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Abstracts of the 22nd International Myeloma Society Annual Meeting

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ORAL PRESENTATIONS

OA-01

TET2 and EZH2 Genetic Alterations Promote Malignant CAR-T Transformation in Anti-BCMA CAR-T Therapy

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Introduction: B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T cell therapy is an effective treatment option for patients with multiple myeloma (MM). Although rare, the development of secondary malignancies, including myeloid and T-cell neoplasms, is a cause for concern. Sporadic cases of T-cell malignancies have been reported in MM patients who have previously received CAR-T therapy. It remains unclear to what extent various factors, including CAR vector insertion, pre-existing somatic or germline mutations, and immune dysfunction, contribute to CAR-T-cell lymphomagenesis. Here we dissect the underlying mechanism of a CAR+ peripheral T-cell lymphoma (PTCL) with skin, peripheral blood (PB), bone marrow (BM), and lymph node involvement following anti-BCMA CAR-T therapy. **Methods:** We isolated CAR+ peripheral T-cell lymphoma (PTCL) from PB and performed single cell sequencing, RNA sequencing, and functional experiments to characterize the secondary malignancy post anti-BCMA CAR-T therapy. To dissect which genomic feature contributed to the secondary malignancy we generated CAR-T cells and knocked down mutational targets. We used BCMA expressing cell lines to elicit an antigen specific response of lab generated CAR-T cells and isolated tumor CAR-T cells. **Results:** Six months post-infusion, a 51-year-old male presented with a facial lesion and lymphocytosis due to a CD4-/CD8- PTCL involving skin, blood, and bone marrow. Our comprehensive genomic analysis revealed the development of new TET2 and EZH2 mutations associated with clonal hematopoiesis of indeterminate potential (CHIP) and T-cell lymphomas. We generated CAR-T cells from the patient at the time of apheresis and isolated malignant CAR-T cells from the PB for comparison of function. Antigen specific stimulation with BCMA cell lines revealed loss of function in cytokine production capacity with no response seen in malignant CAR-T cells. The cytotoxic capability of malignant tumor CAR-T cells against BCMA expressing cells was decreased by 98% compared to cells generated from PB harvested prior to CART therapy ($P < 0.01$). To quantify the individual effects of genomic mutations we generated EZH2 and TET2 CAR-T mutants. EZH2 inhibition in CAR-T cells increased CD69, CD38 and CD127 while reducing FAS expression resisting apoptosis. TET2 knock down in CAR-T cells resulted in enhanced proliferation and enhanced expansion compared to control CAR-T cells. Knock down of TET2 and EZH2 resulted in a decrease in functional killing. EZH2 knockdown mutant resulted in a 28% reduction of cytotoxicity while TET2 knock down reduced killing by 53% when compared to control CAR-T cells ($p < 0.05$). **Conclusions:** TET2 and EZH2 mutations result in epigenetic changes such as open chromatin, leaving the genome more vulnerable to additional alterations. TET2 and EZH2-loss of function mutations in CAR-T cells provide advantages in proliferation and regeneration promoting malignant CAR-T transformation following anti-BCMA CAR-T therapy.

OA-02

Sustained Remission After Limited-Duration of Bispecific Antibody Therapy in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: While bispecific/multispecific antibodies (BsAbs) have transformed the treatment of relapsed/refractory myeloma (RRMM), their continuous administration until progression can result in T-cell exhaustion and elevated infection risk. Hence, data on fixed-duration strategies are urgently needed. **Methods:** We conducted a multi-national retrospective cohort study of patients who received BsAbs either through early-phase clinical trials or as standard-of-care, subsequently discontinued treatment for reasons other than disease progression or death and were alive in remission for at least 3 months post-discontinuation. **Results:** Of 720 consecutive patients screened, 78 were included, with 72% receiving BCMA-targeted BsAbs, 19% GPRC5D-targeted BsAbs, and 9% multi-specific antibody (BCMA + GPRC5D). The median age was 70 (range 26–86) years, 55% were female, 18% identified as Black, 47% had ≥1 high-risk cytogenetic abnormality, and 8% had extramedullary disease (EMD). The median BsAb treatment duration prior to discontinuation was 7 months (range, 1–40), with 80% in complete response (CR) at discontinuation. The most common reason for treatment discontinuation was infections (n = 34; 44%), followed by ectodermal toxicities (n = 12; 15%). At a median follow-up of 16 months from treatment discontinuation, the relapse-free survival (RFS) at 2 years was 67% (95% CI, 55%, 80%). Notably, the 2-year RFS in patients with ≥6 prior lines of therapy was 48%, compared to 79% and 78% respectively in those with 1–3 and 4–5 prior lines. On multivariable analysis for RFS, factors independently associated with inferior RFS included presence of EMD (HR [hazard ratio] = 7.88; 95% CI 1.95, 31.8; p = 0.004), number of prior lines of therapy (HR = 1.79; 95% CI 1.32, 2.43; p = < 0.001), and partial remission (PR) at the time of treatment discontinuation (HR = 28.3; 95% CI 2.06, 3.9; p = 0.012). The cumulative incidence of grade 3 or higher infections post-discontinuation was 22% at 1 year, 32% at 2 years, and 38% at 3 years, with a decrease in cause-specific hazard of first grade ≥3 infection as patients moved further away from treatment. Notably, among the two patients who resumed the same BsAb (both BCMA-targeting) at disease progression, one achieved CR and one did not respond. **Conclusions:** In summary, our data demonstrates that a substantial proportion of patients can sustain disease remission after discontinuation of BsAbs in relapsed/refractory myeloma, with 2-year RFS in patients with up to 5 prior lines of therapy approaching ~80%. In patients achieving deep response with BsAbs, randomized controlled trials (RCTs) are needed to answer whether a limited-duration approach is non-inferior in terms of efficacy to treatment-until-progression, and potentially safer in terms of cumulative infection risk over time.

OA-03

Development and Validation of the SCOPE-MM Score: A Pre-Apheresis Risk Model Predicting Response and Toxicity in RRMM Patients Receiving BCMA-Directed CAR-T Therapy

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Introduction: Current risk stratification models for BCMA CAR-T in relapsed/refractory multiple myeloma (RRMM) primarily assess patients at lymphodepletion. However, this time point represents a 'point of no return' without the option of patient selection, bridging modification, or therapeutic planning. We aimed to overcome this limitation by identifying prognostic factors measurable at a pre-apheresis time point, allowing early prediction of CAR-T efficacy and toxicity. **Methods:** In this multicenter observational study, demographic, laboratory, and clinical data were examined in a training cohort comprising 805 RRMM patients treated with either ciltacabtagene autoleucel (cilta-cel; n = 291) or idecabtagene vicleucel

(ide-cel; n = 514) across 9 international sites. Multivariate Cox regression, time-dependent AUC analyses, and partitioning methods guided model development. **Results:** Median age was 63 years (range 31–88), and patients had received a median of 5 (IQR 4–7) previous treatment lines. Multivariable analysis identified five pre-apheresis factors independently associated with inferior progression-free survival (PFS): elevated LDH levels, CAR-HEMATOTOX score ≥3, prior BCMA exposure, bone marrow plasma cell burden ≥50%, and history of extramedullary disease. Using these factors, we established the Stratification of CAR-T Outcomes at Pre-Apheresis Evaluation (SCOPE) score, assigning 2 points each for prior BCMA exposure and high CAR-HEMATOTOX score, and 1 point for each remaining factor. Applying SCOPE, low-risk patients (0 points) demonstrated significantly superior outcomes compared to intermediate-risk (1–2 points) and high-risk (3–7 points) groups in terms of best objective response ([s]CR rate 58% vs 48% vs 35%, $p < 0.001$), 1-year PFS (71% vs 52% vs 27%, $p < 0.001$), and 1-year overall survival (93%, 80%, and 58%, $p < 0.001$). Furthermore, a distinct ultra-high-risk subgroup (SCOPE score ≥5), comprising 2.5% of patients, exhibited markedly poor outcomes (1y-PFS 5%). Subgroup analysis confirmed effective stratification across both products and geographic regions. Increasing SCOPE scores were associated with a significantly higher grade ≥3 rate for CRS ($p = 0.04$), ICANS ($p = 0.03$), early and late hematotoxicity (both $p < 0.001$), and infections ($p = 0.002$). Higher scores also translated into increased non-relapse mortality (1y-NRM 1.7% vs 5.5% vs 9.6%, $p < 0.001$). Importantly, the prognostic capacity of SCOPE was confirmed in two external validation cohorts, including a real-world dataset (n = 135, PFS: $p < 0.001$) and the ide-cel arm of the KarMMa-3 trial (n = 212, PFS: $p < 0.001$). **Conclusions:** The comprehensively validated and product-agnostic SCOPE model effectively stratifies patients for toxicity and response with BCMA CAR-T before apheresis. This early assessment enables optimization of manufacturing logistics, informs outpatient management decisions, and helps identify high-risk patients who may benefit from more effective bridging, combinatorial strategies, or improved supportive care to mitigate NRM.

OA-04

CD4+ T-Cells Mediate Immune-Related Adverse Events (CirAE) Following BCMA CAR-T Therapy

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Introduction: B-cell maturation antigen chimeric antigen receptor T-cell therapy (BCMA-CART) is standard of care in relapsed/refractory MM, with 2 approved products: idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel). We introduce the term CART immune-related adverse events (CirAE) to describe a spectrum of delayed toxicities, including cranial nerve palsies, parkinsonism, and enterocolitis, that are mechanistically distinct from CRS, ICANS, ICAHT, and IEC-HS. We characterize the incidence, clinical features, and outcomes of CirAE, and perform correlative analyses to identify underlying mechanisms and predictors. **Methods:** 149 patients were treated with commercial BCMA-CART (ide-cel: 68; cilta-cel: 81) between June 2021 and April 2024. Flow cytometry and serum proteomics were performed at baseline, peak CART expansion, and CirAE onset. RNAscope for CAR and immunohistochemistry for T-cell phenotypes were performed on CirAE biopsies. **Results:** CirAE occurred in 19 patients, significantly more often with cilta-cel (21%) than ide-cel (2.9%). The most common CirAE after cilta-cel were enterocolitis (7.4%), cranial nerve palsies (6.2%), and parkinsonism (4.9%), with a median onset of 45 days post-infusion. In contrast, both ide-cel-associated CirAE were pneumonitis, occurring ~1 year post-infusion. Importantly, cilta-cel patients who developed CirAE had inferior overall survival (HR: 3.4; $p = 0.031$), driven by higher non-relapse mortality (HR: 15; $p = 0.016$). One patient (Cilta-cel#2) represented an extreme case, developing polyclonal hyperleukocytosis (lymphocyte peak: 197 × 103 cells/μL), with marked CD4 skewing of CART, and three distinct CirAE: facial palsy, delayed ICANS, and enterocolitis. Flow cytometry showed a shift from naïve CD4 T-cells at baseline to activated effector memory CD4 CART at peak expansion, progressing to terminally differentiated CD4 CART during delayed ICANS (Day 57), and reverting to a naïve-like profile by month 11. Correspondingly, CirAE patients exhibited superior CART expansion, CD4-skewing, elevated proinflammatory (e.g., GM-CSF, IL-6) and reduced anti-inflammatory cytokines (e.g., IL-10, IFN-α2) post-infusion. Risk factors for CirAE were: cilta-cel (OR: 8.8; $p = 0.0047$), day 7 CD4/CD8 ratio >1 (OR: 11.9; $p = 0.028$), peak absolute lymphocyte count (ALC) ≥2.3 × 103 cells/μL (OR: 9.6; $p < 0.001$), and ICANS (OR: 3.9; $p = 0.012$). Intestinal biopsies from 3 patients with enterocolitis confirmed on-target, off-tumor infiltration by predominantly CD4+, CAR+ T-cells, supporting a pathogenic role for CD4 CART in enterocolitis. **Conclusions:** We corroborate recent studies linking ICANS and high peak ALC with an increased risk of delayed neurotoxicity after cilta-cel, extend these correlates to a broader set of clinically diverse CirAE, contribute new insights by implicating a possible pathogenic role for CD4 T-cells, and identify risk factors that may inform strategies (eg. pre-emptive dexamethasone) to reduce non-relapse mortality and improve overall survival.

OA-05

Rapid Peak CAR-T Expansion is Associated with Delayed Neurotoxicity Following Ciltacabtagene Autoleucel in Multiple Myeloma

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Introduction: Cilta-cel has demonstrated deep and durable responses in relapsed/refractory multiple myeloma (RRMM). However, its broader adoption is limited by unique toxicities, particularly delayed neurotoxicity (DNT). The relationship between CAR-T expansion and DNT is not well understood. In this study, we evaluated whether peak CAR-T expansion, measured by flow cytometry, is associated with DNT risk. We also investigated absolute lymphocyte count (ALC) as a reliable surrogate for CAR-T expansion and identified clinically actionable ALC thresholds to stratify DNT risk. **Methods:** We included 256 patients receiving cilta-cel from 2022 to 2024 for RRMM across 3 institutions (ALC cohort). We assessed associations between peak ALC following infusion (day 0) and DNT. In a subset of 54 patients (CAR expansion cohort), weekly flow cytometry quantified CAR-T expansion. **Results:** In the ALC cohort (n = 256), the median age was 64 years (IQR: 57.8, 70), 54% were male and 38% were classified as penta-refractory. Median follow-up was 14.7 months, and median progression-free survival (PFS) was 28.7 months. DNT occurred in 11% (n = 29) of patients, including 8% (n = 20) with cranial nerve palsy and 3% (n = 8) with Parkinsonism. In the CAR expansion cohort (n = 54), baseline characteristics, efficacy, and toxicity were similar. DNT was observed in 16% (n = 8), including Parkinsonism in 7.5% (n = 4). Patients who developed DNT had significantly higher peak CAR-T expansion compared to those who did not ($p = 0.04$). Peak CAR-T levels measured by flow cytometry showed a strong correlation with peak ALC (rho = 0.84, $p < 0.001$), supporting the use of ALC as a reliable surrogate marker for CAR-T expansion. In the ALC cohort, patients who developed DNT had a significantly higher median peak ALC compared to those who did not (5780/μL vs. 2200/μL; $p < 0.001$). Among patients with Parkinsonism, peak ALC was significantly higher compared to those without (13,335/μL vs. 2270/μL; $p < 0.001$). The early rise in ALC from day 7 to 12 was significantly greater in patients with DNT (5360/μL vs 1040/μL: $p < 0.001$). We identified the following peak ALC thresholds as optimal and clinically implementable for DNT risk stratification: (1) either ≥3000/μL between days 7–21, and/or (2) ≥2500/μL between days 7–21 with a ≥2-fold increase from the prior value. These thresholds collectively captured 83% of DNT (including all but one case of Parkinsonism) while excluding 41% of patients who did not develop DNT. **Conclusions:** Rapid and robust CAR-T expansion was associated with an increased risk of DNT. ALC strongly correlated with CAR-T expansion and may serve as a practical surrogate for early identification of high-risk patients. Two peak ALC thresholds between days 7–21 (either 3000/μL at any point or 2500/μL with a ≥2-fold rise) collectively identified the majority of DNT cases and may guide the implementation of preemptive interventions.

OA-06

Inactivation of TRAF3 and CYLD Drive Resistance to T-Cell Based Therapies in Multiple Myeloma by Promoting Inflammation and an Immunosuppressive Microenvironment that Impair T Cell Function

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Introduction: Adaptive T cell therapies using chimeric antigen receptor (CAR) T cells and T cell engagers (TCE) targeting BCMA on plasma cells have recently demonstrated encouraging responses in multiple myeloma (MM). However, responses are not universal and acquired resistance does invariably occur. We have recently reported (Lee H et al, Nat Med 2023) an enrichment of NF-κB activating mutations, including the deletion of its negative regulators, TRAF3 and CYLD, in patients with acquired BCMA antigen escape. Therefore, we herein investigated the impact of NF-κB alterations on the development of resistance to these therapies in MM. **Methods:** Through CRISPR Cas9 gene editing, we generated stable knockout (KO) clones of TRAF3 and CYLD in OPM2 and ARP1 MM cells, along with non-targeting Cas9 transduced cells as a negative control. TRAF3 and CYLD KO protein expression were confirmed by western blot analysis and the activation of the NF-κB canonical (p65) or non-canonical (p52) pathways validated by ELISA. **Results:** In flow cytometry-based cytotoxicity assays, we have first demonstrated that the inactivation of TRAF3 and CYLD drives relative resistance to T-cell-based therapies, including anti-BCMA CAR-T cells (ide-cel) or anti-BCMA TCE (elranatamab), as well as anti-GPRC5D (talquetamab). Transcriptome profiling (scRNA-seq) of TRAF3 and CYLD KO cells and their isogenic controls (Cas9 only) was then performed

to define the factors mediating this resistance. Several differentially activating pathways, including the interferon type I and II and TNF-α signaling, were enriched in the KO cells when compared to their respective controls, suggesting a possible contribution of these pathways in the development of this acquired intrinsic resistance. Furthermore, in a multiplex cytokine assay on the supernatant of the KO cells, we observed elevated levels of multiple inhibitory factors and cytokines, such as sFas, sFasL, TGF-β3, TNF-β, IL-10, and IP-10, compared to the control cells. IP-10 (encoded by CXCL10), in particular, is known to suppress T cell function. Therefore, we next co-cultured OPM2 cells with ide-cel in the presence of IP-10 (200 ng/mL) and observed a significant decrease in T-cell-mediated killing following the addition of this chemokine. Lastly, soluble Fas (sFas) is also recognized to interfere with T cell function by acting as a decoy receptor by blocking the interaction between Fas ligand on T cells and Fas on tumor cells. We have therefore evaluated and confirmed by flow cytometry the upregulation of Fas expression in TRAF3 or CYLD KO as the source for the increased levels of sFas. **Conclusions:** In summary, we have identified a novel mechanism of resistance to T-cell-adoptive therapies mediated by a tumor intrinsic inactivation of TRAF3 and CYLD that results in the upregulation of T cells' suppressive chemokine CXCL10 and the suppression of T cells' death receptor-mediated cell death through the shedding of sFas.

OA-07

Elranatamab in Combination With Daratumumab and Lenalidomide (EDR) in Patients With Newly Diagnosed Multiple Myeloma (NDMM) Not Eligible for Transplant: Initial Results from MagnetisMM-6 Part 1

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Introduction: Elranatamab (ELRA), a BCMA-CD3 bispecific antibody, induced deep and durable responses with a manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM). MagnetisMM-6 (NCT05623020) is a phase 3, open-label, randomized study evaluating the efficacy and safety of ELRA in combination with lenalidomide (R) ± daratumumab (DARA) (EDR or ER) vs DARA + R + dexamethasone (DRd) in pts with transplant-ineligible (TI) NDMM. Part 1 of the study evaluates the optimal dose of EDR or ER in pts with RRMM or NDMM to determine the recommended phase 3 dose for Part 2. Initial results from Part 1 dose level G (DLG) are presented. **Methods:** In DLG, eligible pts had TI (age ≥65 or age <65 years with comorbidities impacting the possibility of transplant) NDMM, measurable disease, ECOG ≤2, and adequate liver, renal and bone marrow function. Pts received subcutaneous (SC) ELRA with a priming regimen followed by ELRA 76 mg SC every 4 weeks (Q4W) on cycle (C) 1 day (D) 1; DARA 1800 mg SC weekly (D1, D8, D15, D22 in C1–C2), every 2 weeks (D1, D15 in C3–C6), and Q4W (D1 in C7+); and oral R 25 mg daily on D1–D21 in 28-day cycles. Endpoints assessed in DLG include safety and preliminary efficacy. **Results:** A total of 37 pts were enrolled in DLG; 34 received EDR. The median age was 75.0 years (range, 67–83); 37.8% were male; 86.5% were White, 13.5% Asian. Five pts (13.5%) had R-ISS stage III disease, 9 (24.3%) had ≥50% baseline bone marrow plasma cells, 1 (2.7%) had an ECOG performance status of 2, none had extramedullary disease, and 9 (24.3%) were frail according to the simplified IMWG frailty score. At data cutoff (Apr 1, 2025), the median follow-up was 7.9 months (range, 1.2–9.5); treatment was ongoing in 32 pts. Treatment-emergent adverse events (TEAEs) were reported in 100% (grade [G]3/4 94.6%) of pts, hematological TEAEs in 83.8% (G3/4 78.4%), and infections in 70.3% (G3/4 18.9%). Frequent (any grade ≥10%) infections were upper respiratory tract infection (21.6%, G3/4 0%) and Escherichia urinary tract infection (10.8%, G3/4 2.7%). There was one G5 Candida pneumonia. CRS occurred in 62.2%, all ≤G2; 1 case of G2 ICANS was reported. Antiviral, anti-Pneumocystis jirovecii, anti-bacterial, and anti-fungal prophylaxis were received by 81.1%, 83.8%, 10.8%, and 16.2% of pts, respectively; 91.9% received Ig replacement. The confirmed ORR (95% CI) by investigator was 97.3% (85.8–99.9); 94.6% with VGPR or better. The median (range) time to response was 1.5 (0.3–4.2) months and to VGPR or better was 2.4 (1.2–4.3) months. **Conclusions:** In pts with TI NDMM, EDR demonstrated a manageable safety profile consistent with the known toxicities of components. High response rates and early responses were observed, with responses expected to deepen with longer follow-up. Enrollment in dose level H evaluating the ER combination is ongoing.

OA-08

Three-Year Follow-Up of FUMANBA-1: a Phase 1b/2 Study of Fully Human Anti-BCMA CAR-T Equecabtagene Autoleucel in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: Equecabtagene Autoleucel (Eque-cel) is a fully human B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma (RRMM). Eque-cel was approved in China to treat adult patients with RRMM who have received three or more lines of prior therapies, including at least one proteasome inhibitor and an immunomodulatory agent. FUMANBA-1, the phase 1b/2 study evaluating the safety and efficacy of Eque-cel, was conducted at 14 sites in China and here we report the updated trial results with a median follow-up of 36.0 months. **Methods:** RRMM patients who had received at least three prior lines of therapy and with progressive disease after the last line of therapy were enrolled. Patients with extramedullary disease (EMD) or prior exposure to BCMA-targeted CAR-T therapy were included. Following lymphodepletion with cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) for three consecutive days, a single infusion of CAR-T cells (1 × 10^6 cells/kg) was administered. Efficacy and safety outcomes were assessed with a data cutoff of December 31, 2024. **Results:** A total of 109 patients received Eque-cel. The median lines of prior therapy was 4 (range 3–23).70.6% of patients had high-risk cytogenetic abnormalities (defined as at least one of t(4;14), t(14;16), t(14;20), Del 17p, and Gain 1q is positive), including 29.4% with two high-risk cytogenetic abnormalities. 12.8% had EMD and 11% had received prior BCMA CAR-T therapy. Among 107 evaluable patients, the overall response rate (ORR) was 96.3%, including a complete or stringent complete response (CR/sCR) in 83.2%. In CAR-T-naïve patients, ORR and CR/sCR rates were 98.9% and 88.4%, respectively. Among 109 patients who received Eque-cel, the median progression-free survival (PFS) was 30.5 months (95% CI: 24.1–42.2), extending to 35.9 months (95% CI: 26.0–47.7) in CAR-T–naïve patients. Median overall survival (OS) was not reached. Minimal residual disease (MRD) negativity was achieved in 95.3% (102/107) of evaluable patients, including all those with ≥CR. The median duration of MRD negativity was 36.5 months (95% CI: 25.6–NE). Cytokine release syndrome (CRS) occurred in 93.6% (102/109) of patients, with only one case ≥ grade 3. The median time to onset was 6 days (range: 1–13), and the median duration was 5 days (range: 2–30). Immune effector cell–associated neurotoxicity syndrome (ICANS) was reported in two patients (grade 1–2). No late-onset neurotoxicity or secondary malignancies were observed. CAR transgene persistence was observed in 52% (39/75) of patients at 12 months and 37.5% (21/56) at 24 months. Anti-CAR antibodies were detected in 24.8% of patients. **Conclusions:** At a median follow-up of 36.0 months, Eque-cel therapy demonstrated deep, durable responses and sustained MRD negativity in heavily pretreated RRMM patients, including those with high-risk features. The long-term safety profile remained manageable, with no new safety signals identified.

OA-09

A Syngeneic Mouse Model of CAR-T Cell Therapy Containing a Translatable Dual Human/Mouse Reactive sdAb Binder in Vk*MYC Mice Reveals Clinically-Relevant Microenvironment Changes

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Introduction: Despite the therapeutic success of approved BCMA CAR-T cell therapies in RRMM, post-CAR-T relapse is near-universal and this may be due to key host-tumour-effector cell interactions of the tumour microenvironment (TME) that are not

modeled in widely used immunodeficient preclinical models of CAR-T cell therapy. We therefore sought to develop a system to study CAR-T cell activity using the immunocompetent syngeneic Vk*MYC model of MM. **Methods:** Llamas were immunized with human BCMA and the resulting single-domain antibodies (sdAbs) were isolated, cloned, and screened for binding to mouse BCMA. The resulting dual species-reactive sdAb was then incorporated into a CAR construct, with CD28 and CD3z domains (sdBCMA2.28z). Murine CAR-T cells were generated by retrovirally transducing activated splenocytes, and assessed by cytotoxicity, proliferation, and cytokine release assays. For the in vivo studies, we I.V. injected C57BL/6J mice with Vk12598 Vk*MYC tumour cells. Groups were balanced based on M-protein by SPEP. The day prior to infusion with either sdBCMA2.28z or mock-transduced T cells (Mock), mice were lymphodepleted with 5Gy total body irradiation. Mice were bled weekly to assess disease burden by M-protein. In landmark studies, mice were euthanized at CAR+3d for harvest of spleens (SPL), bone marrows (BM), and peripheral blood (PB) for flow cytometry. **Results:** In vitro, sdBCMA2.28z CAR-T effectively killed BCMA+ cells, and demonstrated robust proliferation and pro-inflammatory cytokine release following exposure to BCMA+ cells, but not BCMA- cells. In vivo, TBI+CAR mice had significantly improved survival compared to TBI+Mock. We observed expansion of sdBCMA2.28z CAR-T cells that were mostly CD8+ and with an activated phenotype (CD44+) in the SPL, BM, and PB. We saw significant increases in circulating serum IL-6, IL-1b, and TNFa following CAR-T cell infusion, but not with Mock T-cells. Three days following CAR-T infusion, we saw increased CAR+ T-cells in the BM and SPL, along with decreases in CD138+B220- Vk*MYC tumour cells. We also observed an increased frequency of M1-like (CD86+) macrophages, with a slight decrease in M2-like (CD206+) macrophages in the BM of TBI+CAR-treated mice. Untreated disease-bearing mice had higher proportions of circulating myeloid-derived suppressor cells (MDSCs), and TBI+CAR-treated mice had modestly decreased polymorphonuclear MDSCs (Ly6G+ among CD11b+Gr-1+) in the spleen. **Conclusions:** We show improvement in survival of Vk*MYC-engrafted mice treated with sdBCMA2.28z CAR-T cells compared to Mock. The cytokine profile observed is consistent with that observed after CAR-T cell administration in patients. Our studies of the TME provide a rationale for developing immunomodulatory strategies to make the TME more permissive to CAR-T cells. Our strategy enables the study of host-tumour-effector cell interactions, which will better inform the design of novel CAR-T cell therapies in MM.

OA-10

MZB1-Directed HLA-Dependent CAR T Cells for Targeting B-Cell Malignancies

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Introduction: BCMA-directed CAR T cell therapies have improved outcomes for MM patients, and several other targeted CAR T cells are in development. However, one of the main hurdles is the limited availability of tumor-specific cell surface molecules. Unlike conventional CAR T cells, TCR-like CAR T cells can recognize intracellular tumor antigens presented on MHC molecules, mimicking T cell receptors (TCR), and significantly expanding the range of potential cancer targets. We identified MZB1 as a tumor-associated intracellular antigen in MM and predicted putative MZB1 peptides that can be presented in the context of HLA-A*02:01, the most frequent HLA allele worldwide. Importantly, we also evaluated the expression of MZB1 in additional hematological malignancies and observed high levels of MZB1 in Waldenström Macroglobulinemia (WM) and non-Hodgkin lymphoma cells. **Methods:** Based on expression data, we generated a novel antibody recognizing MZB1 bound to HLA-A*02:01 on the cell surface. Using a human scFv antibody yeast surface display library, we identified scFv clones specific to the MZB1/HLA-A2 complex. We confirmed MZB1- and HLA-A2-specific binding by flow cytometry and histology. Next, we used the MZB1-A2 scFv to generate MZB1 CAR T cells. Human T cells from donor PBMCs were transduced to express MZB1 CAR. **Results:** We confirmed the specificity of MZB1 CAR T cells to MZB1/A2 complex and their inability to bind irrelevant pMHCs. In vitro killing assays showed MZB1 CAR T cells had significant cytotoxicity against MZB1+ and HLA-A2+ MM and WM cells, but not against HLA-A2neg and/or MZB1neg cells, in a dose-dependent manner. MZB1 CAR T cells secreted higher levels of IFN-γ, sFas ligand, and granzyme A/B compared to untransduced T cells when co-cultured with MZB1+ HLA-A2+ MM cells. Antitumor activity was evaluated against primary patient myeloma and Waldenström cells. MZB1 CAR T cells displayed significant activity against primary MZB1+ HLA-A2+ CD138+ from BM of ND and relapsed MM patients and MZB1+ CD19+ WM cells. In an in vivo disseminated orthotopic NSG MM mouse model, a single infusion of MZB1 CAR T cells significantly reduced tumor burden. Importantly, we also observed an HLA cross-reactivity of our antibody as well as CAR T product, with MZB1 also being recognized by other HLA-A

alleles, such as HLA-A*24:02 and HLA-A*23:01, which are more common in African Americans and Asian Americans, respectively, suggesting broad applicability of our antibody across patient groups. **Conclusions:** In conclusion, we have generated a MZB1-directed HLA-dependent CAR T cell therapy that exhibit significant activity and specificity against MZB1 and HLA-A2 positive MM and WM cells, both in vitro and in vivo. This study therefore provides the rationale to evaluate MZB1 TCR-like CAR T cell therapy as a therapeutic approach in MM and WM and provide the logic and framework for similar therapies to be developed against other intracellular antigens in MM and other cancers.

OA-11

Baseline and Longitudinal Immune and Inflammatory Correlates of Response to Bispecific Antibodies in Relapsed/Refractory Multiple Myeloma

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Introduction: Bispecific antibodies (BsAbs) are highly efficacious in relapsed refractory multiple myeloma (RRMM), but predictive biomarkers remain incompletely defined. High ferritin, an inflammatory marker, has been linked to worse outcomes in MM, including among CAR T cell recipients. Additionally, a low effector T cell to tumor ratio - potentially reflected by absolute lymphocyte count (ALC) - may impair BsAb-mediated cytotoxicity. **Methods:** We identified 325 RRMM patients treated with BsAbs at Mount Sinai to evaluate the prognostic impact of ferritin and ALC. Descriptive analyses summarized baseline characteristics and ferritin and ALC dynamics. Kaplan-Meier analysis was used to estimate survival. Group-based trajectory modeling identified patient clusters by ferritin and ALC trends. CITE-Seq was performed on bone marrow (BM) and peripheral blood (PB) samples of 45 patients, with associations analyzed via generalized linear models. **Results:** Median age was 68; 45.9% had high-risk cytogenetics and 22.8% extramedullary disease. Most had ≥5 prior therapies; 86.8% were triple-class and 46.2% penta-drug refractory. Nearly 49% received BCMA-targeted BsAbs; 44% talquetamab, 6.5% cevostamab, and 10% combinations with daratumumab and/or IMiDs. Elevated baseline ferritin (>400 ng/mL) was associated with lower overall response rate (ORR) (62.5% vs 74.8%, $p = 0.033$), fewer ≥VGPR responses (43.3% vs 60.6%, $p = 0.005$), shorter PFS (5.1 vs 16.3 mos, $p = 0.00029$), and reduced OS (13.87 mos vs not reached, $p < 0.0001$). Ferritin trajectory analysis identified 3 groups: F1 (rising ferritin, PFS 1.87 mos, ORR 40%); F2 (chronically high, PFS 14.6 mos, ORR 71%); F3 (down-trending, PFS 25.47 mos, ORR 87%). Low baseline ALC ($\leq 0.9 \times 10^3/\mu L$) was linked to shorter PFS (6.87 vs 22.17 mos, $p = 0.00068$), and trajectory analysis revealed 3 groups: A1 (persistent lymphopenia, PFS 1.1 mos, ORR 32%), A2 (stable ALC, PFS 6.47 mos, ORR 67%), A3 (rising ALC, PFS 22.87 mos, ORR 83%). Noteworthy, lymphopenia was associated with being triple-class refractory and previously receiving CAR T or cytotoxic therapy. CITE-Seq of BM revealed that higher ferritin was associated with higher granulocyte-macrophage progenitors ($p = 0.0006$), classical monocytes ($p = 0.01$), and plasmacytoid dendritic cells ($p = 0.02$). In PB, high ferritin was positively associated with CD8CM ($p = 0.02$) and CD8SCM ($p = 0.04$) and negatively associated with CD8EM T cells ($p = 0.05$). While F1 trend was driven by tumor burden, CITE-Seq of PB revealed that patients on the F2 trend had higher CD8CM T cells ($p = 0.02$) and CD56Bright NK cells ($p = 0.04$) and lower gd T cells ($p = 0.01$) and mucosal-associated invariant T cells ($p = 0.02$) compared to F3, suggesting a distinct immunologic basis. **Conclusions:** Elevated ferritin and low ALC correlate with worse outcomes in BsAb-treated RRMM patients, supporting their use as prognostic and dynamic risk markers. Immune profiling linked ferritin levels and trends to distinct cellular patterns, informing resistance biology and potential therapeutic targets.

