, ultimately protecting MM cells from ferroptotic death. Restoration of MAM integrity or disruption of MTCH1–MFN2 interaction reactivated mitochondrial stress signaling, increased ferroptotic vulnerability, and resensitized resistant MM cells to selinexor. **Conclusions:** Our study identifies a previously unrecognized MTCH1–MFN2–MAM regulatory axis controlling ferroptosis susceptibility in selinexor-resistant MM. MTCH1-mediated disruption of ER–mitochondria communication preserves mitochondrial homeostasis and suppresses ferroptotic cell death, thereby promoting therapeutic resistance. Targeting MAM dysfunction and restoring ferroptotic sensitivity may represent a novel strategy to overcome selinexor resistance in MM.

LBA-31

Lipid Nano Particle-mRNA Delivery of a Dual Target TACI-BCMA NK Engager for Potent and Scalable Multiple Myeloma Treatment

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Introduction: Developing innovative therapies for multiple myeloma (MM) is both timely and crucial, given the persistent challenge of relapses in this incurable malignancy originating from plasma cells. Targeting B-cell maturation antigen (BCMA) with antibody-based therapies is a well-established strategy due to its selective and elevated expression on MM cells, but can result in mutational escape. Here we report development of engagers that simultaneously target both BCMA and the related antigen, transmembrane activator and CAML interactor (TACI) using tandem variable heavy of camelid heavy-chain only antibodies (VHH). We have further functionalized this engager with a VHH engaging human NKp30 and a human IgG-Fc domain, delivered as mRNA within a lipid nanoparticle. **Methods:** BCMA-TACI-NKp30-hFc proteins and corresponding single-antigen targeting NK-engagers were synthesized and produced using standard CHO-cell recombinant protein production and protein-A affinity purification. Constructs were then encoded in mRNA format and encapsulated in lipid nanoparticles (LNP) of varying composition. Proteins and LNP-mRNA formats of single and dual-target engagers were screened for antigen binding on NK and MM cells, NK cell activation, and cytotoxicity in vitro using flow cytometry-based assays; followed by in vivo studies for anti-MM efficacy and pharmacokinetics in mouse models. **Results:** NK engagers showed varying binding to MM target cells and NK cell receptors, though dual BCMA/TACI-engagement resulted in higher surface density of staining. In co-culture systems, BCMA-TACI-NKp30-Fc activated potent NK-cytotoxicity against MM cells when either BCMA or TACI were present, with elevated activity in the presence of both targets. Encoding in mRNA-LNP format resulted in strong expression of engagers and favourable in vivo pharmacokinetics. **Conclusions:** This work provides strong proof of concept that the small single-molecular nature of VHH domains makes them highly conducive to engineering immune cell engagers against multiple cancer associated antigen targets. Furthermore, this triple-VHH-Fc format expresses well in mRNA format, and could lead to efficient and scalable treatment options for relapsed or refractory MM.

LBA-32

Efficacy and Safety of Daratumumab-Based DVP-Lite in Newly Diagnosed AL Amyloidosis With Advanced Cardiac Disease or Poor Performance Status: A Prospective Multicenter Study

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Introduction: Daratumumab plus bortezomib, cyclophosphamide, and dexamethasone (D-VCd) is a standard frontline regimen for systemic light-chain (AL) amyloidosis, but patients with advanced organ involvement or poor performance status may not tolerate full-intensity therapy. We developed DVP-Lite, a cyclophosphamide-free, reduced-intensity regimen with less frequent early daratumumab, reduced-intensity bortezomib, and methylprednisolone in place of dexamethasone, and evaluated its efficacy and safety in this high-risk population. **Methods:** In this prospective multicenter study, 35 patients with newly diagnosed, biopsy-confirmed systemic AL amyloidosis received DVP-Lite. Daratumumab 1,800 mg subcutaneously and bortezomib 1.3 mg/m² were given every 2 weeks during cycles 1–6 and every 4 weeks thereafter through cycle 24, with methylprednisolone 40 mg. Eligibility required European-modified Mayo 2004 stage III disease and/or ECOG PS 3–4. Hematologic and organ responses were assessed by consensus criteria, with best response recorded from treatment initiation to progression or subsequent therapy. **Results:** Median age was 69 years; 30 patients (85.7%) had ECOG PS 3–4, and 31 (88.6%) had stage III disease, including 18 (51.4%) with stage IIIb. Two patients were lost to follow-up before first hematologic assessment. Median treatment duration was 4.0 months (IQR, 3.0–9.5; range, 1–25). Among 33 evaluable patients, the hematologic overall response rate was 81.8%, with ≥VGPR in 72.7% and CR in 51.5%. Median time to first hematologic response among responders was 1.0 month. Best cardiac and renal response rates were 51.5% (17/33) and 64.7% (11/17), respectively. Treatment-related adverse events occurred in 3 patients (8.6%) and comprised chills, vomiting, diarrhea, and blurred vision; all were grade 1–2. No grade ≥3 treatment-related adverse events, treatment-related discontinuations, or treatment-related deaths occurred. Seven deaths were confirmed during follow-up: 3 from heart failure, 2 from infection, 1 from heart failure with infection, and 1 from renal failure with infection. All 4 infection-related deaths occurred during second-line therapy, including 3 during BCMA-directed bispecific T-cell engager treatment and 1 during lenalidomide treatment. None was attributed to DVP-Lite. In a conservative landmark analysis counting the 2 patients lost within 1 month as deaths, 30- and 90-day mortality were both 8.6% (3/35). **Conclusions:** DVP-Lite produced rapid, deep hematologic responses and encouraging organ responses in high-risk patients, with no grade ≥3 treatment-related toxicity, discontinuation, or death. Longer follow-up and is warranted to define response durability and survival benefit.