OA-12

First-in-Human Phase 1 Trial of Trimeric APRIL (TriPRIL) CAR-T Cells in Relapsed or Refractory Multiple Myeloma

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Introduction: Antigen escape is a common resistance mechanism from BCMA-directed CAR-T cells, limiting durable responses as well as the utility of further BCMA-directed therapies. TriPRIL CAR-T cells were designed to target both BCMA and TACI with a trimeric ligand-based CAR using their natural ligand APRIL, offering a novel dual antigen-approach. We report initial results from an ongoing first-

in-human phase 1 clinical trial of TriPRIL CAR-T cells for patients with relapsed or refractory multiple myeloma (R/R MM). **Methods:** Eligible patients (pts) with R/R MM had received at least 3 prior lines of therapy or had triple class-refractory disease. The phase 1 trial consists of a 3+3 dose escalation and a subsequent dose expansion cohort. Two dose levels (DLs) have been studied with 1.0 × 108 CAR + T-cells at DL1 and 3.0 × 108 CAR+ T-cells at DL2 with dose expansion continuing at DL2. Lymphodepletion consisted of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 on Days −5 to −3. The primary endpoint was incidence of dose-limiting toxicities (DLTs) and adverse events. Secondary endpoints included response, PFS, and OS. **Results:** As of May 1, 2025, 11 pts have undergone leukapheresis and 10 pts have received TriPRIL CAR-T cells. Among the infused pts, 5 pts were treated at DL1 and 5 pts were treated at DL2. The median age was 73 years old (range: 62–78) and 8 pts (80%) were female. Six pts (60%) had high-risk cytogenetics, 4 pts (40%) had R-ISS stage III disease, and 3 pts (30%) had extramedullary disease. The pts had a median of 6 prior lines of therapy (range: 3–10) with 6 pts (60%) having previously received a BCMA-directed CAR-T cell therapy. There were no DLTs at either dose level. All pts (100%) had CRS (G1 in 8 pts, G2 in 2 pts) with a median onset of 1 day after infusion (range: 0–11). One pt had G2 ICANS at 10 days after infusion which resolved after one day. Infections occurred in 5 pts (50%; G2 in 4 pts and G3 in 1 pt). There were no instances of non-ICANS neurotoxicities including parkinsonism or cranial nerve palsies.The ORR was 80% with a CR/sCR rate of 60%. The ORR and CR/sCR rates were consistent across DL1 and DL2. The median follow-up time among patients who remain alive is 5.5 months (range: 0.9–11.3). Among the entire cohort, the median PFS was 10.4 months (95% CI, 0.9-NE) and the median OS has not been reached (95% CI, 4.2-NE). Among the patients who had received a prior BCMA-directed CAR-T cell therapy, the ORR was 66.7% (CR/sCR 66.7%) and the median PFS was 10.4 months (95% CI, 0.9-NE). **Conclusions:** TriPRIL CAR-T cells demonstrated overall safety in patients with R/R MM with no DLT occurrences. Moreover, TriPRIL CAR-T cells showed high response rates with durable responses notably seen even in patients who had progressed after prior BCMA-directed CAR-T cell therapy. This study highlights the potential of this novel dual-antigen CAR-T cell therapy in both CAR-naïve and CAR-exposed R/R MM patients. *BRP and CEG contributed equally. MVM and MJF contributed equally.

OA-13

Post-Induction Outcomes and Updated Minimal Residual Disease Analysis from GMMG-HD10/DSMM-XX (MajesTEC-5): A Study of Teclistamab-Based Induction Regimens in Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: The multi-cohort, phase 2 MajesTEC-5 trial (NCT05695508) is the first to evaluate teclistamab (Tec), a first-in-class B-cell maturation antigen×CD3 bispecific antibody, combined with standard of care daratumumab (DARA)-based regimens, in patients (pts) with transplant-eligible (TE) NDMM. In an initial analysis of outcomes from 3 induction cohorts, steroid-sparing regimens of Tec with DARA/lenalidomide (DR), ±bortezomib (DVR), led to unprecedented clinical efficacy with manageable safety profiles. Here, we present updated results for these 3 induction therapy cohorts treated with Tec-DR or Tec-DVR, including minimal residual disease (MRD) at 10–5 and 10–6 thresholds. **Methods:** Eligible pts aged 18–70 years with TE NDMM received Tec-DR (Arms A/A1) or Tec-DVR (Arm B) as induction therapy. Pts received 6, 28-day cycles (C) of Tec, preceded by 2 step-up doses in C1. In C2–6, Tec 1.5 mg/kg was given QW in Arm A and at 3.0 mg/kg Q4W in Arms A1/B. DARA (1800mg) was given QW in C1–2 and Q2W in C3–6; lenalidomide (25 mg) was given on Days 1–21 from C2–6. Pts in Arm B also received bortezomib (1.3 mg/m^2) QW in C1–6. Dexamethasone (20 mg) was given in C1–4 (Arm A) or C1–2 (Arms A1/B) only. The primary endpoint was the rate of adverse events (AEs) and serious AEs. Among secondary endpoints, post-induction MRD negativity was assessed at 10^{-5} and 10^{-6} thresholds by next-generation flow cytometry (NGF) and next-generation

sequencing (NGS), respectively. **Results:** Overall, 50 pts were enrolled and 49 received ≥1 dose of study treatment (Arm A, n = 10; A1, n = 20; B, n = 19); median (range) age was 58 (30–68) years. Two (4.1%) pts discontinued all study treatments due to refusal of further treatment. One, 8, and 2 pts discontinued Tec, lenalidomide and bortezomib, respectively, primarily due to AEs. Median (range) duration of induction treatment was 7.0 (2.5–13.2) months. Grade 3/4 treatment-emergent AEs (TEAEs) occurred in 44 (89.8%) pts; hematologic TEAEs were most common. Grade 3/4 infections occurred in 17 (34.7%) pts; serious TEAEs occurred in 26 (53.1%) pts. No TEAEs led to full study treatment discontinuation or death. No immune effector cell-associated neurotoxicity syndrome events were reported; cytokine release syndrome occurred in 32 (65.3%) pts, all grade 1/2. During induction, overall response (≥partial response) was achieved by 100% of pts in all arms. Of 46 MRD-evaluable pts with available samples after C3 and C6, 100% achieved MRD negativity (NGF at 10^{-5}) at both timepoints. Of 46 MRD-evaluable pts with available samples for NGS after C6, all were MRD-negative at 10^{-6}. Of 47 pts who completed stem cell mobilization, median stem cell yield was 8.1 × 106/kg; all except 1 pt had successful stem cell mobilization. **Conclusions:** Tec combined with DR and DVR demonstrates unprecedented clinical efficacy, with 100% of MRD-evaluable pts achieving MRD negativity at 10–5 and 10–6 thresholds at completion of induction. Stem cell mobilization was feasible and no new safety concerns were observed.

OA-14

Cevostamab Plus Pomalidomide (Pom) and Dexamethasone (dex) in Relapsed/Refractory Multiple Myeloma (RRMM): Phase I Dose-Expansion Results from the CAMMA 1 Study

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Introduction: Cevostamab, a FcRH5xCD3 T-cell-engaging bispecific antibody, has shown encouraging activity and manageable safety as monotherapy in patients (pts) with late-line RRMM (Richter et al. ASH 2024). Combining cevostamab with anti-myeloma agents that augment T-cell activity could enhance efficacy. In the Arm B safety run-in of the Phase Ib CAMMA 1 study (NCT03275103), cevostamab plus Pom and dex induced deep and durable responses and had manageable safety in pts with RRMM (Spencer et al. COMY 2025). We present initial data from the Arm B1E randomized dose expansion. **Methods:** Eligible pts had RRMM and had received ≥1 prior immunomodulatory drug and ≥1 prior proteasome inhibitor as part of ≥1 prior line. Pts were randomized (1:1) to 70 mg (low-dose [LD]) or 105 mg (high-dose [HD]) cevostamab given Q2W in Cycles (C) 1–6 (28-day cycle) and Q4W in C7+, which was initiated after a pre-phase with 0.3/3.3 mg double step-up dosing. From C1+, Pom (2 mg) was given on Day (D) 1–21 and dex (20 mg) on D1, 8, 15 and 22. Treatment was continued until disease progression (PD) or unacceptable toxicity. **Results:** At cut-off (January 22, 2025), 32 pts (n = 16 in LD and n = 16 in HD cohorts) were randomized and treated. Among those, 8.3% and 25.0% had a conclusive assay result for high-risk cytogenetics (t(4;14), t(14;16) or del(17p)), and 18.8% and 25.0% had extramedullary disease, respectively. Median number of prior lines was 2 and 3. One and 3 pts in the LD and HD cohorts had received ≥1 prior BCMA-targeted therapy. Triple-class refractory disease was present in 25.0% and 31.3%, and 68.8% in both cohorts were refractory to their last line. Median follow-up was 8.9 and 7.5 months in the LD and HD cohorts, respectively. Objective response rates were 93.8% and 62.5% and very good partial response or better rates were 81.3% and 62.5%. At cut-off, 13/15 (86.7%) and 9/10 (90.0%) responders were still in response, with responses deepening over time. Grade (Gr) 3–4 adverse events (AEs) occurred in 68.8% and 87.5% of LD and HD pts, respectively. Gr 3–4 AEs in ≥20% were neutropenia (56.3%; 62.5%), anemia (31.3%; 12.5%), thrombocytopenia (12.5%; 37.5%), and infections (12.5%; 25.0%). Cytokine release syndrome occurred in 13 pts (81.3%) in each cohort (LD: Gr 1, 56.3%; Gr 2, 18.8%; Gr 3, 6.3%; HD: Gr 1, 56.3%; Gr 2: 25.0%). Rash occurred in 4 (25.0%) and 9 (56.3%) pts; all events were Gr 1–2. Gr 5 (fatal) AEs excluding PD occurred in 2 pts (LD: cardiac arrest in a patient with pre-existing risk factors; HD: parainfluenzae pneumonia); both AEs were considered unrelated to treatment. **Conclusions:** Cevostamab plus Pom and dex induces deep responses and has manageable safety in RRMM. Updated data from the Arm B dose expansion will be presented, including initial data from 32 additional pts in Arm B3E who received triple step-up dosing, and emerging biomarker analyses, including minimal residual disease, which will confirm the pattern of response and AEs with the LD and HD regimens.

OA-15

S100A8/A9 Promotes T Cell Exhaustion and Impairs Response to Bispecific Therapy in Multiple Myeloma

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Introduction: S100A8/A9 is a calcium-binding alarmin released during cellular stress and inflammation. In cancer, it plays a critical role in modulating the immune microenvironment, including in multiple myeloma (MM). Previously, our group implicated S100A8/A9 in resistance to anti-BCMA CAR-T therapy by suppressing cytotoxic function, and we demonstrated that cytotoxicity could be rescued by a monoclonal antibody against S100A8/A9. Here, we explore its role in MM patients treated with bispecific antibodies (BsAb) targeting BCMA and GPRC5D. **Methods:** Peripheral blood serum was collected from 19 MM patients before and during BsAb therapy. S100A8/A9 protein levels were measured and correlated with depth of response (DOR) and progression-free survival (PFS). To study mechanistic effects, patient and healthy donor T cells were exposed to S100A8/A9 in vitro, followed by multiparameter spectral flow cytometry to investigate phenotypic composition, antigen-specific cytokine production, and cytotoxic activity. In addition, we examined the signaling pathways affected by S100A8/A9 using Western blot analysis. **Results:** MM patients achieving less than a very good partial response to bsAb therapy (<VGPR) had significantly higher serum S100A8/A9 levels at baseline and during therapy ($p < 0.05$). Elevated levels were inversely correlated with PFS ($r = -0.53$, $p < 0.05$). When split in two groups, median PFS was ~400 days in patients with low levels of S100A8/A9, vs. ~100 days in patients with high levels ($p = 0.02$). In vitro, S100A8/A9 impaired bispecific antibody-mediated cytotoxicity in a coculture assay. Incubation with S100A8/A9 was associated with an increase in exhausted T cells, as denoted by augmentation of TOX+CD4+ and TOX+CD8+ cells ($p < 0.05$), which could be reversed with the use of a monoclonal antibody against S100A8/A9. Antigen-specific stimulation resulted in less TNF-α production in S100A8/A9-treated T cells. T cell pathway analysis of S100A8/A9-incubated T cells shows a dose-dependent decrease in pERK, pZAP70, and pNF-κB. **Conclusions:** S100A8/A9 promotes T cell exhaustion and impairs T cell function, limiting the efficacy of BsAb therapy in MM. Elevated serum S100A8/A9 is associated with inferior clinical responses and shorter PFS after BsAb therapy. Incubation with S100A8/A9 increased the number of T cells expressing TOX and decreased the phosphorylation of T cell signaling pathways, which corresponded to a reduction in the functional production of cytokines and cytotoxicity in vitro. Our findings support S100A8/A9 as a biomarker of resistance and a potential therapeutic target to enhance the efficacy of T cell-engaging therapies.

OA-16

BCMA CAR T-Cell Therapy in Newly Diagnosed Primary Plasma Cell Leukemia Ineligible for Transplantation: An Open Label, Single-arm, Phase 2 Study (CAREMM-002)

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Introduction: Primary plasma cell leukemia (PPCL) is the most aggressive subtype of plasma cell neoplasms. Following the recent revision of diagnostic criteria by IMWG, the incidence of PPCL had approximately doubled. Despite this, prognosis remains extremely poor-particularly in patients ineligible for transplantation-with median overall survival often less than 2 years. BCMA-directed CAR-T cell therapies have demonstrated deep and durable responses in relapsed/refractory multiple myeloma. However, due to its aggressive biology and rarity, PPCL has been consistently excluded from clinical trials, leaving a significant therapeutic gap. Thus, we initiated CAREMM-002 (NCT05979363), a prospective, single-arm phase 2 trial to evaluate the efficacy and safety of BCMA CAR-T therapy in frontline setting for transplant-ineligible PPCL patients. **Methods:** This single-arm, phase 2 investigator-initiated study enrolled PPCL patients deemed ineligible for ASCT due to age, frailty, comorbidities, or repeated failure of stem cell mobilization. After 3–4 cycles of VRd-based induction treatment, patients received lymphodepletion and a single infusion of BCMA CAR-T cells (3×10^6 cells/kg), followed by consolidation and lenalidomide maintenance. Primary endpoints were safety and MRD negativity following infusion. Secondary endpoints included complete response rate (CRR), PFS, OS, and duration of remission (DOR). **Results:** As of May 10, 2025, nine patients were enrolled, with a median age of 68 years (range, 54–72) and 66.7% female. Eight patients completed BCMA CAR-T infusion, seven are currently in the maintenance phase, one remains in consolidation, and one is still undergoing induction. Among the infused patients, the overall response rate (ORR) was 100%, with 87.5% achieving stringent complete response (sCR). All patients achieved MRD negativity by next-generation flow cytometry (NGF), which was sustained through the most recent follow-up. At a median follow-up of 15.4 months, no relapses or

deaths have been observed. The longest documented duration of remission is 26.7 months. Median PFS, OS, and DOR were not reached. Treatment was well tolerated and showed a favorable safety profile. The most common AEs were hematologic and attributed to lymphodepletion, including grade ≥3 leukopenia (87.5%), neutropenia (62.5%), anemia (37.5%), thrombocytopenia (25.0%), and lymphopenia (100%). CRS occurred in 62.5% (all grade 1–2), with a median onset of 1 days and duration of 4 days. No cases of immune effector cell-associated neurotoxicity syndrome (ICANS) were observed. All patients exhibited robust peripheral expansion. Median Cmax was 65,770 copies/µg gDNA (range, 29,579–147,410), median time to reach peak expansion was 13 days, and AUC0–28 was 430,767 (range, 356,153–2,110,005). **Conclusions:** Frontline BCMA CAR-T therapy demonstrated unprecedented depth and durability of response with manageable safety in transplant-ineligible PPCL patients-a population with historically dismal outcomes and limited therapeutic options.

OA-17

MRI Response According to MY-RADS Correlates with MRD Negativity After Induction in Newly Diagnosed Multiple Myeloma: Results from the GMMG-HD7 Trial

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Introduction: Flow cytometry and next-generation sequencing–based assessment of minimal residual disease (MRD) in the bone marrow (BM) represents the current gold standard for evaluating treatment response in multiple myeloma and is strongly associated with long-term survival. Nevertheless, its diagnostic scope is restricted to focal bone marrow sampling sites, such as the iliac crest, which may limit its ability to capture total disease burden in cases of spatially heterogeneous involvement. Whole-body MRI (WB-MRI) provides comprehensive, non-invasive insight into the entire disease distribution. This study aimed to compare the post-induction MRD status by next-generation flow cytometry and treatment response in WB-MRI assessed according to MY-RADS in patients with newly diagnosed transplant-eligible multiple myeloma (NDTEMM). **Methods:** The GMMG-HD7 is a randomized, active-controlled, phase 3 trial investigating the efficacy of isatuximab in combination with lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed, transplant-eligible multiple myeloma (NDTEMM). 83 patients were enrolled in this imaging substudy. All patients underwent WB-MRI at baseline and after induction, and had post-induction MRD assessment by next-generation flow cytometry (cut-off 1×10^{-5}). WB-MRI scans were analysed using the MY-RADS protocol, a structured and standardized reporting system that scores disease burden based on diffuse infiltration, number and size of focal lesions, and presence of extramedullary or paramedullary disease across multiple body regions. **Results:** Post-induction, a statistically significant association was observed between the diffuse infiltration score and MRD status for both the whole-body (Wilcoxon rank sum test, $p < 0.001$) and pelvic ($p = 0.001$) regions, with lower scores associated with MRD negativity. Patients who showed a decrease in total whole-body MRI scores from baseline had significantly higher odds of achieving MRD negativity ($p = 0.002$; odds ratio [OR] = 7.68, 95% confidence interval [CI]: 2.06–28.57). Similarly, a reduction in total pelvic scores was significantly associated with MRD negativity ($p < 0.001$; OR = 7.09, 95% CI: 2.32–21.65). Baseline MRI scores had no prognostic effect on MRD outcomes. **Conclusions:** Our analysis demonstrates that reductions in WB-MRI scores, assessed using the MY-RADS protocol, are statistically significantly associated with MRD negativity following induction therapy. These findings support the use of standardized WB-MRI as a non-invasive, whole-body imaging biomarker for response assessment and risk stratification in both clinical trials and routine practice.

OA-18

The Value of Progression-Free Survival (PFS) from the Perspectives of Patients with Multiple Myeloma (MM) and Treating Physicians: Quantitative Research Findings from Eight Countries

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Introduction: Advances in MM treatments (Tx) have improved overall survival (OS); yet, relying on mature OS data for regulatory and health authority approval is challenging, emphasizing the need to better understand alternative endpoints, like PFS. We evaluated how patients (pts) and physicians value PFS in Tx decision-making and how progression impacts pts' quality of life (QoL) in the US, UK, Spain, France, Germany, Italy, Japan, and Brazil. **Methods:** Hematologists/oncologists with ≥10 pts with MM and 3–30 y of experience, and pts with MM diagnosed ≤10 y ago, completed an online questionnaire. Questionnaire content was informed by physician and pt qualitative interviews (Kissling A, et al. Value Health 2024;27:S543–544), and used structured questions and best-worst scaling (BWS). Questions focused on understanding of PFS,

progression-related symptoms/impacts, and the role of PFS in Tx decisions. Descriptive statistics were used for analyzing study variables; BWS was analyzed using hierarchical Bayes estimation. **Results:** Physicians had a mean practice experience of 15.6 y (standard deviation [SD], 7.0) and treated a median of 88.9 pts (SD, 119.5) in the past 6 months. Pts (N = 237) had a mean age of 68.8 y (SD, 7.3), 63.7% were male, and mean time since diagnosis was 3.3 y (SD,1.6). Pts were undergoing 1st line (1L; 47.3%; n = 112), 2nd line (2L; 19.8%; n = 47), or 3rd line or later (32.9%; n = 78) Tx. Around half of pts (49.3%) and physicians (55.0%) considered PFS equal or more important than OS; and over two-thirds of physicians for the following pt groups: frail (74.6%), those with pain (73.4%), elderly (71.5%), symptomatic disease (71.5%), comorbid (70.4%), and 4th line (68.9%). When asked why PFS was important in Tx selection, 52.4% of physicians selected that PFS was a surrogate for OS when OS data were unavailable and >95% supported its use in healthcare access and coverage decisions regardless of OS data availability. Among pts who experienced progression (52.7%), 97.6% had ≥1 of the following symptoms: general pain (63.2%), fatigue (50.4%), muscle weakness (48.0%), anemia (32.8%), bone pain (32.0%), fragile bones, breaks, and fractures (32.0%), and kidney problems and/or renal failure (11.2%). Other symptoms affecting QoL included numbness (53.6%), anxiety (40.8%), and depression (27.2%). In the BWS, physicians valued PFS and OS most across Tx lines. QoL attributes were valued more by physicians in 2L Tx decision-making and achieving measurable residual disease negativity when selecting 1L Tx. OS was the most important attribute among pts. Other attributes, including multiple QoL factors and PFS, were similarly valued by pts across Tx lines. **Conclusions:** OS and PFS are important to physicians and pts in Tx-related decisions. Around half of pts and, for certain groups, two-thirds of physicians valued OS over PFS. Nearly all physicians support the use of PFS in healthcare access and coverage decisions. Experiencing progression significantly impacts pts' QoL.

OA-19

Prospective Evaluation of Response Assessment in Newly-Diagnosed Multiple Myeloma with Combined use of 18F-FDG-PET/CT, Whole-Body Diffusion-Weighted MRI and MRD by Next-Generation Sequencing

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Introduction: The IMWG recommends integration of hematologic response with minimal residual disease (MRD) assessment, both in bone marrow (BM) by next-generation sequencing (NGS) or flow, and by imaging. 18F-FDG-PET/CT currently represents the recommended technique in this setting; its use has been standardized following IMPeTUs criteria. A role of other functional imaging techniques, particularly of whole-body diffusion-weighted MRI (WB-DW-MRI), is emerging. Specific response assessment categories (RACs) have been lately proposed by MY-RADS guidelines. We present a prospective single-center study aimed at comparing PET/CT and WB-DW-MRI during diagnosis/staging of newly-diagnosed multiple myeloma (NDMM) and in defining treatment response, in association with BM MRD. **Methods:** Patients (pts) undergo PET/CT and WB-DW-MRI at baseline (B). Techniques resulting positive (pos) at B are repeated before maintenance therapy (transplant-eligible pts) or after 1 year of therapy (transplant-ineligible pts). Pts achieving ≥ very good partial response (VGPR) undergo MRD assessment by NGS. Interpretation of the imaging techniques is based on IMPeTUs and MY-RADS guidelines. **Results:** Between October 2022 and March 2025, 131 NDMM pts were enrolled. Among pts with CT-assessed bone disease (64%), MRI was pos in 100% and PET in 89%; in the remaining 36%, MRI was negative (neg) in 49% (none with PET-assessed focal lesions, FLs) and pos in 51%. MRI detected FLs and paraskeletal disease (PSD) in more NDMM pts than PET (FLs: 76% vs 57%, p = 0.001; PSD: 30% vs 23%, p = 0.001); concordance was perfect in detecting extramedullary disease (EMD) (2%, k = 1) and slight in detecting diffuse disease (DD) (24% vs 34%, p = 0.001, k = 0.4). By WB-DW-MRI, DD was related to higher % of BM plasma cells (p = 0.002), lower Hb (p = 0.002), higher concentration of M protein in serum (p = 0.02) and urines (p = 0.01); presence of >3 FLs was related to R-ISS 3 (p = 0.001) and lower Hb (p = 0.02). To May 2025, 50 pts reached the re-evaluation phase. 26 pts (52%) achieved complete response (CR), 19 (38%) VGPR, 4 (8%) PR, 1 (2%) was non-secretory. MRD was available for 19 pts, resulting neg in 10 (53%) and pos in 9 (47%). 32 pts had pos PET at B: 28 (88%) achieved metabolic CR, 1 (3%) metabolic PR, 3 (9%) metabolic stability or progression. 41 pts had pos WB-DW-MRI at B: 37 (90%) responded (RAC1–2), 4 (10%) had stable or progressive disease (RAC3–5). Among 32 pts repeating both techniques, 30 (94%) had concordant scans (k = 0.6). Among 28 pts achieving ≥ VGPR and imaging response by both techniques, MRD assessment was available for 13 pts, resulting neg in 8 (62%) and pos in 5 (38%). **Conclusions:** Our data support combined use of PET/CT and WB-DW-MRI for MM staging at B and show a good concordance in response assessment, suggesting a potential alternative use in this setting. Updated data with extended follow-up and regarding imaging response and MRD assessment will be presented at the meeting.

OA-20

Temporal Trends in Infectious Risk Among Multiple Myeloma Patients Treated with Daratumumab: A Meta-Analysis

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Introduction: Multiple myeloma (MM) is associated with a significant infectious risk, particularly among patients treated with the anti-CD38 monoclonal antibody (mAb), daratumumab. The design of infectious prophylaxis studies requires granular characterization of infection risk over time, something missing from clinical trial reports. We aimed to characterize the nature, frequency and timing of infections in patients with daratumumab (dara) vs non-daratumumab (non-dara) regimens. **Methods:** We performed an individual patient-level meta-analysis of adverse event (AE) data for phase 2 or 3 randomized clinical trials shared on the Yale Open Access Data (YODA) repository. Included trials compared dara vs non-dara regimens (NDMM trials: MAIA, ALCYONE, GRIFFIN; RRMM trials: POLLUX, CASTOR, and APOLLO). Infectious AE terms were grouped to determine organ involvement, type of pathogen, and severity (CTCAE grading). For patients treated on the GRIFFIN trial, infectious complications within 90 days post autologous transplant were excluded. The primary outcome was to characterize the proportion of patients followed in each 3-month (quarter, Q) with a grade ≥1 infection, for up to 2 years after treatment initiation. **Results:** In total, 2,989 clinical trial patients were included in this analysis (1,500 Dara patients; 1,489 non-Dara patients). Baseline characteristics—including age, performance status, ISS stage, and baseline neutrophil count—were similar between patients who experienced grade 1–2 versus grade 3–5 infections in both the Dara and non-Dara cohorts. Overall, 1,178 (79%) Dara patients and 914 (61%) non-Dara patients experienced an infectious AE within 2 years of treatment. Grade ≥3 infections occurred in 436 (29%) Dara patients and 301 (20%) non-Dara patients. Multiple grade 0–2 infections were observed in 753 (50%) Dara patients and 452 (30%) non-Dara patients, while multiple grade ≥3 infections occurred in 167 (11%) and 101 (7%) patients, respectively. The proportion of Dara-treated patients with infections of any grade was 42.2% in Q1, plateauing at 22.8–28% from Q3–Q8. The corresponding proportions for non-Dara–treated patients were 36.2% in Q1 and 17.8–21.9% from Q2–Q8. The incidence of grade ≥3 infections in Dara-treated patients was 13.1% (Q1), 5.9% (Q2), and 3.1–4.6% (Q3–Q8), compared to 9.8% (Q1) and 3.2–4.0% (Q2–Q8) in non-Dara patients. **Conclusions:** This is the first study to characterize infection risk over time in Dara-treated patients. Infectious risk is higher in dara-treated patients, mostly due to grade 1–2 events. Regardless of treatment, risk of infection is highest in the first 3 months, reaching a plateau in the second quarter and beyond, highlighting the contribution of disease burden to immune deficiency. These findings clarify anti-CD38 mAb toxicity and may guide prophylaxis strategies by identifying the early period as highest risk. An in-depth analysis by line of therapy, patient and disease characteristics and type of infection will be presented at the meeting.

OA-21

Dynamic Frailty Analysis of Transplant-Ineligible (TIE) Patients with NDMM in the Phase 3 MAIA and CEPHEUS Trials of Daratumumab (Dara) + Lenalidomide-Dexamethasone (Rd) and Bortezomib-Rd (VRd)

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Introduction: MAIA and CEPHEUS showed daratumumab (Dara) plus standard of care improved treatment (tx) outcomes, including PFS, in nontransplanted patients (pts) with NDMM, regardless of baseline (BL) frailty. Recent studies suggest that frailty is a dynamic state and that the degree of frailty over time appears to influence PFS more than age or Charlson Comorbidity Index score. Further understanding of changes in pts' frailty over their tx course may have important clinical considerations in tx delivery based on each pt's changing fitness status. For the first time, we assess outcomes based on dynamic frailty (post hoc) in the phase 3 MAIA and CEPHEUS trials (TIE pts). **Methods:** Pts were randomized 1:1 to receive DRd/Rd (MAIA) and DVRd/VRd (CEPHEUS). Frailty (IFM simplified frailty score; nonfrail, score 0/1; frail, score ≥2; ultrafrail, score ≥3) was assessed in MAIA and CEPHEUS TIE pts at BL and year (y) 1, 2, 3, and 4. PFS and overall MRD negativity (neg) (MRD-neg [10-5] with ≥CR) rate were assessed. **Results:** Median follow-up was 64.5 months (mo) in MAIA (median age 73 [range 45–90] y; 122 [17%] pts ECOG PS ≥2) and 58.7 mo in CEPHEUS (median age 70 [31–80] y; 37 [9%] pts ECOG PS 2). At BL, 172/368 (47%) pts assigned to DRd and 169/369 (46%) to Rd in MAIA and 48/144 (33%) TIE pts assigned to DVRd and 35/145 (24%) to VRd in CEPHEUS were frail; ultrafrail pts accounted for 42% and 43% of frail pts in the DRd and Rd arms of MAIA, respectively. In pts with evaluable post-BL scores, frail and nonfrail status changed at y1 compared with BL in 136/658 (21%) pts in MAIA (67 [10%] improved; 69 [10%] deteriorated) and 50/261 (19%) in CEPHEUS

(19 [7%] improved; 31 [12%] deteriorated). Frailty status changed at y4 in 89/354 (25%) pts in MAIA (18 [5%] improved; 71 [20%] deteriorated) and 63/188 (34%) in CEPHEUS (10 [5%] improved; 53 [28%] deteriorated). In nonfrail pts at landmark times (1, 2, 3, and 4 y post BL), MRD-neg rates were improved with DRd (41–55%) vs Rd (16–28%) in MAIA and with DVRd (68–80%) vs VRd (47–59%) in CEPHEUS. MRD-neg rates in frail pts were also higher with DRd (26–43%) vs Rd (9–15%) and with DVRd (54–60%) vs VRd (33–44%) and in ultrafrail pts in MAIA with DRd (28–45%) vs Rd (8–20%). Dara consistently improved PFS in both trials across frailty groups at landmark times. In nonfrail pts, DRd vs Rd led to a 34–50% decrease in the risk of disease progression/death and DVRd vs VRd to a 54–69% decrease. In frail pts, DRd reduced risk by 46–58% vs Rd, and DVRd by 51–65% vs VRd. In ultrafrail pts in MAIA, DRd reduced risk by 56–72%. Future analyses will assess safety across dynamic frailty subgroups. **Conclusions:** Our analyses demonstrate that frailty status is dynamic. Moreover, the changing degree of frailty over time influenced PFS, and D(V)Rd vs (V)Rd improved both MRD-neg rate and PFS in frail and nonfrail pts at landmark times. Furthermore, our MAIA analyses include the first phase 3 dynamic frailty data in ultrafrail pts, in whom DRd vs Rd provided clinical benefit.

OA-22

Comparative Analysis of Four NGS Protocols for Measurable Residual Disease Assessment Testing ctDNA and Bone Marrow Samples in Multiple Myeloma

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Introduction: MRD is a strong prognostic marker in Multiple Myeloma (MM) and MRD-negativity is recognized as an early endpoint for drug approval. NGS is a sensitive and robust method for MRD detection, but its use is limited by assay variability and reliance on non-universal proprietary platforms. Additionally, bone marrow (BM)–based MRD testing is invasive and not suitable for frequent monitoring. Here we report our experience on the application of different assays for patient (pts)-specific clonotype (ID) identification and MRD measurement by NGS, including a liquid biopsy approach, aiming at comparing the concordance between the different approaches and MRD results, in terms of specificity and sensitivity. **Methods:** The study included 50 NDMM pts. ID identification was performed by NGS with 4 different assays (clonoSEQ, EuroClonality (EC)-NGS, EC-NDC and LymphoTrack-Dx) on BM enriched PCs and on ctDNA (only EC-NDC). In 11 pts who achieved complete response, MRD was measured at the end of first line therapy both in nucleate cells (NCs) and in ctDNA. **Results:** At baseline, all samples were successfully analysed using the 5 different methods. A total of 929 rearrangements were identified, of which 605 (65%) were considered valid IDs, according to the assay-specific analytical algorithm. The specificity and originality of each sequence was assessed by an originality score, defined considering V and J regions specificity, CDR3 insertions/deletions and the clonality frequencies, leading to the recognition of 364/605 (60%) MRD-trackable IDs. Trackable ID sequences were compared using IMGT/V-QUEST and BLAST. Concordance was considered acceptable when a full or a partial match (median 55 bp) was identified by at least 3 methods for IgH and Igk, or at least 2 methods for IgH-D and IgL. Overall, concordance rates were 90% for IgH, 80% for Igk, 57.1% for Igl and 74% for IgH-D. The genomic profile was highly comparable between PCs and ctDNA. MRD was measured by Lymphotrack, EC-NGS and ClonoSEQ assays in NCs and by EC-NDC in ctDNA. Overall, 10/11 (91%) measurements were concordant in NCs. Overall, clonoSEQ and EC-NGS proved higher sensitivity and provided more precise quantification. Genomic aberrations were detected in 7/11 ctDNA samples, with 63% concordance with BM-MRD assessments. Moreover, ctDNA was informative in most cases. The results appear broadly consistent and overlapping across methods, supporting the applicability of these assays for reliable MRD monitoring. **Conclusions:** In conclusion, all assays showed high concordance, confirming their validity for ID evaluation with no discrepancies. Different approaches can yield consistent ID results. However, MRD assessment showed variability, with differences in sensitivity and quantification that may affect clinical decisions. Low-invasive methods proved feasible. These findings support the need for harmonized MRD guidelines with standardized criteria for ID identification and analysis.Acknowledgments: BoAIL, IMS-Career Award to S.A., AIRC22059.

OA-23

Circulating Tumor Cells for the Staging of Multiple Myeloma: First Results of a European Pooled Analysis of 2432 Patients with Newly Diagnosed Multiple Myeloma and Plasma Cell Leukemia

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Introduction: Current risk models in multiple myeloma (MM) are prognostic but insufficient for individualized treatment. Circulating tumor cells (CTCs) may offer additional prognostic value, independent of established risk factors such as cytogenetics and tumor burden. Thus, we aimed at defining the clinical significance of CTCs in a large pooled dataset including prospectively collected data from patients from clinical trials and real-world settings. **Methods:** We pooled data from 2364 patients with newly diagnosed MM (NDMM) and 68 with primary plasma cell leukemia (pPCL) across five European groups (Czech Republic, Greece, Italy, HOVON, PETHEMA). All patients had CTC enumeration before treatment by flow cytometry (EuroFlow or other methods); 59% were enrolled in clinical trials (GEM-CLARIDEX, CASSIOPEIA, HOVON-143, FORTE, GEM2012MENOS65, EMN12/HOVON-129) whereas the remaining were treated in routine practice. Median age was 63 years (IQR 57–73) and 54% were transplant-eligible. Induction regimens included doublets (2.2%), triplets (88.87%), and quadruplets (9.2%). **Results:** Median CTC level was 0.017% (IQR 0.01–0.114%) and was consistent across centers ($p = 0.2$). Logarithmic CTC increments defined five subgroups with distinct median PFS (mPFS): ≤0.001% (77 months), 0.001–0.01% (51 months), 0.01–0.1% (40 months), 0.1–1% (31 months), ≥1% (16 months; $p < 0.0001$). Patients with NDMM with ≥1% or ≥2% CTCs had PFS similar to those with pPCL (mPFS 16 vs 15 vs 15 months). As a continuous variable, higher CTCs correlated with inferior PFS (HR 1.17, 95% CI 1.11–1.24, $p < 0.001$), independent of R-ISS, 1q gain/amplification, induction regimen, and transplant eligibility. Subgroup analyses confirmed prognostic value across all clinically relevant subgroups. After determining an optimal cut-off, various CTC thresholds ranging from 0.01% to 0.1% effectively and consistently dichotomized patients based on their risk of progression in both clinical trials and real-world cohorts, regardless of transplant eligibility. CTC increased ability to stratify patients with established risk factors. For example, those having standard-risk cytogenetics with high CTCs had PFS comparable to patients having high-risk cytogenetics [t(4;14), t(14;16) and/or del17p] with low CTCs (42 vs 36 months, $p = 0.48$). Similar results were obtained when CTC was combined with 1q gain/amplification. **Conclusions:** This pooled analysis of prospectively collected data confirms CTCs as an independent prognostic factor in NDMM. Patient stratification according to logarithmic CTC levels offers the most meaningful risk stratification, identifying five subgroups with distinct outcomes, including the identification of NDMM patients having ≥1 or 2% CTCs and survival outcomes similar to those with pPCL. A cut-off in the range of 0.01–0.1% reliably distinguishes patients at different risk of progression and/or death across all clinically relevant subgroups. This study defines CTCs as an essential biomarker for the staging of NDMM patients.

OA-24

Assessment For Circulating Plasma Cell Enhances R2-ISS in Newly Diagnosed Multiple Myeloma

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Introduction: Circulating plasma cells (cPCs) are emerging as powerful biomarkers in multiple myeloma (MM), offering prognostic insight beyond traditional staging systems. Prior studies have proposed thresholds such as ≥0.01%, ≥0.02%, ≥0.07%, and ≥0.105% but a consensus cutoff remains elusive. **Methods:** We retrospectively analyzed 829 NDMM patients diagnosed between 2011–2023 at Mayo Clinic who underwent peripheral blood flow cytometry prior to therapy. Patients with cPC ≥1.2% were excluded to eliminate plasma cell leukemia, based on prior studies. Six-color flow cytometry was used to detect CD45, CD19, CD38, CD138, and cytoplasmic κ/λ expression across 150,000 events. cPC% was computed relative to circulating mononuclear fractions. **Results:** The cohort had a median age of 66.4 years and median follow-up of 3.4 years. Median cPC% was 0.0113% (IQR: 0.072%). We tested 505 unique cPC cutoffs for OS and 501 for PFS using maximally selected log-rank statistics. The optimal OS threshold was 0.302% (~12 cPC/μL), and for PFS, 0.025% (~1 cPC/μL), both yielding C-statistics around 0.58. Five percentage-based thresholds (≥0.01%, ≥0.02%, ≥0.07%, ≥0.1%, ≥0.3%,), two absolute cutoffs (≥1 cPC/μL, ≥12 cPC/μL), and cPC presence were compared with bootstrapping. Among evaluated thresholds, cPC ≥0.02% demonstrated the strongest prognostic performance (C-statistic for OS: 0.567, PFS:

0.565). Addition of a three-tier cPC based staging system (<0.02%, ≥0.02–<0.3%, ≥0.3%) yielded the highest overall performance (C-statistic for OS: 0.576, PFS: 0.577). 0.02% cPC is established independently by 3 studies including this study as a prognostic marker. 0.3% has previously been found to correspond with 2% cPC on blood smear and is studied as a lower threshold for plasma cell leukemia.Adding the three-tier cPC based staging improved the prognostic accuracy of multiple staging systems including ISS, RISS, R2ISS and IMWG high risk criteria (2024). ISS with cPC staging (C-statistic for OS:0.625, PFS:0.66) was comparable to R2ISS alone (OS:0.62 PFS:0.65). R2ISS with three tier staging system yielded overall best performance (OS: 0.655, PFS: 0.687). A composite R2ISS-cPC score was constructed by assigning 0.5 for cPCs ≥0.02–<0.3% and 1 for ≥0.3%. Stages I, II, III, IV were decided as per original R2ISS staging. Incorporating the CPC levels into R2ISS increases classification into both High (from 63 to 105) and Intermediate-High (from 253 to 259) risk categories, indicating risk upstaging in a subset of patients. R2ISS-cPC IV (3.8 years) and III (7.7 years) had inferior median overall survival. ($p < 0.001$). This was comparable to R2ISS IV (3.4 years) and III (6.4 years) median survival. Median survival wasn't reached in remaining two groups in both staging systems. **Conclusions:** This study provides a unifying approach for cPC incorporation into current myeloma staging systems by adding new and previously established thresholds.

OA-25

High Accuracy of Next-Generation Flow (NGF) in Predicting Measurable Residual Disease by Next-Generation Sequencing (NGS) in the 10^{-6} Range: A Prospective Comparison Within the Phase III IsKia Trial

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Introduction: Measurable residual disease (MRD) negativity is the strongest predictor of long-term remission in multiple myeloma (MM). NGS is approved in the US for monitoring MRD in MM, whereas NGF is an alternative technique. In the randomized, phase III IsKia trial, a pre-planned, prospective comparison of NGF and NGS was conducted to assess their concordance. **Methods:** Patients (pts) received isatuximab-carfilzomib-lenalidomide-dexamethasone induction, HDM-ASCT, consolidation and light consolidation vs the same treatment without isatuximab. MRD was assessed by NGF and NGS after induction, ASCT, consolidation and light consolidation in all pts achieving ≥VGPR. Samples were centralized in Torino (IT) and Rotterdam (NL) laboratories. NGS was performed by clonoSEQ® (Adaptive Biotechnologies, Seattle) and was prioritized, as MRD negativity by NGS was the trial primary endpoint. NGF was performed by IT and NL following EuroFlow standardized protocols. Concordance between NGF and NGS was evaluated quantitatively – using positive cells per million in paired samples at the same sensitivity – and qualitatively (negative vs positive) by calculating concordant over total samples. Cohen's κ coefficient (κ) was used to evaluate the strength of concordance. **Results:** After a median follow-up of 35 months (IQR 32–38), 843 bone marrow (BM) samples were analyzed by NGF. A median number of 6.95 million (IQR 3.51–10) total nucleated cells were analyzed with a median limit of detection of 0.0003% (IQR 0.0002%–0.0006%) per sample. In the ITT population, the MRD negativity rates detected by NGF after each time point were superimposable to those detected by NGS. 692/843 (82%) samples were evaluable at the 10-5 sensitivity by both NGF and NGS. At 10-5, concordance was 89% (κ 0.70). A regression analysis showed a strong positive correlation (Spearman's rank [R] 0.76; $p < 0.0001$). Using NGS as standard, the NGF positive predictive value (PPV) was 98%, and the negative (N)PV 65%. Since NGS was prioritized, the maximum sensitivity by NGF (2*10-6) was reached in 319/843 (38%) samples, among which 289/319 (91%)

were evaluable at the maximum sensitivity of both techniques (2*10-6 by NGF; 10-6 by NGS). At the maximum sensitivity of both techniques, concordance was 88% (κ 0.75). A regression analysis showed a R of 0.85 ($p < 0.0001$). The NGF PPV and NPV in predicting the NGS MRD status were 96% and 82%. Analyzing both NGF and NGS at a sensitivity of 2*10-6, concordance was 90% (κ 0.80). NGF PPV and NPV in predicting the NGS MRD status were 96% and 86%. No differences were observed grouping samples by clinical phase or exposure to anti-CD38 mAbs. **Conclusions:** NGF and NGS showed highly concordant results (up to 90% at 2*10-6), suggesting that both may be used to evaluate MRD in the BM in clinical practice. NGF performance was not affected by clinical phase or pt exposure to anti-CD38 mAbs. A higher NPV of NGF in predicting NGS was found when a 2*10-6 sensitivity was reached with NGF.

OA-26

Comparative Analysis of ClonoSEQ MRD Testing from Bone Marrow and Circulating Tumor DNA Assessment in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is the second most common hematologic malignancy in the U.S. Non-secretory MM, a rare subtype, is characterized by the absence of a detectable monoclonal immunoglobulin protein (M-protein) in the serum and/or urine, making disease monitoring particularly challenging. Serial bone marrow assessments are the gold standard for non-secretory MM but are invasive and associated with patient discomfort. clonoSEQ is a next-generation sequencing (NGS) assay that measures minimal residual disease (MRD) by detecting unique rearranged immunoglobulin receptor sequences from DNA in bone marrow (BM MRD); its use in peripheral blood (PB MRD) could offer a more patient-friendly alternative, particularly valuable in non-secretory MM. **Methods:** We retrospectively analyzed 149 PB plasma samples from 100 patients with secretory MM who had a known dominant clonotype identified in the BM. We evaluated the concordance of PB MRD from ctDNA with BM MRD and other conventional disease biomarkers, including M-protein, free light chain (FLC) ratio, extramedullary disease (EMD), and treatment response (based on the International Myeloma Working Group criteria). Specificity (SP), sensitivity (SN), positive predictive value (PPV), and negative predictive value (NPV) were calculated for PB MRD in various clinical contexts. **Results:** PB MRD negativity was significantly associated with deep clinical response, including complete response (CR) ($p < 0.001$) and very good partial response (VGPR) ($p < 0.001$). PB MRD positivity was associated with abnormal FLC ratio (74%; 37/50), detectable M-protein (78%; 39/50 and EMD (26%; 14/50). Using BM MRD as the reference, PB MRD+ had a SP of 90.1% and PPV of 94.9%, but lower SN (33.9%) and NPV (21.7%) [TABLE]. Compared to M-protein detection, PB MRD+ had 83.3% SP, 78.0% PPV, 49.4% SN, and 57.9% NPV. When compared to abnormal FLC ratio, PB MRD+ showed 82.2% SP, 74.0% PPV, 56.9% SN, and 68.2% NPV. For patients in VGPR or better, PB MRD- had 84.0% SP, 93.6% PPV, 80.6% SN, and 60.0% NPV. Most samples in CR were PB MRD– (83/93; 89.3%), while in relapsed (19/19) and nearly all newly diagnosed samples (8/9) were PB MRD +. Among 9 patients with ≥ 3 sequential samples. all samples at diagnosis or with progressive disease were PB MRD+, and all samples in a CR were PB MRD-. **Conclusions:** clonoSEQ PB MRD from ctDNA demonstrates high specificity and PPV relative to BM MRD, with strong correlation to markers of tumor burden and response status. PB MRD + reliably indicates residual disease, while PB MRD– correlates with deep clinical responses. These findings highlight the potential of PB MRD as a non-invasive monitoring tool in MM, and suggest promising clinical utility, particularly for patients with non-secretory disease. BM MRD remains the more sensitive tool for evaluating disease burden, however, further studies are warranted to validate PB MRD as a surrogate for BM-based assessment in clinical practice.

OA-27

Composition and Functional State of T and NK Cells in Extramedullary Myeloma Tumor Microenvironment

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Introduction: Extramedullary disease (EMD) is an aggressive manifestation of multiple myeloma (MM), when clonal plasma cells (PCs) become independent of the bone marrow (BM) microenvironment (TME) and invade distant tissues and organs. The incidence of EMD is increasing and is associated with drug resistance and poor prognosis. There is limited knowledge about the composition of the EMD TME and the fitness of its effector immune cells, potentially responsible for treatment efficacy. **Methods:** Biopsy of 23 EMD soft tissue tumor was performed in relapsed/refractory MM (RRMM)

patients and samples were processed immediately after surgery. Single-cell RNAseq (scRNAseq) was performed using Chromium GEM Single Cell 3' reagent kit v3.1 (10x Genomics) and cell suspensions from the samples. The computational pipeline combined scanpy python framework and R packages enabling comparison of paired and unpaired EMD vs BM samples. For flow cytometry (FC) assessment, samples were stained using 8-color panels to distinguish key subsets. **Results:** ScRNAseq and FC yielded comparable results, confirming that EMD tumor is primarily composed of PCs and the effector: tumor (E:T) ratio is dramatically lower compared to BM. Semi-automated cell type annotation resulted in the identification of 9 distinct T cell and 2 NK cell clusters. CD8+ T cell clusters exhibited markedly lower cytotoxicity and higher exhaustion scores in EMD compared to BM. This trend was attributed to different composition of T cells between the groups. EMD had the highest proportion of cells in the most exhausted tumor-reactive CD8_exhausted-like_TOX cluster, while clusters with high cytotoxicity score, were less prevalent in EMD. Accordingly, using FC we found an increased percentage of T cells positive for exhaustion marker PD-1 in EMD compared to EMD_BM and RRMM_BM. In addition, we observed a substantially lower number of CD4+ T cells in EMD compared to BM resulting in a significantly lower CD4+/CD8+ ratio. Analysis of NK cell compartment revealed significantly higher proportion of less cytotoxic CD16- NK cells in EMD (73.4% vs 0.7%; p = 0.01, and 7.9%; p = 0.01 in EMD_BM and RRMM_BM, respectively), which are typically enriched in solid tumors (Rebuffet et al. 2024, Nature Immunology), compared to BM samples. This finding was further confirmed by FC as well as in an independent validation cohort of 8 EMD samples using spatial transcriptomics. Importantly, CD16- NK cells from EMD exhibited significantly higher expression of inhibitory receptor NKG2A compared to EMD_BM. **Conclusions:** In this study, using scRNAseq and FC data, we revealed that EMD TME is characterized by a high proportion of exhausted tumor-reactive CD8+ T cells and CD16- NK cells. Additionally, we demonstrated that EMD CD8+ T and NK cells overexpress immune checkpoints like PD-1 and NKG2A, suggesting therapeutic opportunity with checkpoint inhibitors.

OA-28

Midnolin Downregulation Promotes Myelomagenesis via Impacting Ubiquitination Independent Pathway of Protein Degradation

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Introduction: Despite advancements in treatment, multiple myeloma (MM) remains incurable, which underscores the need for novel therapeutic targets. Here, we performed a genome-wide CRISPRa screen in 3 MM cell lines to uncover novel tumor suppressor genes that play critical roles in controlling myeloma cell proliferation and survival. We identified a set of 121 dropout genes that ranked in the top 1% (0.25 FDR) and overlapped in at least 2 multiple myeloma cell lines. **Methods:** n/a. **Results:** Among the top hits was MIDN, encoding the protein Midnolin, which mediates ubiquitination-independent protein degradation inducing the degradation of many nuclear proteins including stress-induced transcription factors (Fos, EGR1, NR4A1, etc). We confirmed MIDN overexpression (OE) leads to the suppression of proliferation in myeloma, using both stable and inducible ORF systems. Importantly, we observed uniformly lower expression of MIDN in 2 large cohorts of newly diagnosed MM patients (n = =507 and n = 319) compared to normal plasma cells (n = 21 and n = 16). MIDN expression was also significantly lower in premalignant conditions, suggesting an early downregulation in disease progression. Furthermore, MIDN expression was significantly lower in 6 human MM cell lines compared to B cells from 3 healthy donors. Midnolin stably associates with the proteasome and uses a structural domain that incorporates a free β strand to "catch" its substrates for ubiquitin-independent degradation. Due to its recently discovered role in degrading nuclear factors, we hypothesized that Midnolin suppresses tumor growth by degrading transcription factors important for MM pathogenesis. Indeed, proteome and transcriptomic analyses in MIDN OE cells found MIDN overexpression correlated with the downregulation of pathways key to MM cell growth and viability, such as those dependent on nuclear factor IRF4, including plasma cell signature genes. Further mass spectrometry analysis confirmed that Midnolin binds to 19S and 20S proteasomal subunits, as well as to important myeloma nuclear factors including IRF4. Midnolin contains 3 domains that function in concert to promote proteasomal degradation of bound substrates. It uses a long α Helix to stably bind the proteasome, the Catch domain to interact with substrates, and the ubiquitin-like domain (Ubl) to promote substrate degradation. It's been recently shown to inhibit IRF4's interaction with MIDN at the Catch domain rescuing it from protein degradation and increasing MM cell viability. **Conclusions:** In conclusion, our study shows that downregulation of MIDN, mediating ubiquitination-independent protein degradation, may be a crucial event for MM development and pathogenesis, as its observed universal downregulation increases the key MM cell growth and survival promoting oncoprotein IRF4. Moreover, our data provides an initial attempt to evaluate the functional landscape of putative suppressor genes in MM, which may

expose new vulnerabilities and provide additional therapeutic opportunities.

OA-29

In Situ Visualisation of BCMA Bispecific Antibody and the Myeloma Immune Microenvironment

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Introduction: Despite therapeutic advances, multiple myeloma remains difficult to cure. Novel T cell redirecting therapies such as CAR-T cells and bispecific antibodies have shown promising efficacy in the relapse setting, however durable remissions have yet to be achieved. The mechanisms of resistance and the dynamics of immune cell interactions of T cell redirecting therapies within the bone marrow (BM) remain poorly characterised. Here, we used in situ imaging of the BM in living mice (intravital imaging) combined with spatial transcriptomics to characterise immune cell interactions with myeloma in the context of BCMA bispecific antibody. **Methods:** We used a traceable myeloma cell line derived from the spontaneous Vk*MYC mouse model (Vk14451-GFP) that recapitulates human disease. To visualise the immune response, Vk14451 cells were transplanted into reporter mice where CD8 T cells were labelled with fluorescent tomato protein (E8I-Cre tomato). >Five weeks post-transplant, mice were treated with 1 to 4 weekly doses of CD3-BCMA or CD3-KLH/control bispecific antibody and T cell responses tracked using multi-day intravital imaging of the calvarium BM. To investigate transcriptional responses of T cells and myeloma in the BM, long bones were prepared from cohorts of mice and analysed by spatial transcriptomics. **Results:** Direct visualisation of T cells in situ without therapeutic intervention revealed CD8 T cells were excluded from areas of myeloma infiltration. Furthermore, CD8 T cells that gained entry to tumour had significantly altered behaviour compared to T cells in healthy bone marrow. After treatment with bispecific antibody, significant changes in the biology and spatial distribution of CD8 T cells were observed. Interestingly, the immunosuppressive myeloma microenvironment had no effect on the ability of CD8 T cells to engage with myeloma cells within tumour foci and undergo rapid expansion. However, we did observe altered T cell persistence cells with significant in situ death detected within the myeloma foci. In cohorts of mice that received repeated dosing of bispecific antibody, we observed loss of tumour control. In these mice, we still observed access of T cells to the tumour foci. However, we did not observe sustained interactions and active killing of MM cells suggesting development of a tumour agnostic state of T cells. Additionally, we profiled the expression of 475 genes with subcellular spatial transcriptomics to characterise the molecular state of T cells in situ. Using this approach, we could detect significant changes in T cell phenotype both spatially and temporally within long bones of mice treated with bispecific antibody. **Conclusions:** This dynamic analysis of immune cell interactions with myeloma within the BM microenvironment suggests that targeting persistence of activated T cells may play a key role in the therapeutic efficacy of T cell redirecting therapies.

OA-30

Single-Cell Immune Landscape Associated with Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone Induction Efficacy in Newly Diagnosed Myeloma

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Introduction: Quadruplet regimens combining CD38-targeting monoclonal antibodies, such as Isatuximab or Daratumumab, with proteasome inhibitors, immunomodulatory drugs (IMiDs), and dexamethasone have recently emerged as the standard-of-care induction therapy for newly diagnosed multiple myeloma (NDMM). Despite significant clinical advances, many patients experience incomplete responses, resistance, or relapse. Increasing evidence highlights the critical role of the immune microenvironment in modulating treatment efficacy. However, the immunological impact of quadruplet therapy and the mechanisms underpinning therapeutic resistance remain poorly defined. A deeper understanding of immune dynamics in response to treatment could inform novel immunotherapeutic strategies aimed at enhancing long-term disease control. **Methods:** We analyzed longitudinal samples from the phase III IFM2020-02 "MIDAS" trial, investigating the immune effects of Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone (IsaKRD) in NDMM. Bone marrow aspirates were collected at baseline and after six cycles of induction. We performed single-cell RNA sequencing (scRNA-seq) on paired samples from 85 patients

collecting over 200,000 CD45$^+$ immune cells and applied integrative bioinformatic pipelines to assess transcriptional and compositional changes across immune subsets. Immune remodeling patterns were correlated with treatment response, focusing on minimal residual disease (MRD) status. **Results:** IsaKRD therapy profoundly reshaped the bone marrow immune landscape. This remodeling was marked by a significant reduction in B cells, NK cells, and T cells, coupled with an expansion of myeloid populations—particularly inflammatory monocytes exhibiting NF-κB activation and hypoxia-associated transcriptional profiles, which were specifically enriched in MRD-positive patients. Cytotoxic NK cell subsets were selectively depleted following treatment, especially in MRD-positive individuals, who instead showed an increase in inflammatory, bone marrow–resident NK cells. CD4$^+$ and CD8$^+$ T cells also underwent transcriptional reprogramming toward activated and pro-inflammatory states. MRD-positive patients displayed an enrichment of regulatory and T follicular helper–like CD4$^+$ subsets, along with a reduction in cytotoxic CD8$^+$ T cells. In contrast, MRD-negative patients preserved CD8$^+$ T cell cytotoxicity and showed an expansion of CD4$^+$ T cells with tissue-resident memory signatures highlighting divergent remodeling patterns based on treatment response. **Conclusions:** Our study provides a comprehensive single-cell atlas of the immune microenvironment in NDMM patients before and after IsaKRD induction. We reveal coordinated reshaping of both lymphoid and myeloid compartments, with immune signatures that correlate with MRD status and treatment efficacy. These findings underscore the importance of immune remodeling in shaping therapeutic outcomes and offer potential avenues for biomarker development and immune-based interventions in multiple myeloma.

OA-31

A Comprehensive Map of Genomic Drivers of Resistance to Anti-BCMA Immunotherapies in Multiple Myeloma

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Introduction: The introduction of chimeric antigen receptor T cells (CART) has transformed treatment for relapsed/refractory multiple myeloma (RRMM). Despite high response rates, the mechanisms underlying primary resistance and treatment failure remain poorly defined. **Methods:** To investigate the genomic mechanisms underlying primary refractoriness to anti-BCMA CART, we analyzed 76 whole genomes and 10 whole exomes (WES) from 74 patients treated with anti-BCMA CART (ide-cel, n = 58; cilta-cel, n = 16). **Results:** Genomic complexity (i.e., Maura et al., JCO 2024) correlated with inferior outcomes after CART ($p = 0.03$). This was validated in an independent cohort of 35 cilta-cel–treated patients profiled with MSK-IMPACT sequencing ($p = 0.0016$).Three additional genomic groups were associated with worse outcomes. First, loss of genes essential for plasma cell differentiation (e.g. CD38, XBP1) was linked to poor prognosis. Importantly, XBP1 and CD38 expression correlated with TNFRSF17 in RNAseq data from 1719 MM patients. Second, alterations in NFkB pathway genes (i.e., CYLD, PRKD2, NFKB2, MAP3K14) were associated with resistance to anti-BCMA CART. To validate the link between NFkB and plasma cell differentiating genes and suboptimal response to anti-BCMA immunotherapy, we investigated 5 Vk*MYC mice treated with anti-BCMA T-cell engagers. The two refractory lines showed loss of Xbp1, Map3k14 fusion, and downregulation of Tnfrsf17.The third group associated with poor outcomes included events known to confer high-risk disease such as 1q gain, TP53 mutation, loss of CDKN2C, RPL5, CCSER1, and MAF/MAFB translocations. Using the RNA-seq data set, we observed a correlation between TP53 and TNFRSF17 expression (R2 0.18; $p < 0.0001$). To further explore this, we analyzed single-cell RNA sequencing (scRNA-seq) data from clonal plasma cells in 11 patients collected prior to CAR-T therapy, of which 5 also had matched WGS data, observing increased cell cycle activity and reduced plasma cell features in non-responders - including lower TNFRSF17 expression. Finally, we assessed Tnfrsf17 expression in the newly developed Bclγ1 mouse models, with and without monoallelic loss of Trp53 (Larrayoz et al ASH 2024). Similar to human data, this model showed that monoallelic Trp53 loss was associated with impaired plasma cell differentiation and reduced Tnfrsf17 expression. Finally, co-occurrence of genomic complexity, loss of plasma cell differentiation genes, and NFκB pathway alterations defined a group of patients with primary refractoriness to anti-BCMA CART. Importantly, the prognostic impact of these genomic alterations was independent of the clinically derived MyCARe risk score, presence of EMD, or CART products. **Conclusions:** Overall, these findings suggest that comprehensive genomic profiling can more accurately predict clinical outcomes in MM patients treated with anti-BCMA CART than current clinical models, and may serve as a valuable tool for guiding personalized treatment strategies.

OA-32

Idecabtagene Vicleucel (ide-cel) and Endogenous Immune Profiles Linked to Progression-Free Survival in Relapsed/Refractory Multiple Myeloma (RRMM) Patients

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Introduction: Resistance to anti-BCMA CAR T therapy remains a significant challenge. Improved understanding of how T-cell fitness prior to aphaeresis determines efficacy, and if CAR-T and endogenous T-cell phenotypes associate with progression-free survival (PFS), is needed to aid in patient selection and development of future therapies with greater activity. **Methods:** We characterized immune dynamics and investigate its prognostic value in 120 RRMM patients treated with ide-cel in the KarMMa trial. Multidimensional and computational flow cytometry was performed in 266 bone marrow aspirates collected before and at months 1, 3, 6 and 12 after ide-cel infusion. 116 endogenous T-cell and 43 CAR T clusters were systematically quantified in a pileup analysis. **Results:** There were no differences observed in T-cell phenotypes at screening according to the number of years between diagnosis and treatment, ISS, tumor burden, number of prior lines of therapy, and prior stem cell transplantation. That notwithstanding, there were 41 T-cell clusters significantly associated with PFS. The clusters linked to higher risk of progression and/or death (HR ≥3.0) were defined by GrzmB expression in CD8+ and CD4+/CD8+ T cells, as well as by antigen-dependent differentiation markers such as CD27, CD95, CD45RA and CCR7. Patients having lower percentages of cytolytic and effector CD8 T cells showed longer PFS. Of the 76 patients profiled at month 1 after infusion, 55 had detectable CAR-T cells and in 16/55 the percentage was >1%. These patients showed significantly longer PFS when compared to those with <1% CAR-T cells (medians of 15 vs 8 months, p = 0.015). A CD4/CD8 CAR-T cell ratio >0.09 also identified patients with longer PFS (medians of 11 vs 7 months, p = 0.007). In addition, the CD8+PD1+TIM3+, CD4+CD8+ GranzB+ and CD8+GranzB+HLADR+ CAR T clusters showed the strongest association with risk of progression and/or death (HR ranging from 2.4 to 6.4). Patients having higher percentages of cytolytic and potentially exhausted CAR T clusters showed inferior PFS. There is limited understanding of how the phenotype of endogenous T cells is modified after CAR-T infusion and potential tumor-antigen stimulation with tumor lysis. Notably, 47 of the 116 endogenous T-cell clusters were prognostic at the latest assessment performed after CAR-T infusion. Higher percentages of CD4+ stem central memory T cells (HR: 0.3, p = 0.007) and lower percentages of ICOS+ Tregs (HR: 5.25, p = 0.006) showed the strongest association with longer PFS. **Conclusions:** This is one of the largest studies of dynamic immune profiling in RRMM patients treated with anti-BCMA CAR T cells. We uncovered that T-cell phenotypes prior to aphaeresis are associated with PFS. Furthermore, CAR-T phenotypes after infusion may be as prognostic as its percentage. We also showed how CAR T cells modulate endogenous T-cell tumor surveillance. Altogether, this study supports immune profiling for improved understanding of response and resistance to CAR T cells in RRMM.

OA-33

High-Risk Genomic Consensus Model Validation in a Large Cohort of Newly Diagnosed Multiple Myeloma Patients Using Next Generation Sequencing

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Introduction: The prognostic heterogeneity of multiple myeloma is mainly driven by genomic features of myeloma cells. The International Myeloma Society (IMS)/International Myeloma Working Group (IMWG) recently proposed a revised high-risk (HR) genomic model in order to have a consensus definition of genomic risk. Patients are classified HR if they present (i) del(17p), or (ii) a TP53 mutation, or (iii) a bi-allelic del(1p32), or (iv) a combination of t(4;14) or t(14;16) or t(14;20)/ and either a gain of 1q or a monoallelic del(1p32), or (v) a combination of 1q gain and mono-allelic del(1p32). **Methods:** In order to validate this new

definition, we performed NGS panel in 6735 new diagnosed myeloma patients (NDMM) and 1588 patients at first relapse, between 2019 and 2024. Only patients with a minimal 18-month follow-up were kept for PFS analyses, thus 2703 patients. **Results:** We observed that 23.9% of patients at diagnosis and 36.7% at first relapse were HR according to the IMS/IMWG genomic consensus. The IMS/IMWG consensus added a non-genomic factor to the HR definition: a high beta2 microglobulin level (≥5.5 mg/L) in the context of normal renal function (creatinine <1.2 mg/dL). In our NDMM dataset, beta2-microglobulin and serum creatinine levels were available for 3565/6735 patients. We observed that 257 non-HR patients (7.2% of the global cohort) met these criteria. Overall, according to the IMS/IMWG consensus, almost a third (31.4%) of NDMM patients should be considered as high risk. After a median follow-up of 35 months, the median PFS was 29 months for HR NDMM patients, versus 51 months for non-HR cases ($p < 0.0001$). When restricted to transplanted patients, the median PFS was 62 months for non-HR patients, versus 47 months for HR cases ($p < 0.0001$, median follow-up of 38 months). HR cytogenetic criteria from the Revised-ISS score (del(17p), t(4;14) and t(14;16)) were not able to discriminate patients in HR nor SR IMS/IMWG genomic subgroups. Looking at each criteria independently, we found that the presence of del(17p), TP53 mutation, biallelic del(1p32), or the combination of intermediate risk cytogenetics (gain 1q, del (1p32), and translocations) significantly reduces the PFS compared with standard-risk patients. Moreover, patients cumulating several criteria had an even worse prognosis (one criteria vs 2 or more criteria, median PFS respectively 33 and 10 months). Among standard-risk patients according to the genomic definition with normal creatinine, median PFS of those with high beta2-microglobulin was not significantly different from patients with normal beta2-microglobulin level. **Conclusions:** This study validates the IMS/IMWG genomic definition of high-risk myeloma in a large cohort of patients diagnosed from 2019.