LBA-33

Fixed-Duration Zanubrutinib, Bendamustine, and Rituximab in Symptomatic, Treatment-Naive Waldenström Macroglobulinemia: First Report of the Multicenter Phase 2 ZeBRa Trial (WM-NET2).

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Introduction: VGPR or better is associated with improved PFS in WM. Bendamustine and Rituximab (BR) requires 6 cycles though cumulative alkylator exposure carries long-term risks, including secondary malignancies. Bruton tyrosine kinase inhibitor (BTKi) monotherapy requires indefinite treatment. BTKi responses are adversely impacted by CXCR4 mutations, while BR may overcome this. Combining BR and BTKi may deepen responses across MYD88 and CXCR4 genotypes and permit a fixed duration approach. Moreover, use of 4 cycles of BR may offer similar outcomes as 6 cycles in WM patients (pts). **Methods:** ZeBRa is an investigator-initiated, multicenter, phase 2 study of zanubrutinib, bendamustine, and rituximab (ZBR) in untreated WM (NCT06561347). 65 pts will be enrolled. Eligible pts met IWWM2 criteria for treatment, regardless of MYD88, CXCR4, or TP53 status. Zanubrutinib was administered once daily (320 mg) in 28-day cycles for 15 cycles. Bendamustine 90 mg/m2 IV was given days 1-2 of cycles 1-4, with rituximab day 1 of cycles 1-4. MYD88, CXCR4, and TP53 were genotyped centrally. The primary endpoint was the proportion achieving ≥VGPR by IWWM-11 criteria; secondary endpoints included major (MRR) and overall response rate (ORR), response by genotype, PFS, OS, and safety. **Results:** 56 pts were enrolled as of June 30, 2026, 52 with >1 evaluable response assessments. Median age: 71 years (range, 42-87); BM involvement: 50%; serum IgM: 3,006 mg/dL; and hemoglobin: 10.6 g/dL. MYD88L265P was detected in 96%, CXCR4 mutations in 34%, and TP53 mutations 12.7%. Median follow-up was 7.5 months (95% CI, 4.8-9.9; range, 1.0-17.5). Responses for evaluable pts were as follows: CR, 7.7% [4/52]; VGPR, 36.5% [19/52]; PR, 40.4% [21/52]; MR, 11.5% [6/52], and SD, 3.8% [2/52]. The CR/VGPR rate was 44.2% (95% CI, 30.5-58.7), MRR (PR or better) was 84.6% (95% CI, 71.9-93.1), and the ORR (MR or better) was 96.2% (95% CI, 86.8-99.5). Among MYD88+, the CR/VGPR rate was 43.8% (14/32) and 50% (9/18) for CXCR4 wild-type and CXCR4 mutated pts, respectively. CR/VGPR rates were 42.9% (3/7) and 46.3% (19/41) in TP53-mutated pts and not, respectively.

Treatment was well tolerated with no unexpected toxicities. Grade ≥3 adverse events occurred in 40% (22/55), with Grade ≥3 reversible neutropenia in 18.2% (10/55). Febrile neutropenia occurred in 1.8% (1/55) and Grade ≥3 infection in 16.4% (9/55). Following 2 cases of herpes zoster, antiviral prophylaxis was required with no subsequent cases. **Conclusions:** The fixed duration regimen ZBR showed high ORR and MRR in symptomatic, treatment naïve WM patients, with attainment of CR/VGPR in 44% of response evaluable participants. Importantly, CR/VGPR rates were not impacted by the presence of CXCR4 or TP53 mutations, subgroups historically associated with inferior response outcomes on BTK-inhibitors alone. Follow-up is ongoing to characterize response durability, PFS, overall survival, and safety. Our initial findings support the continued investigation of upfront ZBR in WM.