OA-34

Exploring Molecular Glues to Activate Proteasomes and Develop Shared and Personalized Neoantigen-Based Therapeutics in Multiple Myeloma

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Introduction: Immunotherapy has sparked a revolution in oncology by releasing the power of the human immune system. A main challenge in broadening the range of responses to immunotherapy is the limited source of novel, actionable neoantigens exclusively presented on patient cancer cells. Immune evasion is a cancer hallmark that further thwarts the efficacy of immunotherapy. The immunoproteasome is a highly specialized form of the proteasome that degrades intracellular and viral proteins to generate short peptides which associate with MHC-class I molecules to serve as antigens presented to cytotoxic CD8+ T-cells. Molecular glues (MGs) are small molecules that target currently undruggable proteins to stabilize or induce protein-protein interactions by binding to two protein surfaces, creating a ternary complex and leading to beneficial downstream events. **Methods:** High-throughput screening identified a novel compound (compound A) that specifically increased immunoproteasome activity 3-fold in MM cells. MMCLs and MM patient CD138+ cells were treated ex vivo with compound A, lysates prepared, immunoprecipitated using a pan-MHC class I Ab, bound peptides eluted at low pH and released peptides sequenced by mass spectroscopy. Cell-based, biochemical and biophysical studies further characterized the effect of compound A on the association of accessory proteins with immunoproteasomes. **Results:** Treatment of MM patient tumor cells with compound A increased the presentation of specific, individual MHC-I antigenic peptides and neoantigens up to >100-fold relative to untreated cells. Global proteomic integral stability assays determined that compound A binds the proteasome structural subunit PSMA1 and promotes association of the proteasome activator PA28 (encoded by PSME1/PSME2) with immunoproteasomes. Genetic silencing of PSMA1, PSME1, or PSME2 as well as treatment with immunoproteasome-specific suicide inhibitors abolished the effects of compound A on antigen presentation. Biophysical studies studied the effect of compound A on the stable association of PSME1/2 with immunoproteasomes. Treatment of MMCLs and patient BM CD138+ cells with compound A significantly increased the anti-myeloma activity of allogeneic and autologous CD8+ T-cells. **Conclusions:** Taken together, our results demonstrate that the immunoproteasome represents an actionable therapeutic target that shapes the MHC-I antigenic repertoire on myeloma cells. Novel molecules that activate immunoproteasomes can overcome immune escape and promote T-cell immunity. We have identified commonly shared and individual specific MHC class I NeoAgs presented on MM patient tumor cells. Identification of shared neoantigens across patients provides a promising avenue to develop broadly applicable immunotherapies while discovery of private antigens facilitates the development of personalized therapies. Neoantigens upregulated upon immunoproteasome activation can be exploited to expand the scope of TCR-engineered T-cells, T-cell engagers and cancer vaccines.

OA-35

TRIgnite- 1Study, Phase 1, First-in-Human Study of ISB 2001: A BCMAxCD38xCD3-Targeting Trispecific Antibody for Patients with Relapsed/Refractory Multiple Myeloma (RRMM)—Dose Escalation (DE) Results

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Introduction: MM remains an incurable disease and resistance mechanisms are emerging. ISB 2001, a first-in-class trispecific T cell engager, redirects cytotoxic T cells to BCMA and/or CD38-expressing myeloma cells. By simultaneously targeting two TAA, ISB 2001 enhances avidity binding to tumor cells in vitro, hence potency, while the distal positioning of the CD38 vs CD3 binders minimizes CD38-related off-tumor adverse events. **Methods:** We report data from the DE portion of a Phase 1 study of ISB 2001, assessing safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) in RRMM patients (pts) exposed to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 therapies and refractory or intolerant to established therapies. Prior BCMA-targeted and/or T-cell directed therapies were allowed. ISB 2001 was administered weekly subcutaneously (SC), with double step-up doses on Days 1 and 4. DE utilized an accelerated titration design (initial 3 cohorts with single-patient dosing) followed by a standard 3+3 design. Adverse events (AEs) were graded by CTCAE v5.0; CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Overall response rate (ORR) was assessed by IMWG criteria. **Results:** As of May 08, 2025, 35 heavily pretreated pts received ISB 2001 across 9 dose levels (5–2700 µg/kg) with a median follow-up of 6.3 months (range: 1–16). Median age was 65 years; 66% male, 77% white with a median of 6 prior lines of therapy (range: 3–11). All pts were triple-exposed, 25/35 (71%) penta-exposed, including 5/25 (20%) penta-refractory, and 25/35 (71%) CD38-refractory. Sixteen (46%) and 15 (43%) pts received prior BCMA and T cell redirected (bispecifics and/or CART) therapies, respectively. Ten (40%) pts had a high cytogenetic risk and 12 (34%) had EMD at study entry. No DLT was observed. Overall, 100% of pts reported ≥1 AE regardless of causality, most commonly CRS (any grade [G]: 69%, G1: 54%, G2: 14%), infections (any G: 74%, G3/4: 29%) and neutropenia (any G: 51%, G3/4: 43%). One patient (3%) reported a single G1 event of ICANS. One pt died due to unrelated AE. ORR was 74% across all 9 doses. Among the 33 patients treated at active doses (≥50 µg/kg), ORR was 79%, ≥CR: 30%, ≥VGPR: 64%, MRD negativity rate: 75%. Most patients (81%) remain in response (median Duration of Response not reached). Median time to response was 35 days. ISB 2001 showed near dose-proportional PK, an estimated half-life of 17 days enabling monthly dosing, and consistent T-cell activation, supporting its mechanism of action. **Conclusions:** ISB 2001 was well tolerated with manageable adverse events and demonstrated robust anti-myeloma activity in heavily pretreated RRMM pts (NCT05862012). Expansion Cohorts to further optimize dose and treatment schedules following FDA Project Optimus are open to accrual.

OA-36

Bone Marrow-Homing and Chimeric Antigen Receptor-Engineered Lipid Nanoparticles Enable Sequential miRNA Delivery for Precision Therapy of Multiple Myeloma

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Introduction: Although chimeric antigen receptor (CAR)-T cell therapy has revolutionized relapsed/refractory multiple myeloma (MM) therapy, critical challenges of tumor recurrence after treatment remain. MicroRNAs (miRNAs), with their multitarget regulatory capacity, offer new opportunities to remodeling tumor microenvironment (TME) and potentiate CAR-T efficacy. However, its application is hindered by limited tumor-targeted delivery approach, leading to off-target effects and safety concerns. To address these issues, we have innovatively designed biomimetic lipid nanoparticles (LNPs) using CAR-T cell membrane encapsulation technology. These biomimetic nanoparticles achieve tumor-selective miRNA delivery with the help of "CAR recognition" mechanism. In our study, we found that CAR-T membrane-coated LNP not only enable the sequential delivery of miRNA to bone marrow and MM cells, but also enhance persistence of CAR-T by reprogramming TME, thus providing new opportunities for targeted precision therapy of MM. **Methods:** We engineered alendronate (ALN)-functionalized LNPs through microfluidic synthesis, followed by membrane extrusion-mediated fusion with BCMA-targeting CAR-T cell membranes to construct biomimetic CMLNP@miR-15a. This dual-targeting platform employs a sequential delivery mechanism: ALN-mediated bone marrow homing via hydroxyapatite binding precedes CAR-driven specific recognition of MM cells. This design strategy likely overcomes the barrier limitations between bone marrow and peripheral blood circulation, while synergistically leveraging CAR-T membrane targeting advantages for precise miRNA targeting delivery to MM cells. **Results:** The microfluidic-synthesized CMLNP@miR-15a exhibited uniform nanoparticle characteristics with a hydrodynamic diameter of 50-70 nm (PDI <0.5) and a ζ-potential of 39.0 ± 0.36 mV, as confirmed by transmission electron microscopy and dynamic light scattering. These characteristics facilitated the dispersibility and stability of CMLNP@miR-15a, and established a solid foundation for subsequent in vivo application. Comparative experiments demonstrated a 3.3-fold increase in bone marrow accumulation compared to conventional DSPE-PEG LNPs,

validating the ALN-mediated targeting efficacy. Furthermore, in vitro studies indicated the gradual release profile, high transfection efficiency, and enhanced targeting specificity of CMLNP@miR-15a towards MM cells. Taken together, our study demonstrated that CMLNP@miR-15a possesses exceptional bone marrow homing efficiency and MM cell-specific targeting capability, which suggests its potential as an effective strategy for precision gene therapy in MM. **Conclusions:** Our study established a sequential-targeted miRNA delivery system (CMLNP@miR-15a) that synergistically enhances CAR-T therapeutic outcomes through dual-targeting functionality. It also provides a new strategy for "miRNA+CAR-T cell therapy," which is expected to overcome the relapse post CAR-T therapy and promote the development of MM precision gene therapy.

OA-37

Novel NKp30-Directed Bispecific Natural Killer Cell Engagers Targeting GPRC5D or CD38 for the Treatment of Multiple Myeloma

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Introduction: T cell-based therapies have transformed the treatment landscape of multiple myeloma (MM), yet their efficacy can be hampered by cytokine release syndrome and T cell exhaustion. The engagement of other effector cell populations, such as Natural Killer (NK) cells, represents a promising complementary therapeutic strategy. NK cells distinguish healthy from stressed (virus-infected or malignantly transformed) cells by activating and inhibitory receptors. In this way, they contribute to immune surveillance by exerting cytotoxic activity and producing immunoregulatory cytokines. However, to evade immune recognition, tumor cells downregulate or shed activating ligands. To counteract this, bispecific NK cell engager (NKCE) have been developed to restore NK cell activation by simultaneously targeting an activating receptor, such as NKp30, and a tumor-associated antigen (TAA), and thereby promoting NK cell recruitment and activation at the tumor site. **Methods:** NKp30-specific nanobodies were processed into IgG-like NKCE harboring a Fab-fragment derived either from CD38 antibody daratumumab or G protein-coupled receptor family C group 5 member D (GPRC5D) antibody talquetamab. Both NKCE were produced in CHO-S cells and carry either a silent or an active Fc domain. Simultaneous binding of both, NKp30 and the TAA, was analyzed via flow cytometry using a NKp30-Fc fusion protein. NK cell-mediated tumor cell killing was measured in standard 51Cr release assays using different MM cell lines as targets. Antibody-mediated phagocytosis was analyzed with pHrodo-labeled tumor cells and monocyte-derived macrophages using live cell imaging. NK cell-induced cytokine release was investigated via ELISA. **Results:** A camelid-derived NKp30 nanobody was incorporated into NKCE targeting either CD38 [CD38´NKp30] or GPRC5D [GPRC5D´NKp30] on MM cells. The NKCE demonstrated binding comparable to daratumumab and talquetamab, respectively. In addition, they were capable of simultaneously engaging NKp30 and the corresponding TAA. Furthermore, both, [GPRC5D´NKp30] and [CD38´NKp30], induced effective NK cell-mediated tumor cell killing in the picomolar range. Of note, [GPRC5D´NKp30] also mediated potent tumor cell killing of MM cells with low levels of CD38 that could not be lysed by daratumumab or [CD38´NKp30]. Incorporation of an active Fc domain further enhanced these anti-myeloma effects and additionally induced robust phagocytosis of MM cells. Moreover, while our NKCE triggered some cytokine release by NK cells, the levels were significantly lower than those observed with talquetamab induced cytokine release of T cells. **Conclusions:** Our novel NKp30-targeting NKCE exhibit strong anti-myeloma activity, which can be further enhanced by co-engagement of Fc γ receptors. As a perspective, these NKCE may represent a strategy to further improve MM therapy, with potential application both as monotherapy and in combination with adoptively transferred NK cells.

OA-38

A Phase I/II Single Arm Study of Belantamab Mafodotin, Carfilzomib and Dexamethasone in Patients with Relapsed Multiple Myeloma (Mm): Primary Analysis. Amarc 19-02 Belacard Study

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Introduction: An increasing number of patients with MM are lenalidomide-refractory and double or triple-class exposed at first relapse, underscoring the need for novel agents with distinct mechanism of action. Belantamab Mafodotin (Belamaf, B), a first-in-class anti-BCMA antibody-drug conjugate, has demonstrated efficacy in heavily pretreated relapsed/refractory MM (RRMM). Its combination with carfilzomib and dexamethasone (Kd) may provide anti-myeloma synergistic activity. Here, we report the primary analysis of the BelaCarD study. **Methods:** BelaCarD is an ongoing, single-arm, multicentre phase I/II study evaluating an 8-weekly dosing schedule of B in combination with Kd in patients (pts) with RRMM after 1–3 lines of therapy. Treatment continues until disease progression. Corneal adverse events (AEs) are graded using the

keratopathy and visual acuity (KVA) scale; all other AEs are assessed per CTCAEv5. The primary objective is progression free survival (PFS). **Results:** As of Aug 2023, 70 patients have been enrolled. The median age was 69.8 years (range: 48–81); 27.1% had high-risk cytogenetics and 77.2% had received 2–3 prior lines of therapy. Double- and triple-class refractory disease were present in 11.4% and 8.6% of patients, respectively. Patients received a median number of 11 treatment cycles (range: 1–38). At primary analysis, 67% had discontinued therapy, primarily due to disease progression (40%). Treatment-related adverse events (AEs) occurred in 91% of patients, with grade (Gr) ≥3 in 70%. Grade ≥3 haematologic toxicity and infections occurred in 41% and 39.4%, respectively. Serious AEs (SAEs) were reported in 71%. Ocular symptoms (Blurred vision, photophobia, pain and dry eyes) occurred in 94%, with grade ≥3 events in 12.8%. KVA-defined ocular AEs were observed in majority of patients; BCVA reduction (any grade: 81.4%; grade 3: 37.1%; grade 4: 1.4%) and keratopathy (any grade: 75.7%; grade 3: 51%; grade 4: 0%). BCVA decline to 20/50 or worse in both eyes occurred in 8.5%. Overall, 78.6% (95% CI: 66.8–87.7%) achieved at least a partial response (PR) within the first two cycles, including very good PR (VGPR) or better in 34.3% (95% CI: 23.1–46.9%). The overall response was 82.9% (95% CI: 71.7–91.0) with a complete response rate of 41.4% (95% CI: 29.5–54.2). At a median follow-up of 27.4 months, the median PFS was 22.6 m (95% CI: 8.7–31.2 months) with 12- and 24-months PFS of 56.2% (95% CI: 43.7–67.0%) and 48.9% (95% CI: 36.2–60.4%). Median overall survival (OS) was not reached (95% CI: 32.6 – NA) with 12- and 24-month OS rates of 79.6% (95% CI: 68.0–87.4%) and 70.5% (95% CI: 57.5–80.2%). **Conclusions:** The primary analysis of the BelaCarD study demonstrates that BKd with an extended B dosing-schedule is effective and tolerable. These findings, alongside with other studies incorporating belantamab mafadotin into standard-regimen backbones, support its potential role in early lines of therapy for RRMM.

OA-39

Targeting PHF19 Inhibits Myeloma Progression and Increases IMiDs Sensitivity by Epigenetically Regulating MYC and IRF4 Pathway

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Introduction: Immunomodulatory drugs (IMiDs) basesd immunotherapy has greatly improved the prognosis of multiple myeloma (MM) patients. However, drug resistance remains a significant challenge, and MM is currently incurable. Epigenetic aberration is an important feature of MM, associated with disease progression and drug resistance, and urgently needed to be explored to lay the foundation for improving patient survival. **Methods:** We performed RNA-seq on primary CD138+ bone marrow mononuclear cells (BMMCs) from MM patients with differential responses to IMiD-based combination immunotherapy. PHF19 knockdown (KD) MM cell lines were generated. Cell proliferation, apoptosis and cell cycle upon PHF19 KD were measured using CCK-8 assay and flow cytometry. IMiDs sensitivity was evaluated in PHF19 KD cells. RNA-seq and ATAC-seq were conducted in PHF19 KD cells to further explore mechanisms. **Results:** RNA-seq analysis of myeloma patients' samples revealed that MYC pathway was activated in non-responders (n = 8) to immunotherapy compared to responders (n = 8). Through integrative analysis of upregulated genes in non-responders and survival-associated genes from the MMRF-CoMMpass dataset, we identified epigenetic regulator PHF19 as the top correlated gene with both therapy resistance and poor patient survival outcomes. PHF19 KD impaired cell proliferation and induced cell apoptosis in MM. Mechanistically, RNA-seq revealed significant downregulation of MYC target and Shaffer IRF4 pathways in PHF19-KD cells, partly mirroring the dysregulated signaling observed in non-responders' myeloma cells. Meanwhile, RT-qPCR and Western blot confirmed reductions of MYC and IRF4 at both mRNA and protein levels upon PHF19 depletion. Since PHF19 is an epigenetic regulator, we performed ATAC-seq in PHF19 KD cells and found widespread reduction in genomic accessibility at multiple gene loci. An integrated analysis of RNA-seq and ATAC-seq identified 391 overlapping genes, which enriched in cell cycle pathway. Notably, MYC and IRF4 were involved in those overlapping genes, indicating that PHF19 could maintain the expression of MYC and IRF4 directly through its epigenetic regulatory function. Downregulation of MYC and IRF4 are crucial for IMiDs-mediated cell cytotoxicity. Strikingly, we found that IMiDs sensitivity increased in PHF19 KD cells, in which IMiDs induced more pronounced suppression of MYC and IRF4. **Conclusions:** PHF19 expression was elevated in non-responders to combination immunotherapy. PHF19 directly regulated MYC and IRF4 by modulating gene accessibility. Targeting PHF19/MYC /IRF4 axis enhanced myeloma cell sensitivity to IMiDs, suggesting PHF19 as a promising epigenetic target to suppress myeloma progression and overcome drug resistance.

OA-40

A Novel Dual Proteasome and HDAC6 Inhibitor I3MV-8b Potentiates Anti-CD38 Monoclonal Antibody Efficacy in Multiple Myeloma

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Introduction: Anti-CD38 mAbs are key in multiple myeloma (MM) treatment, with D-VRD as frontline standard. But over 20% of patients develop resistance. Our prior research found I3MV-8b, a new dual proteasome/HDAC6 inhibitor with anti-MM effects. This study showed 8b boosts CD38 on MM cells, restores NK cell cytotoxicity, and enhances anti-CD38 mAb efficacy in MM treatment. **Methods:** The study used C57BL/KaLwRij and NK-humanized NSG mouse models to evaluate 8b's immunomodulatory effects and Dara-mediated ADCC efficacy in vivo. Mouse bone marrow immune profiling was done by multicolor spectral flow cytometry. An in vitro human NK-MM co-culture system used luciferase assays to assess antibody-dependent cytotoxicity. RNA-seq, ATAC-seq, and ChIP-seq were used to study epigenetic mechanisms. **Results:** Compound 8b demonstrated potent immunomodulatory effects in vivo. It expanded the populations of natural killer (NK) cells, $CD8^+$ T cells, dendritic cells, and γδT cells, and simultaneously enhanced the production of interferon-γ (IFN-γ) within the tumor immunosuppressive microenvironment. Concurrently, 8b attenuated the infiltration of myeloid-derived suppressor cells (MDSCs) and downregulated the TIGIT exhaustion markers on NK and $CD8^+$ T cells. Furthermore, 8b significantly enhanced the efficacy of anti-CD38 antibodies (Dara) in both NK-humanized NSG mouse models and human NK-MM co-culture systems. Considering the crucial role of CD38 antigen expression in therapy and the biological characteristics of 8b, a dual inhibitor of proteasome and histone deacetylase 6 (HDAC6), we evaluated the impact of 8b on CD38 expression in MM cells and explored the underlying mechanisms. Transcriptomic and flow cytometry analyses revealed that 8b induced CD38 upregulation in MM cell lines and primary cells. Mechanistically, Western blot analysis showed that 8b significantly increased CD38 levels by enhancing histone H3 lysine 27 acetylation (H3K27ac). Co-immunoprecipitation (Co-IP) data indicated that 8b disrupted the binding between H3K27ac and HDAC6. Chromatin immunoprecipitation sequencing (ChIP-seq) confirmed the enrichment of the CD38 enhancer, and integrated assay for transposase-accessible chromatin using sequencing (ATAC-seq) and ChIP-quantitative polymerase chain reaction (ChIP-qPCR) validated the epigenetically-driven transcriptional activation of CD38 in MM cells. Simultaneously, proteasome modulation counteracted PSMB4-driven CD38 degradation in patients resistant to the D-VRD regimen. Treatment with 8b significantly suppressed CD38 degradation. **Conclusions:** Our findings show I3MV-8b is a new therapeutic strategy. It overcomes MM resistance through dual epigenetic/proteasomal regulation. It activates CD38 transcriptionally via chromatin remodeling, stabilizes its protein expression, restores NK cytotoxicity synergistically (enhancing IFN-γ/suppressing TIGIT), and potentiates anti-CD38 antibody efficacy.

OA-41

Clinical Validation of Revised Diagnostic Criteria for Light Chain MGUS and Risk of Progression to Malignancy

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Introduction: Light chain monoclonal gammopathy of undetermined significance (LC-MGUS) is a precursor to LC multiple myeloma (MM) and other lymphoproliferative disorders (LPD). LC-MGUS is defined by an abnormal free light chain (FLC) ratio, elevated level of the involved LC, and absence of monoclonal heavy chain immunoglobulins and end-organ damage. Previous studies estimate an annual progression risk to malignant disease of 0.3%. However, the criteria for LC-MGUS were recently revised by the iStopMM study group, following updated FLC reference intervals. Here, we aim to evaluate the performance of the revised criteria to better characterize the natural history of LC-MGUS and identify risk factors associated with progression. **Methods:** We used data from the Danish Lymphoid Cancer Research (DALY-CARE) resource including individuals with LPD from Danish national registries. Identified cases were classified by which LC-MGUS criteria they met; A) original, B) revised, or C) only original (some overlapping in A and B). Outcomes were progression to LPD (MM, non-Hodgkin lymphoma, Waldenström's macroglobulinemia and AL amyloidosis). A subgroup analysis stratified individuals by involved/uninvolved FLC-ratio ≥10. Cumulative incidence of progression with death as competing risk was examined using Aalen-Johansen estimation, and hazard ratio (HR) of progression risk was assessed using Cox regression model adjusted for age and sex. **Results:** 359 individuals classified as LC-MGUS by original criteria, 214 by revised (of which 209 met both original and revised criteria and 5 only the revised), and 150 (41%) met only original criteria. In the revised group, 21 progressed during follow-up, hereof 11 to MM and 7 to AL amyloidosis. Only 2 progressed in the original-only group (none to MM or AL amyloidosis) yielding a significantly lower risk of progression (HR 0.08, 95% CI: 0.02–0.36)

compared to revised LC-MGUS. For revised LC-MGUS, the 2- and 5-year cumulative incidence of progression to LPD was 6% and 9.2%, respectively, thus an annual progression risk of approximately 1.8% the first 5 years. Comparing individuals with FLC-ratio ≥10 vs <10 did not show a significant difference in risk of progression to LPD (HR 0.99, 95% CI: 0.39–2.52): notably, only 2 of the 7 individuals, who progressed to AL amyloidosis, had a baseline FLC-ratio >10. **Conclusions:** This study validates the performance of the iStopMM revised criteria of LC-MGUS in a clinical cohort. Applying the revised criteria reduced LC-MGUS diagnoses by 41% with no progressions to MM or AL amyloidosis in the group no longer classifying as LC-MGUS. The annual progression risk of revised LC-MGUS was 1.8%, more comparable to that of conventional MGUS. FLC-ratio ≥10 was not an optimal predictor of progression in our cohort, especially failing to capture patients at risk of AL amyloidosis. This study illustrates the utility and validity of the revised definition of LC-MGUS and underscores the importance and need of more nuanced risk stratification for LC-MGUS.

OA-42

Clonotypic B Cells are Passengers During Malignant Transformation and not Drivers of Disease Progression in Plasma Cell (PC) Neoplasms

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Introduction: Whether multiple myeloma (MM) and light-chain amyloidosis (AL) stem from terminally differentiated PC or earlier clonotypic B cells remains under debate. Addressing this issue would improve accurate diagnosis and treatment monitoring. Therefore, our aim was to identify the cell of origin and tumor reservoirs containing driver genetic alterations within the B cell lineage of MM and AL patients. **Methods:** 18 healthy adults (HA), 22 MM and 17 AL patients (pts) were studied. Single cell RNA and B cell receptor sequencing (scRNA/BCRseq) was performed in sorted B cell precursors, mature B cells and PC. Exome sequencing was performed in sorted CD34 progenitors, B-cell precursors, mature B cells, normal and clonal PC, and T cells as control. **Results:** scRNA/BCRseq yielded paired transcriptomes and Ig gene rearrangements in 61,289 cells, classified into B cell precursors (n = 3,808), mature B cells (n = 28,589) and PC (n = 28,892). Surprisingly, tumor BCR were detected in 0.3% B-cell precursors from MM pts, and in 0.4% and 0.1% mature B cells from MM and AL pts. Phenotypic hallmarks of the B cell differentiation (eg, CD10, CD19, CD20 or CD138) were similarly expressed in non-tumor vs tumor-related B cell subsets. However, the latter showed on average 329 differentially expressed genes when compared to normal counterparts in HA. These results confirm the immature phenotype of clonotypic cells and uncover altered transcriptomes possibly due to the disturbed tumor microenvironment. Exome sequencing unveiled an average of ~30% somatic mutations shared between CD34 progenitors and normal PC from HA and pts. These data indicates a continuum of mutated cells throughout the normal and malignant B-cell lymphopoiesis. In AL, there were 30%, 34%, 31% and 28% shared mutations between clonal PC and CD34 progenitors, B cell precursors, mature B cells and normal PC. In MM, the respective percentages were 20%, 17%, 11% and 17%. Similar results were observed before and after transplant. Interestingly, driver mutations as well as copy number alterations were generally private in clonal PC, and absent in normal cell types from MM and AL pts. We hypothesized that clonotypic B cells with a normal phenotype could result in sporadic cases of NGS+/ NGF- MRD. Such pts should have PFS similar to double negative MRD patients because clonotypic B cells lacked key genetic alterations and therefore cannot drive relapse. Thus, we studied 103 MM pts enrolled in the GEM2012MENOS65 trial who had simultaneous MRD assessment by NGF and NGS. Of the 103 pts, 7 were NGF-/NGS+ despite MRD levels above the limit of detection of NGF. After a median f/up of 80 months, these patients had a median PFS not reached near to those who were NGF-/NGS-. Similar discordances were observed in AL pts. **Conclusions:** Our results define clonotypic B cells as passengers during the malignant transformation of PC neoplasms and not drivers of disease progression. These findings shed light on the pathogenesis and inform on how to monitor MM and AL pts.

OA-43

Monoclonal Gammopathy of Indeterminate Potential (MGIP) as an Early and Premalignant Stage in the Evolution Toward Hematological Malignancies

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Introduction: A newly characterized monoclonal entity, termed monoclonal gammopathy of indeterminate potential (MGIP), has been described in a racially diverse cohort of individuals at high risk for multiple myeloma (MM) through screening with matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS), a highly sensitive technique for detecting and quantifying monoclonal immunoglobulins (Ig). These cases predominantly involve low-level monoclonal gammopathies (MG) that fall below the detection threshold of conventional electrophoresis (<0.2 g/L). Here, we aimed to determine whether MGIP precedes multiple myeloma and other hematologic malignancies, and whether it represents a true premalignant condition. **Methods:** We performed MS on 2,194 serum samples from 491 individuals from the PLCO cohort, including 122 who progressed to MM and others with persistent monoclonal gammopathy of undetermined significance (MGUS) without progression. To further validate the persistence of MGIP, we also analyzed 932 samples from 461 individuals enrolled in the PROMISE screening study. Additionally, we performed single-cell RNA sequencing (scRNA-seq), single-cell B cell receptor sequencing (scBCR-seq) and whole-genome sequencing (WGS) on samples from individuals in the MS-tested cohorts, including PROMISE and PCROWD. **Results:** We observed that MGIP consistently preceded both MGUS and MM, and the persistence of MGIP was further validated in the PROMISE study. Longitudinal MS testing revealed the presence of multiple co-occurring monoclonal proteins (M-proteins) in individuals who progressed to MM and demonstrated dynamic patterns over time, including occasional switching of the dominant clone and isotype class at the individual level. Using scBCR-seq, we confirmed the presence of MM clones corresponding to distinct MGIP-level and MGUS-level M-proteins within a MM patient. Comparing V(D)J amino acid sequences of germline and tumor clones of this patient derived from WGS and scBCR-seq, respectively, along with phylogenetic reconstruction based on posterior probabilities of copy number events from scRNA-seq, suggested that clones producing MGIP-level M-proteins diverged earlier than those producing MGUS-level proteins. In additional two cases with persistent MGIP, we identified B cell clones that produced MGIP-level M-proteins and harbored known lymphoma-associated driver mutations using WGS, scBCR-seq, and scRNA-seq data, further supporting the premalignant potential of MGIP. **Conclusions:** We provide a comprehensive insight into low-level MG by demonstrating that MGIP is a non-transient, stable condition that precedes and may evolve into hematological malignancies. This study contributes to our understanding of clonal heterogeneity and dynamics prior to MM and may help guide future approaches for monitoring individuals at risk of progression.

OA-44

Genomics Define Neoplastic Transformation in Multiple Myeloma Precursor Conditions

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Introduction: Multiple myeloma (MM) is always preceded by precursor conditions—monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma (SMM). While common in adults, a subset of cases precursor conditions progress to MM. **Methods:** To identify genomic features underlying clinical behavior in MGUS and SMM, a total of 375 patients with SMM (n = 295) or MGUS (n = 80) with available whole exome (WES, n = 191) or whole genome sequencing (WGS, n = 184) were included in the study. Overall, none of the patients had evidence of SLiM or CRAB criteria at the time of the biopsy. Based on the center of origin, 98 patients were used to form our study validation set. The remaining patients were assigned to the training set (n = 277, 68 of were either lost to follow-up or enrolled in a clinical trial). **Results:** Based on the distribution of established MM-defining genomic events (Maura et al. JCO 2024), we identified in the training set 28 genomic features associated with progression into MM. Next, we used the training set to develop a workflow that differentiates MGUS and SMM into two genomically distinct entities: one with evidence of neoplastic transformation (i.e.,genomic MM) and one without (i.e., genomic MGUS). Overall, 39% of MGUS and 91% of SMM cases had genomic evidence of neoplastic transformation in the training set (i.e., genomic MM, gMM). Importantly, none of the patients with genomic-MGUS (gMGUS) experienced progression into MM in the training set. When we applied the same workflow and classification to the validation set, 46% and 83% of MGUS and SMM had evidence of neoplastic transformation, respectively. Importantly, also in the validations set none of the gMGUS experiences progression. Moreover, all patients with IMWG 2020 high risk SMM were

classified as gMM in both the training and validation set. Overall, these data demonstrated that the MM genomic background and neoplastic transformation can be acquired early in pathogenesis, even before the SMM phase. Finally, we identified four genomic features significantly associated with a shorter time to progression in patients with evidence of neoplastic transformation: RAS mutations, MYC translocations, APOBEC mutagenesis, and copy number complexity. Integrating these features with the 2020 International Myeloma Working Group (IMWG) model improved its predictive accuracy for progression risk to MM in both the training and validations set. **Conclusions:** Herein, we are introducing the concept that gMM can be identified much earlier in the MGUS/SMM stage. This observation and distinction will be of high importance in recognizing patients that may be considered for interventional trials. Furthermore, we demonstrated that integrating genomic and clinical features significantly enhances the prediction of clinical progression amongst MGUS/SMM patients who already have established gMM.

OA-45

Cell-Free BCL2 exRNA, but not MYC or MIZ1, Identifies Smouldering Myeloma with a High Risk of Progression among Patients in the Myeloma Related Disease Registry (MRDR)

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Introduction: Smouldering multiple myeloma (SMM) is a heterogeneous condition with various risk factors influencing disease progression. The widely used IMWG 2/20/20 risk score, although common in clinical practice, fails to accurately identify some patients who progress to active disease. This highlights the need for improved risk models that can more precisely identify high-risk patients for targeted intervention. While a perfect prognostic model may not be achievable, refining risk stratification strategies rooted in disease biology is crucial for identifying patients who need closer monitoring or early treatment. In this study, we developed a minimally invasive liquid biopsy approach to analyze the expression of MYC, MIZ1, and BCL2 in circulating extracellular RNA (exRNA). Peripheral blood samples were collected from the national M1000 liquid biopsy biobank, integrated with clinical data from the Myeloma and Related Diseases Registry (MRDR). **Methods:** We obtained plasma samples from 64 patients with smouldering multiple myeloma (SMM) enrolled in the M1000 project. Extracellular RNA (exRNA) was extracted from 3 mL of plasma, stored in Streck™ tubes, using the QIAamp Circulating Nucleic Acid Kit (QIAGEN) according to the manufacturer's instructions. Genomic DNA contamination was removed using the TURBO DNA-free™ Kit. Quantification of exRNA targets was performed using the QIAcuity Digital PCR System. Two housekeeping genes, GAPDH and HPRT1, were included to ensure data robustness and normalization. Expression levels of MYC, MIZ1, and BCL2 exRNA were then correlated with clinical outcomes, including progression, using data from the Myeloma and Related Diseases Registry (MRDR). High and low expression groups were defined based on the top and bottom tertiles of expression levels, respectively. **Results:** The SMM cohort included 64 patients with samples collected between November 2014 and September 2021. To date, 21 out of the 64 patients have progressed to multiple myeloma (MM), with the median time to progression not reached (range: 2–48 months). Among patients with high BCL2 exRNA expression (top tertile), 12 out of 20 (60%) progressed, with a median time to progression of 41 months and a hazard ratio of 4.152 ($p = 0.0064$). In contrast, MYC and MIZ1 exRNA levels showed no statistically significant association with progression risk, suggesting that these markers may have limited prognostic value when assessed in peripheral blood. **Conclusions:** High BCL2 exRNA expression in peripheral blood appears to be a potential risk factor for progression from smouldering multiple myeloma to symptomatic disease. These findings warrant validation in larger, independent cohorts. If confirmed, BCL2 exRNA could serve as a valuable biomarker to identify high-risk patients who may benefit from early, targeted therapeutic intervention with BCL2 inhibitors, thereby potentially improving outcomes by reducing the risk of progression.

OA-46

Multicenter Phase 2 Study of Subcutaneous Isatuximab Plus Bortezomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma: Results from ISASOCUT (IFM 2022–05)

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Introduction: Isa-VRd has emerged as a new standard of care (SOC) in transplant-ineligible (TI) newly diagnosed multiple myeloma (NDMM) based on the BENEFIT and IMROZ studies. A subcutaneous (SC) formulation of Isatuximab is currently being evaluated in the phase 3 IRAKLIA study (Isa SC-Pd vs. Isa IV-Pd) in relapsed/refractory multiple myeloma. Here, we present the first report on the efficacy and safety of Isa SC-VRd in NDMM TI patients. **Methods:** ISASOCUT is a prospective, multicenter, open-label, phase 2 study in NDMM TI patients (≥65 years). The initial treatment regimen (cycles 1 to 12) included fixed-dose SC isatuximab administered weekly during cycle 1, then on days 1 and 15 of subsequent cycles. Lenalidomide (25 mg daily, orally) was given on days 1 to 21, dexamethasone (20 mg weekly, orally), and bortezomib (1.3 mg/m^2 SC) biweekly in cycle 1, then weekly thereafter. From cycle 13 onward, isatuximab was administered once monthly (day 1) while lenalidomide dosing remained unchanged. Each cycle lasted 28 days. The primary objective was to assess the ≥ very good partial response (VGPR) rate at 8 months post-cycle 1 day 1. Key secondary endpoints included survival outcomes, response rates and durations, MRD assessments at 8 months (NGS + PET-CT), and safety. Data were analyzed using an intention-to-treat (ITT) approach. **Results:** At data cutoff (January 13, 2025), 74 patients had been enrolled across 23 IFM centers. The median age was 73 years (IQR: 66–83); 25 patients (34%) were >75 years old, 16 (22%) had high-risk (HR) cytogenetics (per the new IMS consensus), 14 (19%) had ISS stage 3 disease, 13 (18%) had R-ISS stage 3 disease. The ≥VGPR rate at 8 months, the primary endpoint, was 87.8% (n = 65) [95% CI, 78–94], consistent with the IMROZ and BENEFIT studies, and observed across all weight subgroups. The ≥CR rate was 24% (n = 18), while MRD negativity rates were 35.1% (n = 26) at 10^{-5} and 27% (n = 20) at 10^{-6}. At a median follow-up of 11.73 months, 4 patients (5%) had discontinued therapy, no relapses had occurred, and 2 patients (3%) had died. Survival data remain immature. Treatment adherence was high, with a relative dose intensity ≥90% for Isa SC (91.8% [range: 53.3–111]). Nearly all Isa SC administrations (99.7%) using the on-body delivery system (OBDS) were successfully completed without injection interruptions. Isa SC did not introduce any new safety concerns. Infusion related reactions occurred in seven patients (9.5%), mostly grade 1. Injection site reactions were reported in 20 patients (27%), with 89.5% being grade 1 and the remaining cases grade 2. Neurological adverse events (all grades) were reported in 35 patients (47.3%). **Conclusions:** The ISASOCUT study met its primary endpoint, demonstrating consistent efficacy of isatuximab in NDMM TI patients, regardless of SC or IV administration. These results support Isa SC-VRd as a new SOC for NDMM TI, offering a longer but less dose-intensive induction regimen compared to IMROZ.

OA-47

Updated Efficacy and Safety Results of Subcutaneous Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Therapy in Newly Diagnosed Multiple Myeloma After Transplant: AURIGA Study

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Introduction: Lenalidomide (R) maintenance (maint.) is the current standard of care following autologous stem cell transplant (ASCT) for patients (pts) with multiple myeloma (MM). Per the primary analysis of the phase 3 AURIGA trial (NCT03901963), addition of subcutaneous daratumumab (DARA SC) to R maint. (D-R) in anti-CD38–naïve pts who were minimal residual disease (MRD) positive (pos) post-ASCT improved MRD-negative (neg) conversion by 12 mo and progression-free survival (PFS) compared to R maint. alone (presented at IMS 2024). Herein, updated AURIGA efficacy and safety results are reported at 24 mo from start of maint. **Methods:** Eligible pts with newly diagnosed MM were aged 18–79 yr, in very good partial response or better (≥VGPR) and MRD pos (10–5; NGS) post-ASCT, and anti-CD38 naïve; received ≥4 induction cycles; and enrolled within 6 mo of ASCT. Pts were stratified by cytogenetic risk and randomized 1:1 to 28-d cycles of R maint. ± DARA SC for ≤36 cycles or until progression, unacceptable toxicity, or withdrawal. The primary endpoint was MRD-neg (10–5)

conversion by 12 mo from maint. start. **Results:** 200 pts were randomized (D-R, n = 99; R, n = 101). Baseline characteristics were balanced between groups. Both groups had received a median of 5 induction cycles (range, 4–8) before study entry. A median of 36.0 and 25.5 maint. cycles has been received by D-R and R pts, respectively; 88.5% and 78.6% completed 12 cycles, and 78.1% and 53.1% completed 24 cycles. At a median follow-up of 40.3 mo, D-R maint. continued to demonstrate higher MRD-neg conversion rates versus R, both at 10–5 (60.6% vs 28.7%; OR, 3.92 [95%CI, 2.16–7.14]; P < 0.0001) and 10–6 thresholds (36.4% vs 13.9%; OR, 3.59 [95%CI, 1.78–7.23]; P = 0.0003). MRD-neg (10^{-5}) conversion rates with complete response or better were 55.6% for D-R and 23.8% for R (OR, 4.11 [95%CI, 2.23–7.59]; P < 0.0001). D-R maint. led to doubling of the ≥6-mo sustained MRD-neg (10^{-5}) conversion rate (D-R 42.4% vs R 17.8%; OR, 3.45 [95%CI, 1.80–6.61]; P = 0.0002) and tripling of the ≥12-mo sustained rate (29.3% vs 7.9%; OR, 4.88 [95%CI, 2.09–11.38]; P = 0.0001) versus R alone. Per investigator assessment, a 45% reduction in the risk of disease progression or death was seen with D-R versus R (HR, 0.55 [95%CI, 0.33–0.91]; P = 0.0183), with estimated 36-mo PFS rates of 76.8% for D-R and 61.4% for R. Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 75.0% of D-R pts and 73.5% of R pts, with neutropenia (49.0% vs 45.9%) and infections (19.8% vs 14.3%) being the most common. Serious TEAEs occurred in 31.3% of D-R pts and 25.5% of R pts, while TEAEs led to maint. discontinuation in 12.5% of D-R pts and 9.2% of R pts. Grade 5 TEAEs occurred in 2 D-R pts and 1 R pt (all infections). **Conclusions:** Updated efficacy and safety data from AURIGA continue to demonstrate the value of adding DARA SC to R maint., as evidenced by continued higher MRD-neg conversion rates and a PFS benefit, with no new safety signals observed.

OA-48

Final Analysis of the GEM-BELA-VRd Phase II Trial: Belantamab Mafodotin Plus VRd in Newly Diagnosed Transplant-Eligible Myeloma After 2 Years of Maintenance with Belantamab and Lenalidomide

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Introduction: Initial results from the GEM-BELA-VRd trial showed that adding belantamab mafodotin (belamaf) to VRd in newly diagnosed transplant-eligible multiple myeloma (NDTE-MM) patients resulted in high rates of deep responses, including complete responses (CR) and minimal residual disease (MRD) negativity. Ocular events (OEs) were common but reversible and manageable. We report the final analysis after 2 years of belamaf-lenalidomide (len) maintenance. **Methods:** GEM-BELA-VRd is a phase II, open-label, multicenter trial evaluating belamaf (2.5 mg/kg IV Q8W) with VRd for 6 induction cycles, followed by autologous stem cell transplant (ASCT), 2 consolidation cycles with belamaf-VRd (2.5 mg/kg IV Q8W), and maintenance with continuous len plus belamaf (1.9 mg/kg Q8W) for up to 2 years. Primary endpoint: safety; secondary endpoints: ORR, CR, MRD negativity, TTP, PFS and OS. Data cutoff: April 28, 2025. **Results:** Fifty patients were enrolled; 9 discontinued prior maintenance, and 41 (82%) initiated it. No new safety signals emerged during maintenance. OEs were less frequent than in previous phases. Among patients with normal best corrected visual acuity (BCVA) at baseline, 11 patients had a decrease to 20/50 or worse in the first year, and 5 in the second year. Only 1 patient reached 20/200, during the first year, recovering within one month. All OEs resolved, with median recovery time of 75 days and full resolution in 175 days (range, 35–476), except in 3 patients with ongoing follow-up and improved BCVA from 20/50. Grade ≥3 neutropenia occurred in 36% in the first year, decreasing to 22% in the 2nd year. Grade ≥3 thrombocytopenia was stable (14%–12%). Grade ≥3 infections occurred in 18% in the first year and 8% in the second one. Four patients discontinued maintenance due to toxicity (cytopenias or infections), occurring in both years. Median follow-up (FU) was 40.0 months (range 36.2–49.0). In the ITT population (n = 50), best ORR was 96%, CR 80%, and MRD negativity 88%. In a per-protocol analysis, MRD negativity was 87.8% at the end of consolidation (n = 41), 91.9% after the first year of maintenance (n = 37), and 93.9% after the second year (n = 33). At last FU, only 3

patients had progressed: one at 7 months (triple-hit), two at 26 and 33 months, with 3-year TTP: 93%. Ten patients died: 5 from infections (4 COVID-19, 1 sepsis), 2 from progression, 1 from inflammatory colitis during induction, 1 unknown and 1 unrelated, with 3-yr PFS: 78% and 3-yr OS: 82%. **Conclusions:** Final analysis of this pilot study of Belamaf-VRd followed by continuous len plus up to 2 years of belamaf confirms deep responses in NDTE-MM patients, with high rates of CR and MRD negativity. OEs and hematological AEs were manageable and belamaf appeared not to add toxicity to len maintenance. Infections, particularly COVID-19, had a notable impact on the trial, influencing outcomes and safety. These results support further evaluation of belamaf in the frontline setting.

OA-49

Insights from Cytogenetic Subgroup Analyses in the GMMG-CONCEPT trial with Isa-KRd in High-Risk Newly Diagnosed Multiple Myeloma

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Introduction: High-risk (HR) multiple myeloma (MM) patients (pts) continue to show impaired survival compared to standard risk pts with newly diagnosed (ND) disease and are therefore in need of novel effective treatment options. The academic, multi-center phase II GMMG-CONCEPT trial (NCT03104842) investigates the quadruplet isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in ND HR MM both transplant-eligible (TE) and ineligible (TNE) pts and is the largest prospective HR trial. We have previously shown high rates of minimal residual disease (MRD) negativity with overall MRD-negativity rates of 86.8% [TE] and 69.2% [TNE] (Leypoldt et al.). Here, we report detailed outcomes from the different HR cytogenetic subgroups of the whole cohort. **Methods:** HR MM was defined by ISS stage 2 or 3 and any of del17p, t(4;14), t(14;16), or ≥3 copies 1q21 (gain1q). Isa-KRd induction (6 cycles), high-dose therapy (for TE pts; 2 cycles Isa-KRd for TNE pts) and consolidation (4 cycles) are followed by 2 years of Isa-KR maintenance. MRD is centrally assessed by next-generation flow with a sensitivity level of 10–5. Clinical data cutoff was 28.04.2025. **Results:** The trial included 245 HR NDMM pts (219 TE, 26 TNE) with a median age of 59.6 (TE) and 74.9 years (TNE); del17p (40.8%) and gain1q (47.3%) were the most common HR cytogenetic aberrations, followed by t(4;14) and t(14;16) (35.1% and 15.5%, respectively). Eighty-five pts (34.7%) had ≥ 2 HRCA; of these, the most frequent double-hit combinations were del(17p) + gain1q (26 pts, 10.6%) and t(4;14) + gain1q (36 pts, 14.7%). As reported, the primary endpoint of MRD-negativity at the end of consolidation was achieved in 74.8% (TE) and 69.2% (TNE) of pts. With regards to HRCA subgroups (in TE pts only due to sample size), the majority demonstrated a similar distribution, including pts with del(17p) and ≥2 HRCA with only slightly lower rates (65.5% [57/87] and 68% [51/75], respectively). Lowest MRD-negativity rates, however, were observed in pts with del(17p) + gain1q (54.2%; 13/24), del(17p) + t(4;14) (46.7%; 7/15), and del(17p) + t(14;16) (37.5%, 3/8), strikingly all marking del(17p) double-hit. In contrast, highest rates of MRD-negativity were seen in pts with t(4;14) only (82.8%, 24/29), pts without del(17p) (81.1%, 99/122), or pts with gain1q + t(14;16) (80%, 12/15). Detailed MRD kinetics (incl. induction, intensification, maintenance) will be presented. **Conclusions:** These data from our CONCEPT trial underline the high potency of Isa-KRd to induce high rates of MRD-negative remissions across different cytogenetic subgroups in HR NDMM pts. An unmet need still remains for patients with double-hit HRCA including del(17p) whereas e.g. pts with gain1q seem to be adequately addressed by this isatuximab-containing regimen. Sponsor: University Medical Center Hamburg-Eppendorf. Funding and IMP: Sanofi, Amgen, BMS/Celgene.

OA-50

Iberdomide, Daratumumab, and Dexamethasone (IberDd) in Transplant-Ineligible/Deferred (TNE) Newly Diagnosed Multiple Myeloma (NDMM): Updated Results from the CC-220-MM-001 Trial

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Introduction: Lenalidomide (LEN) plus daratumumab (DARA) and dexamethasone (DEX) is a standard-of-care treatment for TNE NDMM. Iberdomide (IBER) is an oral CELMoD™ agent with greater potency than LEN; it binds cereblon with higher affinity, leading to more efficient cereblon conformational changes resulting in faster and greater Ikaros/Aiolos degradation and enhanced tumoricidal and immunostimulatory activity. Efficacy and tolerability of IberDd in patients (pts) with relapsed/refractory multiple myeloma (RRMM) have been shown in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030). IberDd also showed high efficacy and a manageable safety profile across dose levels in a cohort of pts with TNE NDMM. Here we report an updated analysis of this pt population with extended follow-up. **Methods:** Eligible pts were adults with untreated NDMM and with no planned or were ineligible for autologous stem cell transplant. Pts were randomized 1:1:1 to receive oral IBER doses of 1.0, 1.3, or 1.6 mg on days (D) 1–21 of each 28-day cycle (C) combined with DARA (1800 mg) on D1, 8, 15, and 22 in C1–2, on D1 and 15 in C3–6, and on D1 in ≥C7, plus weekly DEX (40 mg; 20 mg if >75 years of age). Efficacy, safety, and minimal residual disease (MRD) were assessed. **Results:** As of March 3, 2025, 75 pts in this cohort received IberDd. Of these, 44 (58.7%) were aged ≥75 years and 31 (41.3%) had high-risk cytogenetics. Median follow-up was 22.3 (range, 0.4–28.5) months and 50 (66.7%) pts remained on therapy; pts discontinued due to adverse events (AEs) (9 [12.0%] pts), progressive disease (7 [9.3%] pts), pt withdrawal (4 [5.3%] pts), death (3 [4.0%] pts), and physician decision (2 [2.7%] pts). Median treatment duration was 22.3 (range, 0.3–29.0) months. Safety data were consistent with the primary analysis. Grade (Gr) 3/4 treatment-emergent AEs (TEAEs) were observed in 73 (97.3%) pts; Gr 3/4 hematologic TEAEs were observed in 63 (84.0%) pts, with neutropenia being the most common (78.7%). Excluding infections (52.0%), non-hematologic Gr 3/4 events were infrequent. The overall response rate was 94.7%. Since the primary analysis, pts sustained durable responses that deepened over time; complete response (CR) or better was observed in 51 (68.0%) pts and very good partial responses were observed in 15 (20.0%) pts. Median time to response for responders was 4.1 (range, 4.0–49.0) weeks. Median duration of response and median progression-free survival were not reached. Overall, 64.0% (48/75) pts achieved MRD negativity, and 56.0% (42/75) pts achieved MRD-negative CR (10-5 threshold) in the intention-to-treat population. **Conclusions:** With additional follow-up, IberDd continued to show high efficacy and a manageable safety profile with no new safety signals in TNE NDMM. Pts experienced durable responses that deepened over time. These data support further evaluation of IberDd in NDMM. IberDd is also being investigated in the ongoing phase 3 EXCALIBER-RRMM (NCT04975997) trial.

OA-51

Carfilzomib, Lenalidomide, and Dexamethasone (KRd) after Autologous Stem-Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma: Analysis of High-Risk Subset in Phase 3 ATLAS Trial

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Introduction: Maintenance treatment after autologous stem cell transplantation (ASCT) prolongs remission and may prolong survival. Post-ASCT maintenance with lenalidomide (R) monotherapy is established as the current standard of care. The role of multi-agent maintenance is currently intensively evaluated. Here we report final results from the primary analysis of the phase 3 ATLAS trial, which compared post-ASCT KRd vs R, with post-hoc analysis of subset of patients with high-risk cytogenetics. **Methods:** This international, open-label phase 3 study randomly assigned patients who completed induction and had stable disease or better after ASCT to KRd or R alone (1:1 ratio) as maintenance therapy. Randomization was stratified by post-ASCT very good partial response or better, presence of at least one high-risk cytogenetic abnormality [del(13) (q14), t(4;14)(p16;q32), t(14;16)(q32;q23), del(17)(p13.1), or hypodiploidy)], and by treatment country. For the KRd group, patients with standard-risk cytogenetics and measurable residual disease (MRD) negativity at 10^{-5} after cycle 6 were switched to R maintenance after cycle 8; remaining patients continued KRd up to 36 cycles and then switched to R. The primary endpoint was PFS from randomization. Secondary endpoints included OS and MRD negativity. **Results:** One hundred and eighty patients were randomized (92 to KRd and 88 to R alone). At the data cutoff (21 Oct 2024), median follow-up was 5.7 years. After cycle 8, 40 of 81 patients on KRd switched to

R. For all randomized patients, PFS was superior for KRd vs R, with 4-year PFS of 67.5% vs 38.0% (median, 72.8 vs 37.3 months; hazard ratio [HR] 0.46 [95% CI: 0.30, 0.70]; p = 0.0002). In post-hoc analysis, the PFS benefit was consistent across most of the categories, including 40 patients (22 in KRd and 18 in R) with high-risk cytogenetics (HR 0.52 [95% CI: 0.24, 1.1]). Across all subsets, deeper and more sustained responses were achieved with KRd vs R: rate of MRD < 10- 5 and at least a complete response improved over time and as best response was 73% vs 51% (odds ratio [OR] 2.56 [95% CI: 1.37, 4.77]; p = 0.003). Among the high-risk patients, MRD-negativity rates improved from screening to cycle 6 in those treated with KRd (8 converted to MRD-negative and none lost it; p = 0.013), while no change was observed in the R arm (1 gained and 1 lost MRD negativity), suggesting that KRd may be more effective in deepening responses also in this subset of patients. In all randomized patients, OS was longer with KRd compared to R, demonstrating 4-year OS of 84.3% vs 79.2% (median, not reached vs 82.2 months; HR 0.49 [95% CI: 0.26, 0.90]; p = 0.023. However, this OS was not statistically significant in a high-risk subset of patients. No new safety signals were observed. **Conclusions:** In addition to a superior PFS and OS from the primary analysis of all randomized patients in phase 3 ATLAS trial of post-transplant KRd vs R, this post-hoc analysis shows PFS benefit also in a subset of high-risk patients.

OA-52

Updated Results of a Phase 1 First-in-Human Study of Cemsidomide (CFT7455), a Novel MonoDAC® Degrader, with Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Cemsidomide is a highly potent Ikaros Family Zinc Finger Protein 1/3 (IKZF1/3) cereblon-based degrader. Cemsidomide has demonstrated best-in-class activity in multiple myeloma (MM) preclinical models and has also been shown to stimulate immune activation. **Methods:** CFT7455-1101 (NCT04756726) is an open-label, phase 1/2, multi-center, first-in-human study evaluating safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of cemsidomide in patients (pts) with RRMM and R/R NHL. MM eligible pts must have received lenalidomide, pomalidomide, a proteasome inhibitor, and an anti-CD38 antibody. The primary objective of this portion of the phase 1 study is to characterize the safety of cemsidomide with dexamethasone (DEX) and to determine the maximum tolerated dose and/or recommended doses for phase 2. Secondary objectives include overall response rate (ORR) according to the International Myeloma Working Group (IMWG) response criteria, PK, and PD. Dose escalation was guided by a Bayesian logistic regression model. **Results:** As of April 30, 2025, 64 pts have been treated with cemsidomide at various doses on a 14 day on/14 day off schedule plus DEX (20 or 40 mg weekly) in the dose escalation study. The median age was 67 (range 39–82) and pts had a median of 7 prior lines (range 3–22). 45/64 pts (70%) received prior CAR-T or a bispecific antibody. 20/64 pts (31%) had high-risk disease at screening and 19/64 pts (30%) had extramedullary disease. Systemic exposure of cemsidomide increased dose proportionally. At all dose levels, cemsidomide produced high levels of degradation of IKZF1 and IKZF3 (greater than 50% and 80%, respectively). 4 dose-limiting toxicity events have been observed (one pt in the 62.5 µg cohort and 3 pts in the 100 ug cohort). 77% of pts experienced grade ≥3 TEAEs. Grade 3–4 TEAEs occurring in ≥10% of pts included neutropenia (56%), anemia (25%), infections (28%), lymphopenia (11%), and thrombocytopenia (11%). The majority of grade ≥3 TEAEs occurred in cycles 1–2. 39% of pts received G-CSF and only 8% of pts experienced grade 3–4 febrile neutropenia. 1 pt had an AE resulting in dose reduction and 1 pt had an AE resulting in discontinuation. The ORR among efficacy evaluable pts is 33% (21/63) with 10 additional pts achieving minimal response for a clinical benefit rate of 49%. The ORR is 40% (8/20) at 75 ug and 50% (5/10) at 100 ug, where 1 pt had an MRD (−) CR. 100 ug has been declared safe with 10 additional patients enrolling, and no further dose escalation is planned. **Conclusions:** Cemsidomide with DEX demonstrates compelling efficacy and tolerability as an all-oral therapy in a heavily pre-treated RRMM population, the majority of whom had received a CAR-T or bispecific antibody. Grade 3-4 toxicities consist largely of cycle 1-2 myelosuppression, which has been manageable with limited dose reductions and discontinuations. 100 ug is the maximum administered dose for planned further development.

OA-53

Functional High-Risk (FHR) Phenotype Predicts Poor Survival in Multiple Myeloma (MM) Independent of Frontline Treatment: A Secondary CIBMTR Analysis

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Introduction: FHRMM following autologous stem cell transplantation (ASCT) is generally defined as early progression within 12–24 months of ASCT. For patients (pts) with early progression after suboptimal 1L therapies, it is challenging to assign the disease progression to a true FHR phenotype vs less effective 1 L therapy. While the impact of FHRMM on overall survival (OS) in pts with MM is well established, it is unclear how the 1L treatment path leading to FHRMM impacts subsequent OS. **Methods:** We screened all CIBMTR MM studies with publicly available data (N = 11) and included 3 studies that reported induction therapy prior to 1 L ASCT (MM18-02, MM19-01, and MM20-03). We included pts with FHRMM who received 1L ASCT from 2013–2018, and had progression <12 (FHR12), <18 (FHR18), or <24 months (FHR24) after ASCT. To avoid duplication across studies, we created a unique patient ID using age, sex, race, and ISS stage. We classified induction therapy as standard lenalidomide-containing triplets (VRD/KRD) vs other (VTD/VCD/VD/RD). We studied the impact of 1 L therapy on OS, measured from first relapse (establishment of FHR status) until death from any cause using the Kaplan-Meier method. We assessed the impact of 1 L therapy, age, sex, race, Karnofsky performance status, ISS stage, cytogenetic risk, renal impairment, pre-ASCT response, and year of ASCT on OS using univariable analyses, and included variables with $p < 0.05$ in the multivariable Cox model. **Results:** A total of 465 pts with FHR12 were included; 32% had ISS stage III disease, and 43% had high-risk cytogenetics [t(4;14), t(14;16), t(14;20), del(13q), del(17p), gain(1q), or del(1p)] at diagnosis. Overall, 51% had achieved ≥VGPR before ASCT and 93% received melphalan 200 mg/m^2. The median (m) follow-up was 48 months (95% CI: 37–53), and mOS was 20 months (95% CI: 14–21). The mOS in the VRD/KRD cohort (n = 238) was 21 months (95% CI: 14–31) vs 17 months (95% CI: 12–25) with the other 1 L regimen cohort [n = 227, hazard ratio (HR) 1.2 [95% CI: 0.6–1.06], p = 0.16). In the multivariable model adjusting for age, race, cytogenetic risk, and ISS; the HR for OS was 0.94 (95% CI: 0.7–1.3, p = 0.69) for VRD/KRD vs other regimens. There was no significant interaction between type of 1 L therapy and time from 1 L ASCT to first relapse in predicting OS (HR for interaction term 1.02 [0.9–1.09], p = 0.56). Analyses for FHR18 (n = 672) and FHR24 (n = 853) demonstrated a statistically non-significant difference in the adjusted HRs for OS with VRD/KRD vs other regimens (FHR18 HR 0.8 [0.6–1.04], p = 0.1; FHR24 HR 0.86 [0.7–1.08], p = 0.2). Likewise, there were no significant interactions between type of 1L therapy and time from ASCT to relapse in both these cohorts. **Conclusions:** Among pts with MM undergoing ASCT, the 1L treatment path leading to FHR status did not impact subsequent OS. Early relapse remains a negative prognostic factor irrespective of 1L therapy and warrants consideration of novel immunotherapies as the next line of treatment.

OA-54

Efficacy of Mezigdomide Plus Dexamethasone and Bortezomib or Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma by Line of Therapy: Results from the Phase 1/2 CC-92480-MM-002 Trial

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Introduction: Mezigdomide (MEZI) is an oral CELMoD™ agent with antitumor and immunostimulatory therapeutic effects that has shown promising activity in combination with dexamethasone (DEX) in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM) (Richardson P, et al. N Engl J Med 2023;389:1009–1022). Here we report efficacy data by number of prior lines of therapy (LOTs) among patients with RRMM who were treated with MEZI plus bortezomib and DEX (MeziVd) or MEZI plus carfilzomib and DEX (MeziKd) in the phase 1/2 CC-92480-MM-002 trial (NCT03989414, EUCT 2023-505219-19). **Methods:** Adult patients with RRMM received 0.3, 0.6, or 1.0 mg oral MEZI on days 1–14 of each 21-day cycle plus subcutaneous bortezomib and oral DEX (MeziVd; dose-escalation cohort A,

N = 28); 0.6 or 1.0 mg oral MEZI on days 1–14 of each 21-day cycle plus subcutaneous bortezomib and oral DEX (MeziVd; dose-expansion cohort D, N = 49); or 0.3, 0.6, or 1.0 mg oral MEZI on days 1–21 of each 28-day cycle plus intravenous carfilzomib and oral DEX (MeziKd; dose-escalation cohort C, N = 27). All patients had received prior lenalidomide (≥2 consecutive cycles). The primary objectives of the trial were to determine the recommended dose and regimen of MEZI and to evaluate safety and preliminary efficacy. **Results:** Patients in cohorts A, D, and C (N = 104) had received 1 (n = 31), 2 (n = 43), 3 (n = 23), or 4 (n = 7) prior LOTs. Prior LOTs included immunomodulatory drug (IMiD®) agents (100%), proteasome inhibitors (94.2%), and anti-CD38 monoclonal antibodies (52.8%). Median (range) follow-up for progression-free survival (PFS) was 16.6 mo (1.2–42.2), 12.3 mo (1.0–38.0), 9.0 mo (0.7–60.4), and 9.2 mo (1.5–13.8) among patients with 1, 2, 3, and 4 prior LOTs, respectively. Overall response rates were >70% regardless of the number of prior LOTs: 1 LOT, 83.9% (n = 26); 2 LOTs, 88.4% (n = 38); 3 LOTs, 73.9% (n = 17); 4 LOTs, 71.4% (n = 5). Complete response (CR) or better was observed in 8 (25.8%), 11 (25.6%), and 2 (8.7%) patients with 1, 2, and 3 prior LOTs, respectively; no patients with 4 prior LOTs achieved CR or better. Median (95% confidence interval) PFS was 19.4 mo (10.0–not reached), 12.9 mo (10.2–20.1), 13.0 mo (5.8–31.6), and 9.2 mo (1.5–11.8) among patients with 1, 2, 3, and 4 prior LOTs, respectively; PFS rates (standard error) at 12 mo were 64.1% (9.2), 54.3% (7.8), 58.3% (10.8), and 14.3% (13.2), respectively. **Conclusions:** In this population of patients with RRMM, many were previously exposed to IMiD agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies; a majority of patients treated with MeziVd or MeziKd achieved PR or better, regardless of the number of prior LOTs. Patients receiving up to 3 prior LOTs experienced durable PFS, with median PFS >1 year in each group and 19.4 mo for patients with 1 prior LOT. These data support further investigation of MeziVd and MeziKd in the phase 3 SUCCESSOR-1 (NCT05519085) and SUCCESSOR-2 (NCT05552976) clinical trials.