LBA-34

Treatment De-Escalation During Frontline Intensive Induction for Newly Diagnosed Multiple Myeloma: A Real-World Analysis

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Introduction: Optimal frontline treatment for newly diagnosed multiple myeloma remains challenging, particularly for patients borderline fit for intensive induction. Although intensive regimens achieve deeper responses, treatment-related toxicity and functional decline may necessitate de-escalation to less intensive regimens such as daratumumab, lenalidomide and dexamethasone (DRd). Identifying patients at risk of treatment de-escalation could improve treatment selection and supportive care. **Methods:** Patients with newly diagnosed multiple myeloma commencing a transplant-eligible induction pathway between September 2023 (following Scottish Medicines Consortium approval of DRd) and January 2026 within a single Scottish health board were retrospectively reviewed. Baseline characteristics, treatment toxicities, dose modifications, treatment delays and reasons for de-escalation were recorded. Modified IMWG frailty scores were calculated at baseline. Patients requiring de-escalation to DRd were compared with those completing intensive induction. **Results:** Sixty-two patients commenced intensive induction: D-BTd (37), D-VRd (14), BTD (1), R-CyBorD (8), and R-CyBorD + Isa (2). Fifteen patients (24%) required treatment de-escalation, of whom 13 (87%) de-escalated to DRd. De-escalation occurred after a median of three cycles, most commonly due to comorbidity (38%) or functional decline (30%). Patients requiring de-escalation experienced greater early treatment-related toxicity; during cycle 1, 46% required dose modification and 40% treatment interruption, most commonly due to infection, compared with 27% and 23%, respectively, among those completing intensive induction. Median age (63 vs 61 years) and ECOG performance status (80% vs 89% ECOG 0–1) were similar between groups. Fewer patients requiring de-escalation were classified as fit by modified IMWG frailty score (60% vs 77%), although most were considered fit at baseline. Renal impairment, extramedullary disease, anaemia and adverse cytogenetic abnormalities were more frequent in the de-escalation group. Despite de-escalation, 62% achieved at least VGPR during intensive induction, with 38% subsequently deepening their response after transition to DRd. **Conclusions:** Nearly one-quarter of patients commencing intensive induction required treatment de-escalation, most frequently to DRd. Baseline performance status and modified IMWG frailty assessment alone were insufficient to predict treatment tolerance, as most patients requiring de-escalation were considered fit at baseline. Early infective complications, dose modifications and treatment interruptions were more common among patients requiring de-escalation, supporting the role of dynamic frailty assessment throughout induction. Larger prospective studies with longer follow-up are needed to determine whether these early clinical features predict intolerance of intensive induction and whether treatment de-escalation influences progression-free and overall survival.

LBA-35

Functional Precision Medicine Using Ex Vivo Drug Sensitivity Profiling to Guide Therapy Selection in Relapsed/Refractory Multiple Myeloma: Results of a Prospective Clinical Trial

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Introduction: Relapsed/refractory multiple myeloma (RRMM) remains a heterogeneous disease with variable responses to later-line therapies. Despite advances with proteasome inhibitors, IMiDs, anti-CD38 antibodies, and BCMA-directed treatments, most patients eventually relapse, highlighting the need for personalized therapeutic strategies. Functional precision medicine, based on ex vivo drug sensitivity profiling of patient-derived tumor cells, may help identify effective treatments and guide therapy selection. We conducted a prospective clinical trial (NCT03389347) to evaluate the feasibility and clinical utility of a high- throughput drug sensitivity assay in RRMM **Methods:** Eligible patients had MM or plasma cell leukemia with relapsed/refractory disease after ≥3 prior lines including an IMiD and a PI, < VGPR to initial therapy, or early relapse (< 12 months) after ASCT or first-line therapy. CD138+ plasma cells were isolated from bone marrow aspirate/biopsy, peripheral blood (if circulating plasma cells were present), or plasmacytoma biopsy.