OA-55

Treatment Patterns and Outcomes in Quad-Class Exposed (QCE) Relapsed Refractory Multiple Myeloma (RRMM): Investigating Critical Unmet Needs

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Introduction: RRMM patients (pts) whose disease relapsed after or is refractory to treatments with proteasome inhibitors (PI), immunomodulatory drugs (IMiD), anti-CD38 antibodies, and anti–B-cell maturation antigen (BCMA) targeting therapies have poor prognoses without an established standard of care. We investigated therapies utilized in real-world practice and associated outcomes for this population, thereby establishing a benchmark for developing novel therapies. **Methods:** This retrospective study used data from the Flatiron Health electronic health record database (Jan 1, 2011–Dec 31, 2024) derived from US oncology clinics. Eligible pts were ≥18 years with an MM diagnosis and received ≥3 prior lines of therapy (LOT)—including a PI, IMiD, anti-CD38 antibody, and anti-BCMA therapy—and initiated a subsequent therapy (index date). Pts who received prior anti-GPRC5D therapy or investigational drugs on or after index date were excluded. Patients who had CNS myeloma involvement, plasma cell leukemia, Waldenstrom's macroglobulinemia, or other invasive malignancy not in remission for ≥2 years before index date were also excluded. Descriptive statistics summarized patient characteristics and treatment patterns. Event (ie, progression, initiation of next treatment, or death)-free survival (EFS) and overall survival (OS) were estimated using the Kaplan–Meier method. **Results:** 130 QCE RRMM pts were included: the median age was 68 yrs (range 41–85), 96.9% were RISS stage II–III, 29.2% had high tumor burden (≥50%), and 40.8% exhibited high-risk cytogenetics. Pts had a median of 6 prior lines of therapy (range 3–15): 90% were triple-class (PI, IMiD, CD38) refractory, and 53.8% were quad-class (PI, IMiD, CD38, BCMA) refractory. Index therapies were given between 2020 and 2024 in community (50.8%), academic (43.8%), or both (5.4%) practice settings. The top 5 index therapy classes were infusional chemotherapy (13.8%), anti-BCMA (BsAb, ADC, CAR T; 13.1%), GPRC5D BsAb (11.5%), PI+chemotherapy (6.9%), and PI + anti-CD38 (6.9%). The top 5 index therapy agents were talquetamab (11.5%), teclistamab (8.5%), carfilzomib+isatuximab (4.6%), carfilzomib (3.8%), and cisplatin+cyclophosphamide+etoposide (3.8%). After a median follow-up of 8.8 mo (range 0.2–49.2), 101 (77.7%) pts had an EFS event, and 69 (53.1%) pts died. Median EFS and OS were 4.5 mo (95% CI, 3.5–6.2) and 13.4 mo (95% CI, 10.2–23.2), respectively. For pts receiving anti-BCMA post-QCE, median EFS was 4.9 mo (95% CI, 1.3–10.1), and median OS was 12.9 mo (95% CI, 1.9-NE). For those receiving GPRC5D BsAb post-QCE, median EFS was 4.0 mo (95% CI, 2.3-NE), and median OS was 12.6 mo (95% CI, 4.0-NE). **Conclusions:** QCE RRMM pts were heavily pretreated, with most being triple- or quad-class refractory. Recycling therapies utilizing the same targets resulted in poor EFS and OS. GPRC5D BsAbs offered a new option; however, patients still have poor survival outcomes. Continued therapeutic innovation is critical for this population.

OA-56

Belantamab for the Treatment of Multiple Myeloma: Results from Part 1 of the First-in-Human Phase 1/2 DREAMM-20 Trial

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Introduction: Belantamab mafodotin (belamaf) is a B-cell maturation antigen (BCMA)–targeted monoclonal antibody (mAb) conjugated with a monomethyl auristatin F (MMAF) payload. In the phase 3 DREAMM-7 and DREAMM-8 trials in patients (pts) with relapsed/refractory multiple myeloma (RRMM), belamaf combinations significantly improved progression-free survival vs standard-of-care regimens, with DREAMM-7 also showing a significant overall survival benefit. Belantamab (GSK2857914) is the unconjugated BCMA-targeted mAb without MMAF; therefore, MMAF-related ocular toxicities are not expected. DREAMM-20 is a phase 1/2 study evaluating the safety, tolerability, and clinical activity of belantamab in pts with MM. Here, we present a planned analysis of belantamab dose escalation in part 1 of DREAMM-20 (NCT05714839). **Methods:** Part 1 is a phase 1, open-label, multicenter, dose-escalation study in pts with RRMM with ≥3 prior lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 mAb. Dose escalation was conducted using a modified toxicity probability interval method. The primary endpoint was incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Secondary endpoints included overall response rate (ORR). **Results:** Across 3 cohorts, 18 pts received belantamab 300, 900, or 2000 mg IV Q2W (n = 6 each). Data cutoff (DCO) was Feb 22, 2025. Median age was 76 y (range, 42–86 y); 17/18 pts were triple-class exposed, and 2/18 had prior BCMA-targeted therapy. Overall median duration of exposure was 63.5 d. No DLTs or treatment-related AEs (TRAEs) leading to discontinuation were reported. The most common TRAEs across the 3 cohorts were infusion-related reactions (4/18 [22%]), decreased neutrophil count (4/18 [22%]), and anemia (3/18 [17%]). Grade ≥3 AEs occurred in 13 pts (72%), and serious AEs occurred in 6 (33%); no fatal serious AEs were reported. Two pts (11%) had grade ≥2 corneal events per the Keratopathy and Visual Acuity scale, deemed unrelated to belantamab. The ORR was 28% (5/18 pts); 3 pts (2 receiving 900 mg, 1 receiving 2000 mg) had very good partial responses and 2 (1 each receiving 300 and 2000 mg) had partial responses, with responses observed across all cohorts. No pts had a minimal response, and 28% (5/18) had stable disease. Responses appeared durable, with 3 of 5 pts ongoing at DCO and only 1 pt with progressive disease discontinuing treatment after response. **Conclusions:** Belantamab had a favorable safety profile, with no DLTs, TRAEs leading to discontinuation, or grade ≥2 corneal events associated with belantamab. Encouraging preliminary clinical activity was observed, with durable responses occurring across dose levels in this heavily pretreated, triple class–exposed population. These findings support the potential of belantamab to provide clinical activity with an acceptable safety profile. Further evaluation is ongoing in part 2 of DREAMM-20. Funding: GSK. Monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

OA-57

IVIG and Longer Dosing Intervals Reduce Risk of Infections in Patients with RRMM Treated with Teclistamab

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Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) who are treated with BCMA-directed bispecific antibodies (BsAbs) are at increased risk of infections. Previous studies have shown that treatment with intravenous immunoglobulin (IVIG) reduces the risk for severe infections. However, whether IVIG also reduces all-grade infections and whether prolonging dosing intervals influences infection risk, remains unknown. To address this, we retrospectively investigated 80 patients who were treated with teclistamab. **Methods:** All patients with RRMM who were treated with teclistamab between 2019 and 2025 in Amsterdam University Medical Center in The Netherlands were included. Patients received cotrimoxazole and valaciclovir as antimicrobial prophylaxis. IVIG was prescribed as primary prophylaxis for infections when polyclonal IgG was <4 g/L, or as secondary prophylaxis after a severe infection (CTC grade ≥3) with polyclonal IgG <4 g/L, based on evolving clinical practice.

Annualized infection rates were calculated for each patient by dividing the total number of infections by the total time on treatment and compared between patients who received IVIG and those who did not, using Poisson models. Associations between annualized infection rates and dosing schedules were assessed using negative binomial regression models. **Results:** Eighty patients with RRMM who received teclistamab were included in the study. Fifty-one patients (64%) participated in a clinical trial and 29 patients (36%) enrolled in a compassionate use program. Median age was 65 years (range 42–81). In total, 66/80 patients (83%) received IVIG supplementation, of whom 51 patients (77%) received IVIG as primary prophylaxis and 15 (23%) received IVIG after a severe infection. After a median follow-up of 21 months, in total 390 infections were reported, of which 48 were severe. Treatment with IVIG resulted in significantly lower rates of both severe infections (0.33 versus 0.93 per patient-year, $p < 0.001$) as well as of all-grade infections (3.15 versus 4.41 per patient-year, $p < 0.01$). Older age and elevated beta-2-microglobulin were found to be independently associated with risk for severe breakthrough infections. During weekly dosing, 6.08 all-grade infections occurred per patient-year (py). These numbers were 3.54/py during biweekly ($p < 0.01$), 2.93 during monthly ($p < 0.01$) and 2.25 during bimonthly dosing schedules ($p < 0.001$). Severe infection rates decreased from 0.81 per patient-year during weekly, to 0.39 during biweekly ($p = 0.19$), 0.29 during monthly ($p = 0.07$) and 0.1 during bimonthly dosing ($p < 0.05$). Importantly, a sensitivity analysis in 66 patients who received IVIG prophylaxis, revealed that a reduction in severe infections was still observed, when patients switched to longer dosing intervals. **Conclusions:** We here show for the first time that there is a benefit of longer dosing intervals for reducing the risk of severe infections during treatment with teclistamab, also in patients receiving IVIG supplementation.

OA-58

Isatuximab Subcutaneous via an on-body Delivery System versus Isatuximab Intravenous, Plus Pomalidomide and Dexamethasone, in Relapsed/Refractory Multiple Myeloma: The Randomized Phase 3 IRAKLIA Study

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Introduction: Intravenous (IV) isatuximab-pomalidomide-dexamethasone (Isa-Pd) is approved to treat relapsed/refractory multiple myeloma (RRMM) patients (pts) based on the ICARIA-MM study. A Phase 1b study showed safety and efficacy of Isa subcutaneous (SC) via an on-body delivery system (OBDS), plus Pd, in RRMM pts. Isa SC offers shorter duration, fixed dose and smaller administration volume. Here, we report results of the multicenter, open-label IRAKLIA trial (NCT05405166); Isa SC vs IV + Pd in RRMM pts, the first Phase 3 myeloma trial reporting use of an OBDS. **Methods:** Pts aged ≥18 years (y) with ≥1 prior line of therapy (LOT) were randomized 1:1 to Isa SC (1400 mg) or Isa IV (10 mg/kg) weekly in Cycle (C)1, then every 2 weeks + P (4 mg/day, Day [D]1–21) + d (40 mg [age ≥75 y: 20 mg] weekly). Pts had 4-week cycles until progression, unacceptable toxicity or patient request. Co-primary endpoints were overall response rate (ORR; non-inferiority [NI] margin, 0.839) and Isa trough level (Ctrough) at steady state (C6D1 predose; NI margin, 0.8). **Results:** 531 pts (SC n = 263; IV n = 268 [4 not treated]) were randomized. Baseline characteristics were balanced (median age 66 y; median 2 prior LOT). After median 12 months follow-up, ORR was 71% (SC arm) and 71% (IV arm; relative risk [95% CI] = 1.008 [0.903–1.126]; lower CI > NI margin). Mean (SD) Ctrough at C6D1 was 499 (259) µg/mL for SC and 340 (169) µg/mL for IV. Ctrough geometric mean ratio (90% CI) was 1.532 (1.316–1.784); lower CI > NI margin. Co-primary and all 4 key secondary endpoints including pt experience are in the Table. Grade ≥3 treatment-emergent adverse events occurred in 82% (SC) and 76% (IV) of pts; with treatment discontinuation rates of 8% and 9%. Injection site reactions (ISRs) occurred in 4% (11/263) of the SC

arm and in 19 (0.4%) of 5145 SC injections (all Grade 1–2). 99.9% of OBDS injections were completed without interruption.

Table

	Isa SC + Pd	Isa IV + Pd
Efficacy, %	N = 263	N = 268
ORR	71	71
≥VGPR	46	46
PK*, µg/mL	N = 131/ 121	N = 126/ 121
Geometric mean Isa C_{trough} at C2D1/C6D1	360/426	277/278
Safety, %	N = 263	N = 264
All grade IR	2	25
Pt satisfaction with injection method at C5D15, %	70	53

*PK was analyzed at C6D1 with PP PK population and at C2D1 with PP CT4W population.CT4W, Ctrough at 4 weeks; IR, infusion reaction; PK, pharmacokinetics; PP, per protocol; VGPR, very good partial response.

Conclusions: IRAKLIA showed efficacy and pharmacokinetic NI between Isa SC vs IV. No new safety signal besides low ISR incidence was observed, showing excellent Isa SC local tolerability with OBDS. Far fewer infusion reactions and higher pt satisfaction were also noted for SC vs IV. Efficacy and safety are comparable to Isa IV in ICARIA-MM. These results support potential use of Isa SC via OBDS, designed to improve practice efficiency. **Funding:** Sanofi. ©2025 American Society of Clinical Oncology (ASCO), Inc. Reused with permission. This abstract was accepted and previously presented at the 2025 ASCO Meeting. All rights reserved.

OA-59

The Anti-BCMA Antibody-Drug Conjugate HDP-101 with a Novel Amanitin Payload Shows Promising Data in Relapsed/Refractory Multiple Myeloma in a Phase 1/2a Clinical Trial as it Advances into Cohort 7

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Introduction: HDP-101 is a novel antibody-drug conjugate (ADC) targeting B-cell maturation antigen (BCMA) with a synthetic amanitin payload. It exhibits cytotoxicity in vitro against BCMA-positive myeloma cells, even those with low BCMA density. **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). Phase 1 aims to determine the Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D), using an adaptive Bayesian logistic regression model (BLRM). As of April 15, 2025, 34 patients (11 female, 23 male; median age 68.5, range 43–82) were enrolled in seven dose cohorts (20–112.5 µg/kg). Patients were heavily pretreated (median 7 prior regimens, range 2–15). Cohort 7 is fully enrolled, DLT period completed; Cohort 8 (140 µg/kg) is enrolling. Dose escalation was initially performed with dosing every 3 weeks (Q3W) up to Cohort 5 (100 µg/kg). From Cohort 6 (90 µg/kg), based on PKPD modeling, dose optimization strategies were introduced including split dosing and/or premedication with corticosteroids and antihistamines, to mitigate the risk of adverse events like thrombocytopenia and liver enzyme elevations. These strategies were evaluated in three arms and further tested in Cohort 7 (112.5 µg/kg). Escalation continues with these new strategies. **Results:** Safety Treatment was generally well tolerated. No drug-related deaths, infusion reaction, lung, or ocular toxicity were observed. Q3W dosing caused transient liver enzyme elevations and asymptomatic thrombocytopenia (Grade 1–4). No bleeding was associated with thrombocytopenia and platelet count recovered quickly and spontaneously.Weekly or split dosing with premedication significantly reduced these effects, leading to discontinuation of Q3W dosing. Efficacy: No responses were observed below 90 µg/kg. From 90 µg/kg/cycle, multiple responses emerged. At 100 µg/kg, three of six patients had partial responses (PR), including one stringent complete response (sCR) lasting 19 months to date. This patient had prior BCMA CAR-T and GPRC5D/CD3 bispecific antibody therapy. In Cohort 6 (90 µg/kg/cycle), two of ten patients showed PR. In Cohort 7 (112.5 µg/kg), 3 patients are ongoing; two have PR. Cohort 8 (140 µg/kg) is actively enrolling. PKPD: Noncompartmental analysis revealed dose-proportional pharmacokinetics (Cmax, AUC) for all analytes, with a ~10-day half-life. A two-compartment model with linear clearance best described the PK of the total antibody, with minimal free payload observed in serum. PKPD modeling and simulation analyses confirmed that split dosing and/or premedication reduced the impact of HDP-101 on thrombocytes and LFTs. **Conclusions:** HDP-101 showed a favorable safety profile up to 112.5 µg/ kg/cycle, with MTD not reached. Dose escalation continues at 140 µg/kg. Responses observed from 90 µg/kg suggest that optimized dosing maintains antitumor efficacy while enhancing tolerability.

OA-60

Updated Interim Results of Sonrotoclax + Dexamethasone in Patients With t(11;14)-Positive Relapsed/Refractory Multiple Myeloma (R/R MM): An All-Oral Treatment

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Introduction: Despite the clinical efficacy of BCL2 inhibition in t(11;14)-positive MM, no BCL2-targeted treatments (tx) are approved. Sonrotoclax (sonro; BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. BGB-11417-105 (NCT04973605) is an ongoing phase 1b/2 study of sonro as mono- or combination tx in patients (pts) with t(11;14)-positive R/R MM. Updated results in pts treated with sonro + dexamethasone (dex) are presented. **Methods:** Eligible pts had R/R MM with centrally confirmed t(11;14) and received oral sonro (320 or 640 mg QD) + dex (40 mg QW). Tx-emergent adverse events (TEAEs) were graded by CTCAE v5.0 and efficacy was assessed by the investigator per IMWG criteria. **Results:** As of Jan 20, 2025, 14 and 36 evaluable pts were enrolled in the sonro 320-mg and 640-mg cohorts, respectively; median (range) follow-up was 6.2 mo (2.6–34.5) and 12.1 mo (0.1–28.9), respectively. The median (range) prior lines of tx were 3 (1–7) in the 320-mg cohort and 3 (1–12) in the 640-mg cohort; 78.6% and 66.7% of pts were refractory to 3 tx classes, respectively. At data cutoff, 7 pts (50.0%) in the 320-mg cohort and 14 (38.9%) in the 640-mg cohort remained on tx; progression was the most common reason for discontinuation (35.7% and 41.7%, respectively). The ORR (95% CI) was 64.3% (35.1–87.2) in the 320-mg cohort and 80.6% (64.0–91.8) in the 640-mg cohort, with VGPR or better rates (95% CI) of 35.7% (12.8–64.9) and 55.6% (38.1–72.1), respectively. The median time to response was 0.7 mo in both cohorts. Median (95% CI) duration of response was 5.9 mo (1.8–not estimable [NE]) in the 320-mg cohort and 12.2 mo (8.3–18.9) in the 640-mg cohort. Median (95% CI) PFS was 6.6 mo (2.9-NE) in the 320-mg cohort and 13.3 mo (9.0–19.6) in the 640-mg cohort. The most common TEAEs were fatigue (35.7%) in the 320-mg cohort, and insomnia (38.9%) and diarrhea (38.9%, all grade 1/2) in the 640-mg cohort. Grade ≥3 TEAEs occurred in 5 pts (35.7%) in the 320-mg cohort and 17 pts (47.2%) in the 640-mg cohort; serious TEAEs occurred in 3 (21.4%) and 10 (27.8%), respectively. Grade ≥3 hematologic TEAEs occurred in 1 (7.1%) and 9 (25.0%) and grade ≥3 infections in 3 (21.4%) and 4 (11.1%) pts, respectively. Two pts (14.3%) in the 320-mg cohort and 2 (5.6%) in the 640-mg cohort died during the tx-emergent part for reasons unrelated to tx (320 mg, pneumonia RSV and COVID-19; 640 mg, hypoventilation [related to pulmonary involvement with PD] and metastatic pancreatic cancer). Four more deaths occurred >30 d after the last 640-mg dose. **Conclusions:** This ongoing study showed that the all-oral combination of sonro + dex is tolerable, with low rates of infection and hematologic toxicity, and promising efficacy, with an ORR of 81% in the 640-mg cohort, in this t(11;14)-positive R/R MM population. Additional tx combinations with sonro are being investigated.

OA-71

Concurrent Administration of BCMA and GPRC5D Chimeric Antigen Receptor (CAR) T Cells for the Treatment of Relapsed or Refractory Multiple Myeloma: Results from the Phase I TANDEMM Clinical Trial

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Introduction: Therapies targeting B cell maturation antigen (BCMA) and G protein coupled receptor class C, group 5, member D (GPRC5D) represent a major advance in the management of multiple myeloma. However, relapses are common and multi-antigen targeting has been proposed as a potential approach to achieve durable responses. **Methods:** We conducted a phase I, dose escalation trial of concurrent infusion of BCMA and GPRC5D CAR T cells, MCARH125 and MCARH109 in patients with relapsed or refractory myeloma. All patients received lymphodepleting chemotherapy with fludarabine and cyclophosphamide followed by CAR T cell infusion at one of 3 dose levels (DL): DL 0, 150 × 106 cells of MCARH125 alone; DL 1, 50 × 106 cells of MCARH109 and 150 × 106 cells of MCARH125; DL 2, 150 × 106 cells of MCARH109 and 150 × 106

cells of MCARH125. The primary objective was to assess safety of MCARH125 alone or in combination with MCARH109, while the secondary objective was to assess anti-myeloma efficacy. Translational studies included assessing the antigen expression by immunohistochemistry and flow cytometry, T cell phenotyping by multi-omic profiling, and expansion of both CART products by quantitative polymerase chain reaction (qPCR). **Results:** 19 patients with multiple myeloma and at least 3 prior lines of treatments were enrolled, and 15 patients were treated across the 3 doses levels. No patients in DL 0 and 67% of patients in DLs 1/2 had prior BCMA treatment. All patients (100%) had cytokine release syndrome with 1 (17%) patient at DL 0 and 2 (22%) patients at DLs 1/2 having grade 2 CRS; there were no grade 3 or higher CRS. One patient each at DL 0 and DL 2 had grade 3 immune effector cell associated hemophagocytic syndrome and this was considered a dose limiting toxicity (DLT). There were no instances of non-ICANS neurologic toxicities which have been reported with both BCMA and GPRC5D-directed therapies. Among the 15 treated patients, 13 (87%) patients achieved an objective response. This included all 6 (100%) patients at DL 0, and 7 (78%) of 9 patients treated at DLs 1/2. The median PFS for DL 0 and DL 1/2 were 20.1 months (95% CI: 17.5 to NR months) and 18.2 months (95% CI: 6.4 to NR). Down-regulation of one or both antigens was an important factor in patients with relapsed or refractory disease after treatment. Pre-infusion products among responders were enriched for CD8+ T cell memory populations by single cell RNA and ATAC sequencing. We also show that expansion of one CAR population can limit expansion of the second population, as dual-CAR treated patients (DLs 1/2) had significantly less BCMA-CAR expansion than BCMA-CAR alone treated patients (DL 0), despite equivalent BCMA CAR T cell doses at infusion. **Conclusions:** In this proof-of-concept trial, we demonstrate feasibility, safety, and efficacy of concurrently targeting two myeloma specific antigens BCMA and GPRC5D by co-administering two different CAR T products manufactured from a single apheresis.

OA-72

Deciphering Myeloid Cell Dynamics within the Osteolytic Lesion Tumor Microenvironment to Overcome Immunosuppression in Multiple Myeloma

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Introduction: Understanding myeloid cells in the tumor microenvironment is crucial for identifying new targets against immunosuppressive barriers in multiple myeloma (MM). This study focused on neutrophils as potential targets for immune therapies by analyzing freshly isolated myeloid cells from focal lesions and bone marrow through single-cell RNA sequencing, imaging, and functional assays. **Methods:** BM from healthy donors and BM and FL samples from 13 MM patients were freshly collected. CD11b+ myeloid cells were freshly isolated and selected cells were immediately used for scRNA-seq. In-vivo and in-vitro experiments conducted using MM models. **Results:** We assessed 105192 sorted CD11b+ cells from the MM TME in BM and FL sites, alongside 10086 cells from healthy BMs. Integration of these cells showed no new developmental clusters in MM-associated neutrophils, indicating a single developmental trajectory in both healthy and MM tissues. However, MM-associated neutrophils (TANs) exhibited distinct transcriptional profiles, forming three unique clusters enriched for CXCR2, differing from healthy donors. Inflammatory mediators were elevated in MM BM neutrophils, while immunosuppressive genes were higher in FL neutrophils. We found that CXCR2+ neutrophils accumulated near malignant plasma cells in high tumor burden areas, particularly in FL using immunofluorescence. These findings align with scRNA sequencing data, showing more mature TANs with increased tumor burden. FL mature CXCR2+CD10+ neutrophils produced more chemokines involved in chemotaxis and migration and proinflammatory cytokines(CCL3 and CCL4) than those from MM BM and HD, suggesting a positive feedback loop enhancing CXCR2+ neutrophil recruitment in FL. FL mature TANs released more inflammatory and immunosuppressive cytokines, including IL-6,IL-1α compared to MM BM and HDM. Co-culture experiments revealed that CXCR2+CD10+ FL neutrophils suppressed T cell proliferation, indicating an immunosuppressive environment. Using the VK*MYC murine model, we investigated the impact of CXCR2 inhibition on tumor growth. CXCR2 inhibitor reduced tumor burden and improved survival compared to controls, with synergistic effects when combined with BOR/DEX. In relapse, CXCR2 inhibition also decreased tumor burden and improved survival, showing synergistic benefits with triplets. Flow cytometry indicated increased anti-tumor cytokines, particularly with combination therapies. **Conclusions:** By analyzing BM and FL samples after sorting myeloid cells prior to sequencing allowed us to identify uncommon and/or labile subpopulations that are challenging to detect when sequencing entire CD45+ leukocyte populations. We discovered a maturation continuum from immature to a predominant population of mature TANs within FL. This suggests that neutrophils may mature and acquire an alternate development trajectory in FL. Targeting these neutrophils with CXCR2 inhibition reduces tumor burden and enhances survival, highlighting its potential as a therapeutic strategy in MM.

OA-73

Longitudinal Multi-Omic Profiling Uncovers Immune Escape and Predictors of Response in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is an incurable malignancy of clonally expanded plasma cells. Advances in MM-targeted therapies, autologous stem cell transplantation (ASCT), and immunotherapy have improved outcomes. Several features contribute to MM's response to therapy including cytogenetics, tumoral heterogeneity, and composition of the immune microenvironment (IME). However, the dynamics of the IME through treatment and interplay between MM and the IME during disease progression remains incompletely understood. **Methods:** To this end, we longitudinally evaluated MM and the IME at disease onset, response after therapy, and disease progression in patients from the MM Research Foundation CoMMpass study (NCT01454297). To facilitate a comprehensive characterization of the disease course, we generated single-cell profiles of 243 CD138neg bone marrow biopsies collected across the disease course from 102 patients. Combining the IME analysis with bulk RNA and whole-genome sequencing data from the malignant CD138pos compartment enabled characterization of mechanisms by which MM escapes surveillance and leads to disease progression. **Results:** Single-cell RNA sequencing of 243 CD138neg bone marrow samples from 102 patients generated profiles of 631,226 high-quality cells after quality control and doublet filtering. Longitudinal analyses from baseline to first response after induction and ASCT revealed that CD8+ T effector cells were significantly increased (Log2 Fold Proportion, L2FP = 1.35, adj. p = 2.4e-5), while limiting the proportion of CD8+ T effector memory cells (L2FP = − 0.94, adj.p = 8.0e-3), potentially impairing immune surveillance. These shifts appear to be influenced by interferon gamma signaling (adj.p = 1.5e-3). Stratifying patients by duration of response after ASCT revealed that patients with sustained response had greater naïve B cell proliferation (L2FP = 1.96, adj. p = 8.6e-4) which supported robust humoral reconstitution and correlated with improved progression-free survival (HR = 0.48, p = 2.3e-4). At disease progression, MM cells upregulated cancer-testis antigens (CTAg; p = 4.9e-5) and immune effector genes (p = 5.7e-10). This was accompanied by impairment of the IME, including depletion of B cell subclusters (adj.p's < 0.05), enrichment of myeloid-derived suppressor cell genes in monocytes (adj.p's < 0.05), and T cell exhaustion (adj.p's < 0.05)—highlighting a distinct transcriptional program that may promote immune evasion and disease acceleration. **Conclusions:** Our longitudinal analysis of one of the largest cohorts of CD138neg scRNAseq and CD138pos bulk sequencing adds to the valuable insights produced by the CoMMpass study. Naïve B repopulation and diverse Ig production post-ASCT are promising biomarkers to enhance post-ASCT risk stratification. CTAg enrichment at disease progression appears to promote multi-faceted IME escape mechanisms. Ongoing studies will build on these findings to provide critical insights for design of targeted therapeutics to enhance response to therapy.

POSTER PRESENTATIONS

PA-001

BCMA-Directed CAR-NK and BiKE Therapies Enhance NK Cell Cytotoxicity in Primary Multiple Myeloma

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Introduction: Multiple myeloma (MM), characterized by the uncontrolled expansion of malignant plasma cells in the bone marrow (BM), requires more innovative therapies. Chimeric Antigen Receptor (CAR) T cells and Bispecific T cell Engagers (BiTEs) have demonstrated success in MM but pose risks such as cytokine release syndrome (CRS) and neurotoxicity. Natural killer (NK) cells offer advantages including possibility to be used from allogeneic sources and reduced risk of CRS. Their combination with CAR and Bispecific NK Engagers (BiKEs) might present promising therapeutic strategies. BiKEs are engineered to bind an activating receptor on NK cells, such as NKp30, and a tumor antigen on malignant cells. B-cell maturation antigen (BCMA), highly expressed on myeloma cells, is a validated target antigen for MM immunotherapy. Membrane-bound BCMA can be shed into a soluble form through gamma-secretase activity. Inhibiting this process with gamma-secretase inhibitors (GSIs) may improve therapeutic response. Given NK cells' potential in MM immunotherapy and the lack of preclinical studies using primary MM samples, this study investigates the anti-tumor potential of nanobody-based BCMA-targeted CAR-NK cells and BiKEs against pMM. **Methods:** BM mononuclear cells (BMNCs) were isolated from BM aspirates by RBC lysis. MM cells were confirmed by flow cytometry using CD38, CD138, CD45, CD56, CD19, and

BCMA. CAR-NK cells were generated by lentiviral transduction, expanded, and co-incubated with target cells at varying E:T ratios for 4 h at 37°C. For BiKE assays, expanded NK cells from healthy donors were co-cultured with target cells with or without BCMA/NKp30 BiKEs. BCMA-positive and -negative controls were included. Surface CD107a was measured as a marker of NK activation. MM samples were pretreated with 10 or 50 nM GSI for 16 h to evaluate the impact of BCMA expression on NK cell cytotoxicity. Data were analyzed by flow cytometry. **Results:** MM samples (n = 14) showed diverse immunophenotypes. Despite this, BCMA-CAR NK cells significantly enhanced cytotoxicity against myeloma cells (E:T = 1:2, NK vs. CAR-NK: 28.1% ± 3.9 vs. 50.7% ± 6.1; $P < 0.001$), with minimal effects on normal BMNCs ($P = .46$). Surface BCMA expression positively correlated with CAR-NK sensitivity ($r = 0.596$, $r^2 = 0.356$, $P = 0.040$), though other factors also influenced outcomes. BCMA-CAR NK cells showed higher CD107a expression than control NK cells (MFI 3159 vs. 2467). A low BiKE dose (5 nM) increased CD107a and NK cytotoxicity (NK vs. NK + BiKE: 21.6% ± 9.1 vs. 39.1% ± 10.4). GSI pretreatment stabilized surface BCMA and increased BiKEs specific killing in samples with low-BCMA expression from 1.47% to 9.0% and 14.2% ($P < 0.01$), without intrinsic toxicity. **Conclusions:** BCMA-CAR and BiKE enhance NK cells' ability to recognize and eliminate MM cells while sparing non-malignant BMNCs. GSIs can further improve the efficacy of both BCMA-targeted CARs and BiKEs. Treatment outcomes may depend on MM cell characteristics.

PA-002

Safety and Efficacy of Ciltacabtagene Autoleucel for Relapsed/Refractory Multiple Myeloma: A CIBMTR Study

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Introduction: Ciltacabtagene autoleucel (cilta-cel), an anti-B-cell maturation antigen chimeric antigen receptor T-cell (CAR-T) therapy, was approved in 2022 for relapsed/refractory multiple myeloma (RRMM). This study evaluates the safety and efficacy of cilta-cel in standard-of-care (SOC). **Methods:** The study cohort included RRMM patients in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry who received SOC cilta-cel between April 2022 and December 2023, meeting commercial release specifications. Multivariable analyses of predictors for grade ≥ 2 cytokine release syndrome (CRS) and survival were conducted using logistic and Cox regression models, respectively. **Results:** Among 595 patients who received cilta-cel, median age was 64 years, 57% (n = 340) were male, and 70% had ≥1 clinically significant comorbidity (n = 416). Penta-class exposure occurred in 55% (n = 328), International Staging System (ISS) ≥ II in 41% (n = 106/260), and high-risk cytogenetics in 27% (n = 142/530). Extramedullary disease and marrow plasma cell burden (PCB) ≥50% were present in 13% (50/382) and 14% (n = 54/373) of patients, respectively. The median number of prior lines of therapy was 7 (range, 4–24), with 5 patients receiving prior CAR-T and 8% (n = 45) prior BCMA therapy: 6% (n = 37) belantamab mafodotin, 1% (n = 7) teclistamab, or a combination of both (n = 1). Lymphodepletion included fludarabine/cyclophosphamide (78%, n = 461), bendamustine (19%, n = 111), and others. Median follow-up was 12 months (range, 1–25 months). CRS occurred in 80% (n = 475, ≥ grade 3: 4%), immune effector cell-associated neurotoxicity syndrome (ICANS) in 22% (n = 133, ≥ grade 3: 4%) and immune-effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome in 4% (n = 21). Non-ICANS neurotoxicity was seen in 5% (n = 31), including Parkinsonism in 2.7% (n = 16) and cranial nerve (CN) palsies in 2.5% (n = 15), primarily CN VII (n = 12/15). Clinically significant infections were seen in 47% (n = 281) of patients. Multivariable analysis identified PCB ≥ 50% as an independent risk factor for grade ≥2 CRS. The best overall response rate was 87%, very good partial response rate was 40%, and complete response (CR)/stringent CR rate was 35%. Estimated 12-month progression-free survival (PFS) and overall survival were 73% (95% CI: 68–77%) and 85% (95% CI: 81–88%), respectively. Male sex, high-risk cytogenetics, prior BCMA therapy, ECOG PS ≥2, PCB ≥50%, elevated baseline lactate dehydrogenase, and ferritin ≥150 ng/mL were associated with inferior PFS on multivariable analysis. At last follow-

up, 15% (n = 91) of patients have died, including 5% (n = 27) due to non-relapse mortality, most commonly from infections (44%, n = 12). **Conclusions:** This is the largest SOC study of cilta-cel in heavily pretreated RRMM patients. Safety and efficacy profiles were favorable and support its use in clinical practice, despite patient heterogeneity and a high prevalence of clinically significant comorbidities.

PA-003

Real-World Comparison of Idecabtagene Vicleucel and Ciltacabtagene Autoleucel in Relapsed/Refractory Multiple Myeloma: A Center for International Blood & Marrow Transplantation Research (CIBMTR) Study

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Introduction: Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) are BCMA CAR-T products approved for relapsed/refractory multiple myeloma in 2021 and 2022, respectively, with distinct safety profiles. In the absence of head-to-head trials, we used CIBMTR data to compare their safety and efficacy in a real-world setting. **Methods:** We included patients (pts) who received commercial ide-cel (May 2021–Aug 2023) or cilta-cel (Apr 2022–Dec 2023) with adequate follow-up. To reduce confounding and balance baseline characteristics, we used inverse probability of treatment weighting (IPTW) based on propensity score model. Multivariable analysis was conducted using logistic and Cox regression models. **Results:** Of 1581 pts, 595 received cilta-cel and 986 ide-cel. Baseline characteristics were generally comparable, except cilta-cel cohort had lower comorbidity burden (HCT-CI ≥2: 50.5% vs 58.9%, $p < 0.01$), better performance status (ECOG ≥2: 3.2% vs 5.1%, $p = 0.03$), fewer with extramedullary disease (8.4% vs 11.6%, $p < 0.01$), and less penta-exposed disease (55.1% vs 60.4%, $p < 0.01$), while a greater proportion achieved ≥ partial response at infusion (24.3% vs 21.6%, $p < 0.01$). Median follow-up of survivors was 12.0 months (range, 1.1–25.4) for cilta-cel, and 12.9 months (range, 1.4–34.6) for ide-cel. Any grade CRS occurred in 79.3% vs 82.1%, and grade ≥3 in 4.3% vs 2.9% (cilta-cel vs ide-cel). Any grade ICANS was seen in 22.3% vs 27.3%, and 6-month treatment-related mortality (TRM) was 4.0% (95% CI, 2.6–5.8) vs 2.9% (95% CI, 2.0–4.1), respectively. After IPTW adjustment, cilta-cel remained associated with lower odds of any grade CRS [odds ratio (OR), 0.72, $p = 0.0004$)], and any grade ICANS (OR 0.75, $p = 0.0005$), but higher odds of grade ≥3 CRS (OR 1.50, $p = 0.041$), with no difference in grade ≥3 ICANS (OR 0.97, $p = 0.8$). In the unadjusted cilta-cel cohort, 5% had non-ICANS neurologic events—Parkinsonism (2.7%) and cranial nerve palsies (2.5%), most commonly involving the facial nerve (12/15); no such events were reported with ide-cel. At 12 months, cumulative incidence of overall response rate (ORR) and complete response (CR) was higher in cilta-cel (ORR: 88.9% vs 75.3%; CR: 36.2% vs 24.4%). One-year progression-free survival (PFS) was 72.6% vs 46.7%, and overall survival (OS) was 84.5% vs 73.6% (cilta-cel vs ide-cel). After IPTW adjustment, cilta-cel remained associated with higher odds of ORR (OR 1.7; 95% CI, 1.56–1.84; $p < 0.0001$) and CR (OR 1.88; 95% CI, 1.66–2.14; $p < 0.0001$), and longer PFS [hazard ratio (HR) 0.47; 95% CI, 0.41–0.53; $p < 0.0001$] and OS (HR 0.82; 95% CI, 0.70–0.95; $p = 0.008$). However, TRM was higher with cilta-cel (HR 1.45; 95% CI, 1.06–1.98; $p = 0.018$). **Conclusions:** In this largest real-world comparison to date, cilta-cel showed deeper responses and improved PFS/OS, but was associated with more delayed neurotoxicity and higher TRM—highlighting the need for optimized patient selection and proactive risk mitigation strategies.*AA & MJ contributed equally.

PA-004

Real-World Bispecific Antibody Therapy for Multiple Myeloma: Insights from Dutch Nationwide Registry

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Introduction: Bispecific antibodies (BsAbs) are approved for treating relapsed/refractory multiple myeloma (RRMM) after ≥3 prior lines of therapy (LOT), if triple-class exposed (TCE). Real-world data are crucial to assess efficacy and safety beyond clinical trials. **Methods:** This nationwide, multicenter observational study collects real-world data on teclistamab (TEC; anti-BCMA) and talquetamab (TAL; anti-GPRC5D) for RRMM patients treated in a compassionate use program, focusing on infection occurrence, prophylactic measures, treatment schedule modifications, and quality of life (QoL) using EORTC QLQ-C30 and QLQ-MY20 questionnaires. **Results:** As of May 28, 2025, 337 RRMM patients received TEC and 39 received TAL across 28 hospitals in the Netherlands. Currently, 182 patients are included in the registry, with a median of 4 prior LOT, all TCE, and 71% were triple-class refractory. Four patients had prior BCMA CAR-T therapy and 29 received sequential TEC/TAL. Seven patients could not initiate BsAb therapy due to rapid disease progression and 44% would not have met MajesTEC-1 or MonumenTAL-1 trial eligibility.Among 156 TEC-treated patients, the overall response rate (ORR) was 65%, with 57% achieving at least a very good partial response (≥VGPR) at 7.7 months median follow-up. Median progression-free survival (mPFS) was 11.9 months; among trial-ineligible patients, mPFS was 8.1 vs. 16.0 months in eligible patients. The median duration of response was not reached at 15.8 months follow-up, with 58% maintaining response at 24 months. Among seven patients with secondary AL amyloidosis, 86% achieved ≥VGPR at a median follow-up of 15.7 months. Patients previously treated with BCMA CAR-T therapy had an ORR of 50%, while those previously treated with TAL had an ORR of 80%. CRS and ICANS were reported in 51% and 6% of patients, respectively, mostly grade 1–2, with one fatal CRS case. Tocilizumab was administered to 41% of patients with CRS. Inflammatory pain flare occurred in 13%. Infections were observed in 64% of patients (grade ≥3 in 46%), IVIG and antibiotic prophylaxis in 89% and 90% of patients, respectively. TEC dosing intervals were extended at six months in 39% (biweekly), 13% (four-weekly), 3% (six-weekly), and 3% (eight-weekly), and at one year in 50% (biweekly), 5% (three-weekly), 19% (four-weekly), 2% (six-weekly), and 7% (eight-weekly). Among 21 TAL-treated patients, the ORR was 71%, with 48% achieving ≥VGPR at a median follow-up of 6.5 months, with mPFS 4.8 months. Patients previously treated with TEC had an ORR of 65% with TAL, with 53% achieving at least VGPR at 5.0 months of follow-up. **Conclusions:** The response rates and PFS observed in this real-world registry align with clinical trial outcomes, reinforcing the effectiveness of these treatments in broader clinical practice. Infectious complications were frequent, but hospitalization rates were lower, likely due to prophylaxis and adjusted dosing. Ongoing QoL data collection will provide further insights into the impact of these therapies.

PA-005

The Role of Trogocytosis in BCMA CAR T Cell Therapy with Gamma-Secretase Inhbition

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Introduction: BCMA CAR T cells have substantial efficacy in relapsed/refractory multiple myeloma (MM).γ-Secretase inhibitors (GSIs) increase surface BCMA, reduce antigen shedding and improve cytotoxicity in preclinical studies.Increased BCMA density after GSI has correlated with improved outcomes (ORR, PFS and OS) in a phase I clinical trial.Nonetheless, most patients relapse. Trogocytosis —the transfer of membrane-bound antigens from tumor to CAR T cells—has emerged as a potential mechanism of antigen down-modulation, T cell dysfunction, and fratricide. We investigated the effects of GSI on trogocytosis kinetics and its consequences in vitro, and in concert with clinical data from two Phase I trials of BCMA-targeted CAR T therapy. **Methods:** Human T cells transduced with BCMA-directed 4-1BB/CD3ζ CAR (EGFRt$^+$), were expanded and sorted. MM cell lines (H929, MM.1R, MOLP8) and BCMA-mCherry$^+$ K562 cells were co-cultured with CAR T cells (E:T 1:1) for 10 min–24 h ± GSI [crenigacestat] (0.1 μM, 24 h).BCMA density and trogocytosis were evaluated by flow cytometric (FC) analysis. Latrunculin A (1 μM) was used to inhibit trogocytosis.BCMA-acquiring CAR T cells (Trogo$^+$) were sorted after 6 h co-culture and re-plated with naïve CAR T cells for 24 h to assess fratricide.Patient samples from two Phase I trials—FCARH143 (NCT03338972) and FCARH143+GSI (NCT03502577) were analyzed for trogocytosis, CAR T persistence (qPCR) and clinical response. **Results:** GSI significantly increased BCMA density, enhanced CAR T cell cytotoxicity, but also increased trogocytosis, particularly in high-antigen-density cell lines (H929+GSI vs H929; 30 min ($P < 0.0001$), 1 h ($P < 0.0001$), 2 h ($P < 0.0001$), 6 h ($P < 0.0001$), and 24 h

($P < 0.0001$) and in $CD4^+$ CAR T cells (CD4 vs CD8 CAR T cells; 10 min ($P = 0.01$), 2 h ($P = 0.01$), and 6 h ($P = 0.004$). CAR T $Trogo^+$ cells exhibited reduced proliferative capacity, diminished cytotoxic function (CAR T Trogo+ vs CAR T; ($P = 0.0002$), and higher exhaustion/activation markers (CD4+ CAR T Trogo+ vs CD4 CAR T; PD-1+LAG-3+, PD-1+TIM-3+, and TIM-3+LAG-3+; ($P = 0.04$, $P = 0.03$, and $P = 0.002$). In fratricide assays, CAR T $Trogo^+$ cells were susceptible to killing by naïve CAR T cells (CAR T Trogo+ alone vs CAR T Trogo+ and CAR T, $P = 0.0005$).Confocal microscopy and live imaging confirmed trogocytosis and fratricide. BCMA trogocytosis was found in patient samples, although an association with reduced CAR T cell persistence and treatment response did not reach statistical significance. **Conclusions:** We report disparate effects of GSI on BCMA CAR T cell therapy including enhancement of tumor targeting and promotion of trogocytosis-associated dysfunction. Trogocytosis may contribute to antigen modulation, CAR T cell exhaustion, and fratricide, potentially limiting full realization of the benefits from increased antigen density. Future clinical trials incorporating early time-point sampling and mechanistic assessments may facilitate further optimization of GSI administration and inform strategies to mitigate trogocytosis-associated resistance mechanisms.

PA-006

Comparative Effectiveness of Teclistamab vs Real-World Physician's Choice of Carfilzomib-and/or Pomalidomide-Based Regimens in LocoMMotion and MoMMent in TCE RRMM

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Introduction: A pooled analysis from the prospective, noninterventional, multinational LocoMMotion (NeT04035226) and MoMMent (NeT05160584) studies demonstrated suboptimal outcomes in patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM), even when treated with carfilzomib and pomalidomide regimens. MajesTEC-1 (NCT04557098) is a single-arm phase 1/2 study evaluating teclistamab, a B-cell maturation antigen×CD3 (BCMA) bispecific antibody in patients with RRMM who are TCE. Here, we compared efficacy outcomes of patients who received teclistamab in MajesTEC-1 with those treated with carfilzomib and/or pomalidomide-based regimens in LocoMMotion and MoMMent pooled analysis. **Methods:** An external control arm, Real-World Physician's Choice (RWPC), was created from a pooled analysis of LocoMMotion (clinical cut-off: Oct 22) and MoMMent (clinical cut-off: Aug24) and compared with treated patients who met MajesTEC-1 eligibility criteria (teclistamab 1.5 mg/kg weekly; clinical cut-off: Aug 2023). Inverse probability weighting was used to adjust for imbalances in baseline covariates. For binary endpoints such as overall response rate (ORR), relative effect of teclistamab versus RWPC was estimated with an odds ratio and relative response rate (RR) and 95% confidence interval (CI), derived from weighted logistic regression. Weighted Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% CIs for time-to-event endpoints [duration of response (DOR), progression-free survival (PFS), time-to-next-treatment (TTNT) and overall survival (OS)]. **Results:** After reweighting, baseline characteristics were balanced across cohorts. Patients treated with Teclistamab in MajesTEC-1 had significant improvements in all evaluated efficacy outcomes. Teclistamab-treated patients were almost 2-fold more likely to reach ORR (RR = 2.10 (1.30–3.40), with durable responses DoR HR = 0.31 (0.19–0.53) and longer TTNT HR = 0.48 (0.36–0.66) compared with eligibility-matched patient cohorts treated with carfilzomib and/or pomalidomide in RWPC from the LocoMMotion/MoMMent pooled dataset. In addition Teclistamab demonstrated statistically significant improvements in PFS HR = 0.50 (0.36–0.68) and OS HR = 0.66 (0.47–0.93) vs this RWPC subgroup. **Conclusions:** Teclistamab demonstrated improved effectiveness compared to the RWPC subgroup treated with carfilzomib and/or pomalidomide-based regimens, reinforcing its clinical value in delaying disease progression and extending the time to subsequent therapies in patients with TCE RRMM.

PA-007

Talquetamab Dosing Strategies in the United States: Real-world Insights From Over 250 Patients

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Introduction: Talquetamab (Tal), a first-in-class GPRC5D-targeted bispecific antibody, was approved in the United States (US) for patients (pts) with relapsed/refractory multiple myeloma (RRMM) who have received ≥4 prior lines of therapy (LOTs) and are triple-class exposed (TCE). Real-world (RW) data on Tal step-up dosing (SUD), dosing patterns, and time to less frequent dosing (LFD) after starting weekly (QW) or biweekly (Q2W) dosing are limited. **Methods:** Pts with TCE RRMM who received Tal between Aug 9, 2023 (US approval date), and Jan 10, 2025 (last data cut) were identified via the Komodo Healthcare Map™ database. The index date was the date of the first outpatient (OP) Tal SUD (3 mg/1.5 mL) claim or the admission date of an inpatient (IP) Tal encounter. Pts with ≥1 multiple myeloma (MM) diagnosis code before or on index

and ≥1 medical or pharmacy claim for Tal were included. Pt characteristics were described for the 6-mo baseline period prior to index. Tal administration, utilization, and time to next treatment (TTNT) were reported descriptively. **Results:** 257 pts were identified, with a median (IQR) age of 67.0 (62.0, 74.0) y. 53.3% were male, 64.2% were White, and 66.5% had Medicare. Pts frequently reported hypogammaglobulinemia (45.9%) and infections (45.5%) as comorbidities ≤6 mo prior to index. The median (IQR) duration since MM diagnosis was 6.1 (3.8, 8.1) y. The median (IQR) no. of prior LOTs was 5 (4, 7), and 113 (44.0%) pts had prior penta-drug exposure. Prior exposure to ≥1 commercial BCMA-targeted therapy was reported in 150 (58.4%) pts; overall, 143 (55.6%) pts had prior exposure to T-cell–redirecting therapy. Most pts received Tal monotherapy (n = 232; 90.3%), followed by those who received Tal with teclistamab (n = 4; 1.6%), pomalidomide (n = 4; 1.6%), or other agents. Tal SUD was received IP by 170 (66.1%) pts, OP by 76 (29.6%) pts, and hybrid (IP+OP) by 10 (3.9%) pts. Among 152 pts on QW or Q2W dosing with ≥3 doses post-SUD, 56 (36.8%) switched to every 4 weeks (Q4W) dosing or LFD (median time to switch, 4.7 mo). At the end of follow-up, among pts with ≥3 doses after SUD, 24/52 (46.2%) initially on QW dosing switched to Q2W dosing, and 11/52 (21.2%) switched to every 3 weeks (Q3W) dosing or LFD, and 28/100 (28.0%) initially on Q2W dosing switched to Q3W or LFD. At the end of follow-up, among 183 pts with ≥3 doses post-SUD, 23 (12.6%), 107 (58.5%), 8 (4.4%), and 27 (14.8%) were on QW, Q2W, Q3W, and Q4W dosing schedules, respectively. 58/257 (22.6%) pts had initiated a next LOT by the end of follow-up. With a median (IQR) follow-up of 5.2 (2.5, 8.2) mo, the median TTNT was not reached. **Conclusions:** Pts treated with Tal were heavily pretreated, with 58.4% having prior BCMA-targeted therapy. Most pts received Tal monotherapy, though some received Tal-based combinations. One third of pts received SUD in an OP setting. Q2W was the most common dosing schedule, with some pts switching to LFD. TTNT data suggest Tal was effective in a RW setting.

PA-008

Economic Value of Tocilizumab Prophylaxis to Prevent Cytokine Release Syndrome (CRS) during Outpatient Teclistamab (Tec) or Talquetamab (Tal) Initiation for Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Tec and Tal are bispecific antibodies approved for triple class-exposed RRMM, based on high overall response rates in the MajesTEC-1 (TEC-1) and MonumenTAL-1 (TAL-1) trials, respectively. Due to risk of CRS at initiation, step-up doses (SUDs) should be administered in the inpatient setting per label. However, several studies have shown outpatient administration of SUDs that can reduce healthcare resource utilization to be feasible, and prophylactic use of tocilizumab can be used to facilitate outpatient SUDs by reducing CRS incidence and severity. Early data from the Phase 2 OPTec study showed that only 6.25% (1/16) experienced grade [Gr] 1 CRS and none experienced Gr 2+ CRS when tocilizumab was administered before the first outpatient Tec SUD. The present study assessed the economic impact of adopting prophylactic tocilizumab to support outpatient administration of Tec or Tal, from a United States healthcare institution perspective. **Methods:** An economic model was developed to calculate costs for Tec and Tal during the SUD period under two alternative approaches for SUD administration: (1) outpatient administration with prophylactic tocilizumab (ACTEMRA®) before the first SUD (additionally, for Tal, prophylactic dexamethasone after each SUD); or (2) inpatient administration (with tocilizumab only as reactive treatment of Gr 2+ CRS, including recurrent Gr 2+ CRS). The two approaches were compared for each bispecific regimen: Tec, Tal weekly (QW), and Tal biweekly (Q2W). Patients with Gr 2+ CRS despite prophylactic tocilizumab were assumed to receive all remaining SUDs inpatient and retreated with tocilizumab. Risks of Gr 2+ CRS were based on OPTec (Tec) or a sub-analysis of TAL-1 (Tal) under the outpatient approach, and TEC-1 (Tec) or TAL-1 (Tal) under the inpatient approach. Costs of Tec, Tal and tocilizumab acquisition, outpatient administration, and inpatient stays were estimated in 2025$ based on trial data, drug labels, public databases, and literature. Pre-medication and prophylactic dexamethasone costs were not included due to minimal impact. A sensitivity analysis was conducted using the price of tocilizumab-aazg (TYENNE®), a biosimilar tocilizumab. **Results:** Total per-patient costs under the outpatient versus inpatient approaches were estimated to be, respectively, $18,797 vs. $27,639 (difference: −$8,841) for Tec, $18,419 vs, $26,964 (difference: −$8,545) for Tal QW, and $40,767 vs, $53,388 (difference: −$12,621) for Tal Q2W. Cost differences were largely attributable to fewer inpatient days under the outpatient approach. The cost savings with outpatient (vs. inpatient) SUDs were even greater in sensitivity analyses that used biosimilar tocilizumab pricing (Tec: −$9,725; Tal QW/Q2W: −$9,506/−$13,586). **Conclusions:** For patients initiating Tec or Tal for RRMM, an outpatient SUD approach with prophylactic tocilizumab was associated with lower costs of care than the conventional inpatient SUD approach.

PA-009

Acquired FCRL5 Mutation Leading to Cevostamab Resistance in Multiple Myeloma

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Introduction: The recent expansion of immunotherapies, notably bispecific T-cell engagers and CAR T-cell therapies, has shown remarkable clinical activity for the treatment of multiple myeloma (MM). However, responses are not uniform across all patients, underscoring the need to identify predictive factors to optimize treatment strategies. In this study, we aimed to identify tumor intrinsic mechanisms of resistance to cevostamab, a bispecific T-cell engager targeting Fc receptor-homolog 5 (FcRH5) and CD3, with encouraging clinical activity and durable responses in heavily pre-treated MM. **Methods:** n/a. **Results:** We present the case of a 63 year old male diagnosed with Kappa light chain MM harboring a Del(17p) treated with cevostamab as a single agent in the fifth line of therapy. Previous treatment lines included dexamethasone, cyclophosphamide, proteasome inhibitors (bortezomib and ixazomib), and IMiDs (lenalidomide and pomalidomide). Bone marrow aspirates were collected at baseline and progression for DNA and RNA extraction from sorted CD138+ cells. Tumor whole genome and transcriptome sequencing were performed at baseline, and whole exome sequencing and transcriptome sequencing was performed at cevostamab progression. The patient was initially treated with 60 mg of cevostamab for one year and then escalated to a higher dose cohort (90 mg) in the second year, achieving stringent complete response as the best response. At progression, whole exome sequencing detected a clonal FCRL5E115A missense mutation (allelic frequency = 56%) and a subclonal FCRL5G455Efs*19 frameshift deletion mutation (allelic frequency = 5%). Importantly, both FCRL5 mutations were absent at baseline. FCRL5 gene expression was marginally down-regulated at progression compared to baseline (log2FC = −0.4). Following cevostamab progression, the patient was treated with daratumumab and a bispecific T-cell engager targeting B-cell maturation antigen (BCMA) and CD3. The patient achieved complete response and has been in remission for four years. **Conclusions:** By integrating longitudinal genomic characterization with clinical response, we present an acquired clonal FCRL5 mutation as a putative novel mechanism of resistance to cevostamab. Functional studies to characterize this mutation are ongoing. These findings provide insight into tumor intrinsic mechanisms associated with immunotherapies targeting FcRH5.

PA-010

Efficacy/Safety of Cilta-Cel ± Lenalidomide Maintenance in Patients With Multiple Myeloma Who Had Suboptimal Response to Frontline ASCT: Updated Follow-Up From CARTITUDE-2 Cohort D

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Introduction: CARTITUDE-2 (NCT04133636) is a phase 2 multicohort study evaluating ciltacabtagene autoleucel (cilta-cel) across various clinical settings. Cohort D is evaluating cilta-cel ± lenalidomide (len) maintenance in patients (pts) who achieved < complete response (CR) after autologous stem cell transplant (ASCT) frontline therapy (tx). We report updated efficacy and safety for this cohort with a longer median follow-up (mFU) of 40.2 mo. **Methods:** Adults with newly diagnosed MM per IMWG criteria; best response of < CR and ≥ stable disease after 4–8 cycles of initial tx, including induction, high-dose chemotherapy, and ASCT ± consolidation, and without exposure to CAR-T or anti-BCMA tx received a single cilta-cel infusion 5–7 d post lymphodepletion. Per protocol, safety was assessed in the first 5 pts who received cilta-cel only, without len maintenance; subsequently, 12 pts initiated continuous len maintenance ≥21 d post cilta-cel. Primary endpoint was MRD-negative rate at 10^{-5} based on next-generation sequencing or flow. **Results:** As of Feb 2025 (mFU, 40.2 mo [range, 4.7–55.9]), 17 pts received cilta-cel (without len maintenance, n = 5; with len maintenance, n = 12). Median age was 54.0 yrs and 17.6% had high-risk cytogenetics at baseline. Compared with the previous report (22-mo mFU), ORR and rate of ≥CR were unchanged (16/17, 94.1% [95% CI, 71.3–99.9]; 1 pt withdrew consent at 4.7 mo with response not evaluable). 14/16 pts were alive in ≥CR (87.5%, [95% CI, 61.7–98.5]) at last contact (follow-up range, 13.4–55.9 months); 1 pt progressed and died of MM at 11 mo, and 1 pt died in a motor vehicle accident while in response at 42 mo. Overall, of 16 MRD-evaluable

pts, 13 (81.3%, [95% CI, 54.4–96.0]) achieved MRD negativity at 10^{-5} at any time; median time to MRD negativity was 1.7 mo (range, 0.9–11.5). MRD-negative ≥CR rate was 71.4% at 12 mo (95% CI, 41.9–91.6; 10/14 evaluable pts), 72.7% at 24 mo (95% CI, 39.0–94.0; 8/11 evaluable), and 75.0% at 36 mo (95% CI, 34.9–96.8; 6/8 evaluable). Pts with MRD negative ≥CR were characterized by a trend toward lower pre-infusion sBCMA, higher effector-to-target ratio (peak expansion over pre-infusion sBCMA), and enhanced T cell fitness (ie, higher level of naive T cells and lower level of effector memory T cells). 6 pts had CAR-T cell related neurotoxicities; most events were low grade and transient except 1 with grade 3 diplopia (recovered) and 1 with grade 1 paresthesia ongoing from d 18 at the time of withdrawal from study at 4.7 mo post infusion. There were no cases of parkinsonism or Guillain-Barré syndrome, and no new safety signals were observed. **Conclusions:** In pts who had < CR after frontline ASCT, a single cilta-cel infusion ± len maintenance led to deep and durable responses, with no new safety signals at this longer follow-up. The efficacy and safety of cilta-cel in cohort D continues to be favorable, especially given the historically poor clinical outcomes seen for these pts.

PA-011

Absolute Lymphocyte Count as a Key Biomarker for Monitoring Safety After Ciltacabtagene Autoleucel

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Introduction: Ciltacabtagene autoleucel (cilta-cel) demonstrated high efficacy in relapsed/refractory multiple myeloma (RRMM) in CARTITUDE-1 and CARTITUDE-4. After implementation of mitigation measures, the incidence of movement and neurocognitive treatment-emergent adverse events (MNT) decreased to 1% in CARTITUDE-4. An association between elevated CAR+ T-cell expansion and MNT was first seen in CARTITUDE-1 (Cohen, et al. Blood Cancer J 2022). A real-world analysis suggested that elevated absolute lymphocyte count (ALC) at early time points post infusion was associated with MNT and cranial nerve palsy (CNP) (Lim, et al. TANDEM 2025, p274). Herein, we investigated biomarkers associated with MNT/CNP pre and post cilta-cel. **Methods:** Longitudinal samples from patients (pts) with RRMM who received cilta-cel in CARTITUDE-1 (n = 97), CARTITUDE-2 cohorts A/B (n = 62), and CARTITUDE-4 (n = 196) were analyzed for ALC, immune cell phenotypes, and serum soluble markers. Spearman correlations evaluated relationships between 2 continuous variables. Wilcoxon rank sum test compared continuous variables in pts with MNT/CNP vs controls (pts without CNP, MNT, or grade ≥2 immune effector cell–associated neurotoxicity syndrome [ICANS]). Logistic regression models were fit to predict MNT/CNP and to identify multivariable associations. **Results:** ALC and CAR+ T-cell counts peaked at a median of 14 days (d) post cilta-cel, after the median onset of cytokine release syndrome (7d) and ICANS (8d). ALC and CAR+ T-cell counts correlated significantly d10-28 post infusion and at peak expansion (d14: $R = 0.79$; $P < 0.0001$). Eight (2.3%) pts developed MNT and 20 (5.6%) CNP; 288 served as controls (39 did not meet criteria). Median time to CNP and MNT onset was 22d and 41d, respectively. Pts with MNT had significantly higher CAR+ T-cell counts (median 5520 vs 384 cells/μL; $P < 0.0001$) and ALC (median 17,600 vs 970 cells/μL; $P < 0.0001$) vs controls on d14 post cilta-cel. Pts with CNP also had significantly higher CAR+ T-cell counts (median 1230 vs 384 cells/μL; $P < 0.001$) and ALC (median 2180 vs 970 cells/μL; $P < 0.0001$) vs controls on d14. Despite limited numbers of MNT/CNP events, multivariate analyses identified elevated ALC, CAR+ T-cell peak expansion, and CD4+ T-cell counts in the first 14d post infusion as biomarkers associated with MNT/CNP, with ALC showing the strongest association. Additional inflammatory biomarkers, including IL-6, IL-8, C-reactive protein, alongside regulatory T cells, and neutrophil/leukocyte ratio pre and post cilta-cel infusion, were also associated with MNT/CNP. **Conclusions:** These data suggest that heightened CAR+ T-cell expansion levels post infusion may be associated with MNT/CNP. ALC is an early biomarker for identifying pts at risk for MNT/CNP after cilta-cel infusion, at and closely before/after peak CAR+ T-cell expansion, which may help guide closer monitoring and preemptive interventions (eg, short course dexamethasone [Turner, et al. TANDEM 2025, p290]).

PA-012

Clonal Hematopoiesis of Indeterminate Potential (CHIP) Does not Impact the Efficacy of BCMA-Directed Chimeric Antigen Receptor (CAR)-T Cells in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is the presence of hematologic malignancy-associated somatic

mutations that drive hematopoietic stem cell clonal expansion and are seen in patients without hematologic malignancies. In multiple myeloma (MM), the implications of CHIP on chimeric antigen receptor (CAR)-T cell outcomes and toxicities have yet to be fully explored. This study aims to investigate associations between CHIP and clinical outcomes in patients with MM undergoing CAR-T cell therapy. **Methods:** We performed a retrospective, single center study at UCLA Medical Center of adults with multiple myeloma who received commercial CAR-T cell therapy from 6/1/2021 to 12/31/2024. Patients were required to have NGS data from a bone marrow sample within 1 year prior to CAR-T cell infusion. Patients were excluded if they had a prior diagnosis of myelodysplastic syndrome or acute myeloid leukemia. CHIP mutations were defined as somatic mutations with VAF > = 2% and <40%, and KRAS, NRAS, EZH2, and TP53 mutations were excluded. **Results:** Of the 68 adult patients identified, 21 (31%) patients had CHIP mutations. The mean age was comparable between groups at 63 years old without CHIP and 66 years old with CHIP. The median number of prior lines of therapy in both groups was 4 (ranges 2 to 11), and the presence of high-risk cytogenetics was similar between groups (45% with CHIP vs. 50% no CHIP). A single CHIP mutation was detected in 15/21 patients, while six patients had two or more mutations in different genes with DNMT3A as the most common mutation. The overall response rate (95% in CHIP vs. 91% in no CHIP; p = 0.99) and the complete response rate did not differ by CHIP status (81% in CHIP vs. 61% in no CHIP; p = 0.10). Similarly, CHIP mutations did not impact progression free survival (PFS of 1.3 years in patients with CHIP mutations vs. 1.5 years without CHIP mutations;HR 0.95; 95% CI: 0.41–2.23; p = 0.91) nor overall survival with a 1-year OS of 87% (95% CI: 69–94%) in patients with CHIP mutations vs. 86% (95% CI: 69–94%) in patients without CHIP mutations (HR 0.84; 95% CI; 0.22–3.26; p = 0.80). Patients with CHIP mutations were more likely to develop CRS (100% vs. 70%; p = 0.007) and to receive tocilizumab for CRS (90% vs. 60%; p = 0.01) than patients without CHIP mutations; however, there was no difference in the incidence of ICANS (33% in patients with CHIP vs. 17% in patients without CHIP, p = 0.20). While there was no difference in cytopenias at days 90 or 120, there was a notable increase in the amount of G-CSF used between days 90–120 (27.8% in CHIP vs. 5% without CHIP, p = 0.02). **Conclusions:** Although CHIP did not negatively influence the response rate, complete response rate, survival, or progression free survival in MM patients after CAR-T cell therapy, it did confer a higher risk of inflammatory response seen with increased frequency and grade of CRS.

PA-013

Synergistic Anti-Tumor Effects of CAR T Cells and a Personalized Tumor Vaccine

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Introduction: Chimeric antigen receptor (CAR) T cell therapy has shown great efficacy in hematologic malignances. However, relapse is common due to mechanisms such as antigen loss, CAR T cell dysfunction and limited persistence. We developed a personalized dendritic cell (DC)-based cancer vaccine whereby diverse tumor antigens are presented in the context of autologous MHC. In clinical trials, the vaccine has shown safety and immunogenicity. We hypothesized that a combinatorial immunotherapy strategy integrating CAR T cells with our vaccine will enhance CAR T efficacy overcoming single-antigen targeting limitations and promoting durable tumor-specific immunity. **Methods:** To evaluate this approach, we used the A20 murine lymphoma model. Syngeneic BALB/c T cells were transduced with a CD19-targeting CAR. The DC/tumor vaccine was generated by PEG-mediated fusion of A20 cells and BALB/c DC. For in vitro studies, CAR T or T cells were ex vivo primed with vaccine. For in vivo studies, vaccine-primed T cells (Vac T) were isolated from vaccinated mice and ex vivo expanded with CD3/CD28 Dynabeads and 4-1BB antibody. Naïve T cells from matched unvaccinated mice served as controls. Lymphoma was induced by A20 tail vein injection. Vac T or CAR T cells were infused 1 or 7 days later, respectively. Mice were lymphodepleted 24 hours prior to CAR T infusion. Tumor burden was assessed by luciferase activity in $CD19^+$ (Firefly) and $CD19^-$ (Renilla) A20 cells. **Results:** Ex vivo vaccine priming enhanced CAR T activation and persistence, resulting in heightened tumor cytotoxicity. Yet, ex vivo vaccine primed CAR T remained unable to target tumor variants lacking the CAR antigen. The combination of CAR T and ex vivo primed T cells resulted in enhanced in vitro killing of tumor cells, regardless of their expression of the CAR antigen, compared to either monotherapy.In vivo, the combination of CAR T and Vac T cells demonstrated a synergistic effect, with median survival not reached at 8 months post-tumor inoculation (vs 21, 22, and 46 days in mice treated with naïve T, Vac T, or CAR T cells, respectively). Similarly, in a model of limited CAR T cell efficacy, the combination therapy demonstrated a survival advantage ($p \leq 0.05$ vs control) not achieved by either therapy alone. Importantly, in an in vivo heterogenous tumor model composed of antigen-positive and -negative tumor clones, the combination efficiently targeted both tumor populations (median survival 40 days vs 22-34 in CAR T or Vac T alone; p vs naïve $T \leq 0.001$; p vs CAR $T \leq 0.05$). **Conclusions:** The DC/tumor vaccine enhances CAR T persistence and elicits a polyclonal T cell response capable of targeting tumor clones refractory to CAR T killing due to antigen-loss. The combination of CAR T and vaccine may represent a novel strategy to overcome resistance and improve the durability of responses to CAR T therapy. A clinical trial of vaccination and CAR T therapy is planned for patients with advanced myeloma.