Samples were processed at the CLIA-certified Quellos HTS Core (University of Washington). Tumor cells were screened against 170 agents in Oncopanel2 v1 (n = 30) and 46 agents in Oncopanel2 v2 (n = 10), including FDA-approved and investigational compounds. Drug sensitivity was quantified using IC50, AUC, and Drug Sensitivity Scores (DSS) calculated via Breeze 2.0. Assay results informed treatment recommendations. For drugs with adequate sample size, ROC analysis assessed DSS performance in predicting clinical response, with optimal thresholds defined by Youden's J index **Results:** Forty patients were enrolled (2018–2024), with a median of 5 prior lines (range 2–15). Prior exposure included lenalidomide (100%), bortezomib (97.5%), carfilzomib (85%), daratumumab (82%), pomalidomide (77.5%), and BCMA CAR-T (12.5%). Top-ranked agents by DSS in v1 included bortezomib (median DSS 47.7), carfilzomib (47.3), panobinostat (47.0), and romidepsin (45.4). In v2, leading agents were marizomib (46.1), carfilzomib (40.2), ixazomib (37.2), and oprozomib (31.6). Thirty-eight patients received assay-guided therapy, achieving an ORR of 51.4% (PR 29.7%, VGPR 13.5%, CR 5.4%). Median PFS was 5.7 months (95% CI 2.5–13). ROC analysis for bortezomib (n = 12) and selinexor (n = 8) yielded AUCs of 0.471 and 0.462, respectively. Selinexor responders showed a trend toward higher DSS (27–35) versus non-responders (20–30), though not statistically significant (p = 0.1). **Conclusions:** High-throughput drug sensitivity testing was feasible in heavily pretreated RRMM and generated actionable results in nearly all patients. DSS-based prediction varied across agents, highlighting the need for drug-specific thresholds and larger validation cohorts. These findings support further development of functional precision medicine as a complementary tool to refine therapeutic decision-making in RRMM

LBA-36

GEM-BELACOMBOS: First Real-World Evidence of Belantamab Mafodotin-Based Combinations at First or Second Relapse in Patients With Multiple Myeloma in Spain

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Introduction: GEM-BELACOMBOS: First real-world evidence of belantamab mafodotin-based combinations at first or second relapse in patients with multiple myeloma (MM) treated in Spain **Methods:** This retrospective, observational, multicenter study included patients with MM treated with BVd or BPd at first or second relapse through a compassionate use program in Spanish hospitals between Nov-24 and Mar-26. The analysis assessed baseline characteristics, prior therapies and refractoriness, treatment selection, ORR by IMWG criteria, time to response and best response, treatment modifications, and frequent AEs. Data were analyzed as of 15 July 2026. The study was approved by Salamanca Hospital's Ethics Committee. **Results:** A total of 50 patients from 15 sites were analyzed. Median age was 78 years (range 42-90), 10% had ECOG ≥2, and 13 (26%) had GFR < 50 mL/min at initiation of therapy. Plasmacytomas were present in 17 patients (34%), and 21 patients (42%) had high-risk cytogenetics. BVd was administered to 17 patients (12 in first relapse) and BPd to 33 patients (11 in first relapse); the median (range) number of prior lines of therapy was 2 (1-2). Overall, 48 patients (96%) had received prior lenalidomide, and 46 (92%) an anti-CD38 monoclonal antibody. Refractoriness data were available for 49 patients: 40 (82%) were refractory to lenalidomide, and 42 (86%) to anti-CD38 antibodies. Finally, 17 patients were refractory to a proteasome inhibitor. Median follow-up was 7.8 months (range, 4.7-10.8). The ORR in the 48 evaluable patients was 79% (95%CI, 0.65-0.90) and 24 (50%) ≥VGPR. Two patients were not evaluable (early death and absence of data), mTTR was 28 days (IQR, 23.5-50.2), and mTTBR was 4.1 months (IQR, 1.86-7). Belantamab mafodotin dose reduction due to AEs occurred in 71% of patients receiving BVd, only in one patient (3%) in the BPd group, and interval extension occurred in 76% of patients in BVd (>every 3 weeks) and 70% of patients in BPd (>every 4 weeks). The most frequent AEs leading to dose modifications were ocular events (58%) followed by hematological toxicities (18%). AEs leading to permanent discontinuation of any study treatment occurred in 11 (22%) patients. **Conclusions:** RWE indicates that BVd and BPd are effective, readily available, and outpatient-feasible BCMA-targeted ADC regimens for patients with MM at first or second relapse. Both combinations demonstrated broad, rapid, and clinically meaningful responses with a manageable safety profile in a broad patient population. This analysis of 50 patients constitutes the first and largest RWE dataset to date evaluating BVd and BPd at first or second relapse.

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