PA-014

Outpatient Step-Up Dosing of Teclistamab (TEC): An Implementation Process Shifting from the Academic Inpatient (IP) to Community Outpatient (OP) Setting

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Introduction: Step-up dosing (SUD) of TEC can mitigate severity of cytokine release syndrome (CRS). In trials, patients (pts) are admitted for 24–48 hr monitoring after each SUD, but bed capacity may limit in the real world. Outpatient (OP) SUD experience is growing but mostly at experienced academic centres, leaving access gaps in the community. We present a structured approach to shift TEC SUD from the IP to OP setting, and from academic to community centres. **Methods:** To start, we formed a TEC Working Group (providers, nurse educator, pharmacists, project manager) adapting TEC SUD protocols from IP trials to the OP setting. We then tested protocols in a pilot cohort of 13 pts at our academic centre, reviewing pts in sequence for logistics and safety (treatment metrics, toxicity management, resource use). Safety concerns/inefficiencies led to process modifications and re-testing in subsequent pts. Learnings were collated in a Handbook for community implementation. **Results:** All 13 pilot pts were triple-drug refractory, median 3 prior lines, median age 67 (54–82), non-frail (ECOG 0-2, Rockwood frailty score <6). Various SUD schedules were used, most MWF. During the 3 SUD period, pts were seen daily until 48 hrs post-SUD3. CRS occurred in 6 pts (46%; all grade 1), onset 1–2 days after SUD2 only. In the OP setting, we mandated tocilizumab (TOCI) for CRS grade 1 (fever only): 5 pts received TOCI, defervescing in 1.5–4.1 hrs, enabling 4 to go home same day. Two were admitted for monitoring but discharged next day without intervention. Grade 1 ICANS occurred in 2 pts, 1 received steroid × 1. 6/13 (46%) had SUD delays (mostly SUD3). OP chair time was 3 hrs 27 mins, with 1hr monitoring post-dose. 85% required additional supports on daily visits (fluids, transfusions, imaging). Selected pilot learnings include: Simple fitness assessment can guide OP selection; daily visits during SUD period safely captures most toxicity events and supports additional care; Mon/Wed/Mon SUD schedule best avoids weekend CRS intervention and is flexible for SUD3 delays; CRS can be treated as an OP using a 4-hr holding space to monitor CRS resolution after TOCI; preemptive TOCI for grade 1 CRS may reduce severity and leads to efficient TOCI use (38% received 1 dose). The TEC Working Group then compiled pilot learnings into a practical Handbook with 3 sections: TEC OP Logistics (selection, resources, training), Patient Resources (alert card, home monitoring, education), and Management Guide (e.g. OP treatment of CRS). The Handbook is now undergoing implementation at a partner community site, with 3 others planned. Evaluation of caregiver burden is ongoing. **Conclusions:** Here we demonstrate a structured process for using academic expertise to shift a complex IP-based treatment into the OP community setting, promoting capacity and access closer to home. Though our Implementation Science pilot focuses on TEC in myeloma, processes can be applied to other complex therapies across cancer types.

PA-015

Non-linear Impact of BMI on Anti-BCMA CAR-T Outcomes: Overweight Paradox in Myeloma

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Introduction: Anti-B cell maturation antigen (BCMA) chimeric antigen receptor T cell therapies (CAR-T) have been transformative in relapsed/refractory multiple myeloma (RR MM), yet predictors of response and toxicity remain incompletely understood. Obesity and metabolic co-morbidities may influence the outcomes via immune dysregulation and therapy tolerance. In this study, we investigated the relationship between BMI, and metabolic co-morbidities with efficacy and safety post-CAR-T. Our findings aim to optimize patient selection and risk stratification in this vulnerable population. **Methods:** We retrospectively evaluated a cohort of patients treated with anti-BCMA CAR-T for RR MM at Massachusetts General Hospital from 2016–2023. We utilized restricted cubic spline modeling to evaluate the relationship between BMI and progression free survival (PFS). PFS and overall survival (OS) were estimated using the Kaplan-Meier method and compared with log-rank tests. Multivariate Cox proportional hazards models for PFS and OS were utilized to predict factors associated with CAR-T outcomes. **Results:** Cubic spline modeling revealed a non-linear association between BMI and CAR-T outcomes. Overweight patients (BMI 25.0–29.9 kg/m^2) had significantly worse PFS compared to normal weight (<25.0 kg/m^2) and obese (≥30.0 kg/m^2) cohorts: 12-month PFS was 51.9%, 28.8%, and 62.6% for normal-weight, overweight, and obese groups, respectively ($P < 0.001$). Similarly, 12-month OS was 82.9%, 61.4% and 84.2% ($P = 0.006$), while the complete response rate was 42.9%, 36.4% and 56.1% ($P = 0.185$) for normal-weight, overweight, and obese groups. Rates of cytokine release syndrome (CRS), immune effector cell neurotoxicity syndrome

(ICANS), and inflammatory markers (ferritin, CRP, or LDH) were similar between all groups. Multivariate analyses adjusting for significant univariate factors (prior lines of therapy, transplant history, pre-lymphodepletion hemoglobin, platelets, ferritin, and CRP) confirmed superior PFS and OS in both normal-weight and obese patients compared to overweight patients. **Conclusions:** Our findings of a U-shaped BMI-survival relationship in MM patients treated with CAR-T challenges conventional linear analyses, suggesting that metabolic dysregulation may differentially impact CAR-T efficacy at different BMIs. We found a robust effect of BMI on CAR-T outcomes, with overweight BMI patients having worse outcomes than those with normal or obese BMIs. Given that obesity and metabolic disorders affect >40% of the global population and overweight/obesity rates continue to rise, understanding modifiable risk factors that can refine patient selection, or affect toxicity mitigation, and supportive care strategies for CAR-T recipients is critical.

PA-016

Delayed Hematologic Recovery after BCMA CAR-T is Associated with Progressive Loss of Endogenous T cell Diversity after CAR-T Infusion

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Introduction: BCMA-directed CAR-T can induce deep and durable remissions in myeloma patients, but a significant subset develop prolonged cytopenias. We previously reported (Avigan et al, ASH 2024 abstract 3329) that patients with prolonged cytopenias beyond day 100 have decreased survival and persistently increased inflammatory markers after CAR-T. The endogenous T cell repertoire, as reflected by native T cell recovery after lymphodepletion and CAR-T, is similarly associated with outcomes and may be both a reflection and important mediator of inflammatory dysregulation. We therefore hypothesized that patients with delayed hematologic recovery after CAR-T would show a distinct endogenous T cell recovery pattern, which may contribute to ongoing hematotoxicity. **Methods:** We reviewed patients treated with cilta-cel with available NGS of their T cell receptor (TCR) repertoire within 2 years and prior to relapse. Patients were divided by hematologic recovery before or after 100 days post-CAR-T, with recovery defined as the first of a consecutive 30-day period without grade 3 toxicity or growth-factor support. T cell clones present at more than 3× the upper limit of the polyclonal background were considered clonally expanded, in accordance with our center's validated protocol, and Fisher's exact test compared clonality distributions between groups. TCR diversity within top 10 clones was calculated by the Shannon equitability index and compared by Wilcoxon rank-sum test, as well as by multivariate linear regression analysis modeling diversity over time and adjusting for age and prior lines of therapy. **Results:** A total of 32 TCR samples across 21 patients were included. Patients had a median age of 63.5 and median 5 prior lines of therapy; 11 (52%) had sustained hematologic recovery prior to day 100, and 10 (48%) had prolonged cytopenias beyond 100 days. Patients with delayed hematologic recovery had a trend toward increased prevalence of expanded monoclonal TCR populations compared to those with early myeloid recovery (60% vs 27%, $p = 0.08$), including both at timepoints before 6 months (50% vs 17%) and beyond 6 months post-CAR-T (57% vs 22%). While both groups showed similar TCR diversity at early timepoints, patients with delayed hematologic recovery had significantly lower T cell diversity after 6 months ($p = 0.029$). Similarly, a multivariate linear regression of native TCR diversity showed stable diversity in those with early hematologic recovery but highlighted progressive loss of endogenous TCR clonal diversity over time after CAR-T in the patients with delayed myeloid recovery ($p = 0.032$). **Conclusions:** Patients with delayed hematologic recovery after CAR-T showed increased TCR clonal dominance and decreased diversity in endogenous T cell populations, with a marked disruption in diversity after 6 months. Our current efforts are aimed at understanding and characterizing the role of native T cell diversity in driving inflammatory dysregulation, hematologic toxicity, and disease response after CAR-T.

PA-017

Bispecific Outpatient Step-Up Dosing with Prophylactic Dexamethasone: The BOSS Program Experience in Myeloma

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Introduction: While outpatient step-up dosing (SUD) for bispecific antibodies (BsAbs) is increasingly adopted, mitigation strategies for CRS/ICANS vary significantly across institutions. The BOSS (Bispecific Outpatient Safe Step-up) program at MGH implements a distinctive approach using prophylactic dexamethasone without preemptive tocilizumab, combined with structured remote monitoring. **Methods:** The BOSS program was designed to facilitate

Table 1 (abstract PA-017) Incidence of CRS, ICANS, and Infections by BsAb in BOSS and iSUD Cohorts

	BOSS				iSUD			
	Elran n = 11	Tec n = 3	Talq n = 1	Total n = 15	Elran n = 30	Tec n = 28	Talq n = 39	Total n = 97
CRS, n (%)	2 (18.2%)	0	0	2 (13.3%)	16 (53.3%)	13 (46.4%)	23 (59.0%)	52 (53.6%)
ICANS, n (%)	1 (9.1%)	0	0	1 (6.7%)	7 (23.3%)	6 (21.4%)	7 (17.9%)	20 (20.6%)
Infections, n (%)	1 (9.1%)	1 (33.3%)	0	2 (13.3%)	6 (20%)	3 (10.7%)	7 (17.9%)	16 (16.5%)

outpatient administration of BsAbs for patients with plasma cell disorders, allowing SUD on Days 1 and 3, followed by full dose on Day 8. Supportive care included standard pre-medications on BsAb days plus prophylactic dexamethasone (12 mg on Days 2, 4–7, and 9–10) and daily telehealth symptom assessments. A retrospective analysis was conducted on 15 patients enrolled in the BOSS program (elranatamab n = 11, teclistamab n = 3, talquetamab n = 1), who met eligibility criteria (adequate organ function, low disease burden, and proximity to the treatment facility). Additionally, data were collected from 97 patients who received standard inpatient SUD (iSUD), focusing on CRS, ICANS, and infection rates through Day 14. **Results:** A total of 112 patients who received all SUD and first full dose were included (median age 72 years). The BOSS cohort (n = 15) had 13.3% CRS (2/15, 0% recurrent, all G2 with median onset 41 hours post-SUD#1), 6.7% ICANS (1/15, G1), 13.3% infections (2/15), and 87% with no hospital stay (13/15). The iSUD cohort (n = 97) had 53.6% CRS (52/97, 11% recurrent, 41% max G1, 12% max G2), 20.6% ICANS (20/97, G1-3) and 16.5% infections (16/97), with a median 8-day hospital stay. The timing of CRS differed; CRS in BOSS occurred exclusively post-SUD#1, vs. CRS in iSUD were 34% post-SUD#1, 42% post-SUD#2, 11% post-SUD#3 (talq q2w only) and 13% post-full dose. The median onset for ICANS occurred earlier in BOSS (6 hours) compared to iSUD (77 hours). Table 1 presents the incidence of CRS, ICANS, and infections classified by each BsAb for both BOSS and iSUD cohorts. **Conclusions:** The BOSS program's outpatient SUD strategy, featuring prophylactic dexamethasone without preemptive tocilizumab, led to markedly lower rates of CRS (13 vs. 54%) and ICANS (7% vs. 21%) compared to historical inpatient management. With 87% of patients avoiding hospitalization, this approach offers a viable alternative for select myeloma patients receiving BsAbs. Outcomes analysis is in progress to further assess the long-term implications of BOSS strategy. These results support further evaluation of optimized outpatient protocols to improve patient convenience and resource utilization.

PA-018

Severe Tumor Flare Pain Syndrome During Step-Up Dosing of Teclistamab in High-Risk Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab (TEC) is the first approved B-cell maturation antigen×CD3 bispecific antibody for the treatment of triple-class exposed relapsed/refractory multiple myeloma (RRMM). In the MajesTEC-1 trial, TEC produced profound and durable responses with a manageable safety profile, with 3.6% of patients complaining debilitating bone pain episodes. In contrast, we have observed a higher frequency of such events in our outpatient setting, particularly during the step-up dosing (SUD) phase. This study aimed to assess the incidence, presentation, and outcomes of tumor flare pain syndrome associated with TEC. **Methods:** We conducted a retrospective, single-center analysis of patients ≥18 years of age with RRMM treated with TEC in the outpatient setting. Tocilizumab prophylaxis 8 mg/kg was administered before SUD 1 of TEC. The SUD regimen consisted of 0.06 mg/kg subcutaneously (SC) on day 1, 0.3 mg/kg SC on day 3, and 1.5 mg/kg SC on day 5. TEC 1.5 mg/kg SC was then given weekly, until MM progression or unacceptable toxicity. The primary endpoint was the incidence of severe tumor flare pain syndrome occurring during SUD (equivalent to bone pain grade ≥3 per CTCAE v5.0). **Results:** A total of 49 patients who received teclistamab were reviewed. Among them, we identified 7 subjects (5 males, 2 females) who developed tumor flare pain syndrome during SUD, including 3 patients with plasmablastic myeloma and 1 with plasma cell leukemia. Median age was 63 years (39–79 years). Each of these patients had extramedullary disease at the beginning of TEC administration. One patient experienced grade 2 CRS, none had ICANS. Median time until the onset of tumor flare pain syndrome was 3 days (range: 2–4) after the first TEC dose, and the median duration was 5 days (range: 2 to 7). Tumor flare pain syndrome only occurred during SUD. Imaging finding on PET-CT or CT-scan included (in contrast with baseline imaging) progression of bone lesions (n = 4), progression of extramedullary plasmacytomas (lung and peritoneum; n = 2) and a new muscular lesion in one patient. Four patients required hospitalization for pain control. All received opioids, and 4 (n = 4/7) were relieved by dexamethasone 10 mg PO/IV q 6 h. All 7 patients were evaluable for clinical response; with complete response in 2, partial response in 2, and stable disease in 3. **Conclusions:** Clinicians should be aware that tumor flare pain syndrome is an underreported manifestation occurring during the SUD phase of T-cell redirected therapies. It is associated with intense

pain sometimes requiring hospitalization and may mimic disease progression radiographically (pseudoprogression). Dexamethasone seems most beneficial for pain management, but prospective studies are needed to guide optimal relief strategies.

PA-019

Factors Associated with Response, Neurotoxicity, and Survival in Patients with Multiple Myeloma Treated with Chimeric Antigen Receptor T-cell (CAR-T) therapy

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Introduction: Chimeric Antigen Receptor T-cell (CAR-T) therapy is emerging as a standard treatment for patients with relapsed/refractory multiple myeloma (RRMM). However, its associated side effects can be disabling and reliable predictive factors for responses and toxicities remain unclear. **Methods:** A retrospective study of RRMM patients who received Ide-cel or Cilta-cel at our institution between 2021–2025 was conducted to identify factors associated with duration of response (DoR), neurotoxicity (NT), cytokine release syndrome (CRS), and overall survival (OS). **Results:** A total of 93 patients who received Ide-cel (24/93), or Cilta-cel (59/93) were included in this study. The median age at the time of CAR-T therapy infusion was 66 years (range: 35–83). 45/77 patients (58.4%) had high-risk cytogenetics. Patients received a median of 4 prior lines (range: 0–22) and 42% had progressive disease at the time of CAR-T infusion. Among the 93 patients, 72 (77.4%) developed some grade of CRS (G1–G2: 68/72, 94.4%), while 15 (16.1%) experienced NT. The median onset of NT was 13 days, with 7 patients (7.5%) presenting with delayed NT, including cranial nerve palsies and strokes, after day 15. An increase of ≥50% from baseline ferritin ($P = 0.0008$) or C-reactive protein (CRP) ($P = 0.04$), and a peak absolute lymphocyte count (ALC) >1 × 109/L ($P < 0.0001$) were associated with CRS. High MM stage ($P = 0.026$), peak ferritin >400 ng/mL ($P = 0.004$), and peak ALC >1 × 109/L ($P = 0.046$) were linked to the development of NT, while type of product ($P = 0.04$) and ≤3 prior lines ($P = 0.07$) to the severity of NT. Elevated IL-6 and IL-8 levels were detected in the serum or cerebrospinal fluid of patients with severe NT. Median follow-up was 8.5 months. The overall response rate (ORR), including partial responses or better, was 92.5%. Ide-cel therapy, poor pre-CAR-T response, and absence of CRS were associated with inferior ORR. 12/58 evaluable patients (21%) experienced progression within 6 months of infusion. The median DoR was 25.3 months (95% CI: 14.2–36.2). Variables influencing DoR included type of product ($P = 0.003$), pre-CAR-T response ($P = 0.008$), age >60 years ($P = 0.02$), number of prior lines ($P = 0.07$), onset of CRS ($P < 0.001$), baseline ferritin >200 ng/mL ($P = 0.012$), peak ferritin >400 ng/mL ($P = 0.018$), CRP increase of >50% ($P = 0.008$), peak ALC >3 × 109/L ($P = 0.06$), and soluble C5b9 >250 ng/mL ($P = 0.08$). The median OS was 38.7 months, with 3-month and 9-month OS estimates of 97% and 62%, respectively. Factors associated with OS included peak ALC >1 × 109/L ($P = 0.09$), peak AMC >0.3 × 109/L ($P = 0.02$), and C5b9 >250 ng/mL ($P = 0.09$). **Conclusions:** Patients with NT had higher ferritin, peak ALC, and cytokine levels. While peak ALC was associated with NT, it also correlated with longer DoR and OS. Steroid prevention has been suggested to reduce delayed NT, but since peak ALC alone may not be a definitive biomarker, a collaborative effort is needed to evaluate toxicity risks while balancing clinical responses.

PA-020

Real-world Outcomes Among Patients (Pts) with Relapsed or Refractory Multiple Myeloma (RRMM) Initiating Teclistamab (Tec) at a Large Community Oncology Center in the US

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Introduction: Most U.S. pts with multiple myeloma (MM) are treated in community oncology clinics, whose practices may differ from academic centers. Tec, the first BCMAxCD3 bispecific antibody approved for RRMM, is increasingly used in clinical practice, but real-world data from community settings are limited. This study describes step-up dosing (SUD) patterns, safety, and effectiveness of Tec in pts treated at a large U.S. community oncology network. **Methods:** Patient chart and EMR data for adult pts with RRMM and ≥1 record for Tec between 10/26/2022–12/31/2024 were used. Pts were followed from index (date of first Tec SUD) to the earliest of last activity, death, or data cutoff. All variables were summarized descriptively for all pts (overall) and for subgroup of pts who would have been MajesTec-1 eligible (Tec-eligible). Time-to-event outcomes were estimated using the Kaplan-Meier method. **Results:** A total of 50 pts met the study criteria (median [IQR] age 73 years [45-88]; 70% White; 18% Black; 36% R-ISS stage III; 46% high-risk cytogenetics; 6% ECOG ≥2; 6% prior BCMA exposure). Of the 50 pts, 37 (74%) were Tec-eligible (median age [IQR], 73 years [45–88]; 84% White; 14% Black; 32% R-ISS stage III; 43% high-risk cytogenetics). Both cohorts had a median of 4 prior lines of therapy. A total of 38 pts (76%) in overall and 30 (81%) in Tec-eligible were referred to another institution for inpatient SUD, while the remaining pts (12 [24%] in overall and 7 [19%] in Tec-eligible) completed SUD

in the outpatient setting. All pts referred to another institution for SUD returned to the community clinic for first treatment dose within a median of 15 days after SUD completion. During SUD, cytokine release syndrome (CRS) occurred in 19 (38%) overall pts (32% Grade [G]1, 6% G2) and 17 (46%) Tec-eligible pts (38% G1, 8% G2); 2 pts in both cohorts experienced immune effector cell-associated neurotoxicity syndrome (ICANS; 1 G1, 1 G2). All CRS and ICANS events were resolved. At a median follow-up of 14.3 months, infections occurred in 34 (68%) overall pts and 27 (73%) Tec-eligible pts; only 4 needed hospitalization for treatment of infections, while others were resolved outpatient. Pts received a combination of antibiotics, antivirals, IVIG as prophylaxis for infections; 46% pts received at least one dose of IVIG prophylaxis in both cohorts. The overall response rate was 74% in all pts and 73% in Tec-eligible. Estimated 12-month PFS rate was 65% in overall and 76% in Tec-eligible pts; 12-month OS rates were 75% and 78%, respectively. **Conclusions:** Overall, pts treated with Tec in community settings experienced numerically comparable effectiveness and safety outcomes as compared with MajesTec-1 trial, despite being elderly with high-risk cytogenetics, high disease burden, and heavily pretreated pts. Most adverse events were low grade, highlighting the feasibility of safely administering Tec and effectively managing AEs in outpatient and/or community settings.

PA-021

First-in-Human Study of GPRC5D-Targeted CAR T-cell Therapy CT071 with an Accelerated Manufacturing Process for the Treatment of Relapsed/Refractory Multiple Myeloma

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Introduction: Relapsed or refractory multiple myeloma (RRMM) remains incurable. CT071 is a fully human, autologous chimeric antigen receptor (CAR) T-cell therapy targeting the G protein-coupled receptor, class C group 5 member D (GPRC5D) that is manufactured using an accelerated process resulting in younger T cells. In this first-in-human, single-arm, open-label clinical trial, we evaluated the safety and efficacy of CT071 in RRMM patients (NCT05838131). **Methods:** RRMM patients previously treated with ≥3 prior lines of therapy (LOT) including a proteasome inhibitor and an immunomodulatory agent, or were refractory to both drug classes, and had progressed on the last LOT, with ECOG 0-2 were enrolled. CT071 was administered as a single infusion at doses of 1.0 × 105 or 3.0 × 105 CAR+ T cells/kg using i3+3 design for dose-escalation and dose-expansion. **Results:** A total of 20 patients received CT071 with a median age of 63.0 y; 70% with high-risk cytogenetics; 20% ≥1 extramedullary plasmacytoma; 95% Revised International Staging System (R-ISS) stage II/III; median 5 prior LOT with 95% double-class refractory, 65% triple-drug refractory, 25% penta-drug refractory, and 25% BCMA or BCMA/CD19 targeted CAR T cells exposed – 9 patients at 1.0 × 105 cells/kg and 11 patients at 3.0 × 105 cells/kg. As of December 9, 2024, no dose limiting toxicity (DLT) was observed. Twelve (60%) patients experienced cytokine release syndrome (CRS) either at Grade 1 (n = 9) or Grade 2 (n = 3). Only 1 (5%) patient reported immune effector cell-associated neurotoxicity syndrome (ICANS) at Grade 3. Onychomadesis and skin rash were reported in 4 patients (20%) and 1 patient (5%), respectively; all were Grade 1. Seven (35%) patients experienced treatment-related serious adverse events, including Grade 3 or 4 thrombocytopenia (n = 2), Grade 3 pneumonia (n = 3), Grade 2 viral encephalitis (n = 1), Grade 3 ICANS (n = 1) and Grade 2 decreased appetite (n = 1). With a median follow-up of 10.7 months (range, 4.3 to 16.8), the objective response rate was 100% (95% CI, 83.2%–100%) including 10 patients (50%) with stringent complete response (sCR), 4 patients (20%) with very good partial response (VGPR) and 6 patients with (30%) partial response (PR). Notably, 7 patients achieved complete response or better by week 4. All 5 patients (25%) previously treated with an anti-BCMA CAR T (n = 1) or anti-BCMA/CD19 CAR T (n = 4) responded with two patients achieving PR, one patient achieving VGPR and the other two reaching an sCR. Eighteen out of 20 patients (90%) achieved minimal residual disease (MRD) negativity at 10^{-6} threshold. **Conclusions:** The initial findings from this Phase 1 study of CT071 demonstrate an acceptable safety profile and promising clinical efficacy in patients with RRMM, including those with prior exposure to BCMA. These results warrant further clinical evaluation.

PA-022

Real-World Long-Term Effectiveness and Safety Outcomes Among Patients Receiving Teclistamab for the Treatment of Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: In the MajesTEC-1 clinical trial, teclistamab (Tec) demonstrated an overall response rate (ORR) of 63% (median follow-up 30.4 months) in adult patients (pts) with RRMM. Pts in clinical trials may not fully reflect real-world (RW) pt populations, including pts with no prior anti-BCMA targeted therapy exposure. RW studies of Tec report ORRs of 59% to 66%, but many are limited by short follow-up periods. To address this evidence gap, this study aimed to assess long-term outcomes of pts treated with Tec in a RW setting. **Methods:** This retrospective observational study included adult pts with RRMM treated with ≥1 dose of Tec from October 2022 (FDA approval) to March 2025 at a large academic center in the US (cut-off date of April 1, 2025). Pts were assessed from the index date (date of Tec initiation) to death or the end of data cut off, whichever came first. Pt characteristics (frequency (%) or median) and treatment history were recorded at the index date. Dosing schedule and safety and effectiveness outcomes (IMWG criteria) were recorded during the follow-up period. Progression-free survival (PFS) and overall survival (OS) were reported (Kaplan Meier). **Results:** Of 123 pts included in the study, the median age was 71 years, 34.3% were ≥75 years old, 53.6% were female, and 19.5% were Black. High-risk cytogenetic abnormalities (including 1q+, del(17p), t(4;14), t(14;16), and t(14;20)) was present in 49.1% of pts. Pts had a median of 5 (range: 3–19) prior lines of therapy, 35.8% were BCMA-exposed (20.0% CAR-T, 2.5% bispecifics, 13.0% antibody-drug conjugates), 32.5% had extramedullary disease and 61.8% had received a stem cell transplant. After a median follow-up of 17 months (95% confidence interval: 14–20), ORR was 61.6% among 112 response-evaluable pts (47.3% had a best response of very good partial response or better). After 18 months of initiating Tec, response was maintained by 59% of pts. The 18-month PFS and OS rates were 36% and 60%, respectively. Step-up dosing (SUD) was completed by 95.9% of pts, with most (92.7%) administered in an inpatient setting (outpatient: 4.1%, hybrid: 3.3%). During SUD, cytokine release syndrome occurred in 54.5% of pts (all grade (G) 1/2) with 9.8% of pts experiencing an event after the first full dose. Immune effector cell-associated neurotoxicity syndrome occurred in 13.0% of pts (G1/2, except for one G4 event); 5.7% of pts experienced an event after the first full dose. Infections at any time during Tec treatment occurred in 71.5% of pts (G1: 8.9%, G2: 23.6%, G3: 29.3%, G4: 2.4%, G5: 7.3%). Among 121 pts, ≥1 dose of intravenous immunoglobin was administered to 6.5% as primary prophylaxis and to 44.6% to treat hypogammaglobulinemia and/or infection. **Conclusions:** Pts treated with Tec in the RW had comparable long-term effectiveness and safety outcomes to the MajesTEC-1 trial pts, despite pts in this analysis being older, more heavily pre-treated (including prior BCMA exposure), with more pts having high burden of disease and high-risk cytogenetics.

PA-023

Outcomes of Teclistamab (Tec) Step-Up Dosing in Outpatient/Hybrid Settings Among a Large Sample of Relapsed Refractory Multiple Myeloma (RRMM) Patients Treated with Tec

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Introduction: Tec is a first-in-class BCMA × CD3 bispecific antibody approved for the treatment of RRMM and is initiated using step-up dosing (SUD). In clinical practice, Tec SUD is shifting towards outpatient (OP) or hybrid (HY) initiation, although real-world (RW) evidence on Tec has been largely limited to academic centers with SUD conducted primarily in inpatient settings. To address these gaps, clinical outcomes of Tec patients (pts) were assessed in a large, multi-center data predominantly from US community practices and in a subgroup of pts who received Tec in OP/HY settings during SUD. **Methods:** This was a retrospective, multicenter chart review study. Data were extracted from electronic medical charts of eligible pts from a large oncology provider network. Adult pts with RRMM initiating Tec since FDA approval (10/25/22) were included. Characteristics and treatment history were captured during the baseline period; cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infections were captured during the treatment period; and clinical outcomes were captured during the follow-up period. Variables were analyzed in all included pts and in a subgroup of OP/HY pts (i.e., who completed SUD fully in OP setting or had ≥1 SUD dose in the OP setting). **Results:** The overall cohort and OP/HY SUD subgroup included 222 and 71 pts (29 OP, 42 HY), respectively, with 66% of all pts treated by community providers. The overall cohort had a median age of 68 years, with 60% male, 75% White and 19% Black (OP/HY SUD: median age 63 years, 61% male, 78% White and 18% Black). At Tec initiation, 37% of the overall cohort had R-ISS stage III disease (OP/HY: 27%), 77% had an ECOG score of 0-1 (OP/HY: 78%), 38% had high-risk cytogenetics (OP/HY: 42%), and 95% were triple-class exposed (OP/HY: 93%). Median prior lines of therapy were 4 in both the overall cohort and OP/HY subgroup. During SUD, CRS occurred in 33% (highest grade (G) 1: 21%, G2: 10%, G3: 2%) of all pts and 27% (G1: 16%, G2: 9%, G3: 3%) of OP/HY pts; ICANS occurred in 5% (highest G1: 3%, G2: 2%, G4: 1%) of all pts and 4% (G1: 3%, G2: 1%) of OP/HY pts. Primary prophylaxis for infections was administered to 81% of all pts and 72% of OP/HY pts. At a median follow-up of 5.4 months, infections occurred in 15% (highest G1: 6%, G2: 7%, G3: 1%, G5: 1%) of all pts and 18% (G1: 9%, G2: 6%, G3: 3%, G5: 1%) of OP/

HY pts during Tec treatment. Treatment discontinuations due to CRS, ICANS and infections occurred in 2%, 1%, and 2% of all pts, respectively. The overall response rate (ORR) was 70% in all pts and 78% in OP/HY pts. **Conclusions:** In this RW study of pts treated with Tec in primarily community settings, safety (CRS, ICANS, infections) and effectiveness (ORR) outcomes appeared comparable between pts receiving Tec SUD in OP/HY settings and the overall cohort, demonstrating that it is feasible to administer Tec SUD in OP/HY settings with focus on appropriate prophylaxis and management.

PA-024

Teclistamab and Talquetamab in Relapse/Refractory Multiple Myeloma (RRMM) Patients with Severe Renal Insufficiency: Case Series

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Introduction: While Multiple Myeloma (MM) is not curable, novel therapies have increased time to disease progression. Teclistamab (Tec) and Talquetamab (Tal), bispecific antibodies, approved for relapsed-refractory Multiple Myeloma (RRMM) but patients with creatinine clearance (CrCl) < 40 mL/min were excluded in the studies. To include these patients in standard therapies, we present five patients with renal insufficiency who responded to Tec and Tal without added toxicity. **Methods:** A retrospective, single-center analysis of Tec or Tal initiations at OhioHealth between October 2022 to November 2025 with a history of renal insufficiency and CrCl less than 40 ml/min at time of treatment initiation. **Results:** Patient 1: 67 y/o M with Kappa light chain MM, progressed on 8th line of therapy. CrCl was 31 ml/min. Labs at progression: Serum kappa light chain (KLC) 3726 mg/L, K/L ratio 240.10. Started Tec 6/30/23, at usual prescribed dose. No neurotoxicity (ICANS) or cytokine release syndrome (CRS). Achieved a stringent complete response (CR). Time to first response (TTFR) (≥ Partial Response) 1 month. He had improved CrCl 23 ml/min. Patient 2: 75 y/o F with Lambda light chain MM progressed on 7th line of therapy. CrCl was 13.44 ml/min. Labs at progression: LLC 1759 mg/l. Started Tal 3/27/24, at usual prescribed dose. No ICANS or CRS. Reported dysgeusia but maintained weight. Achieved a very good partial response (VGPR). TTFR 1 month. She had improved CrCl 24 ml/min. Patient 3: 80 y/o F with IgG Kappa MM progressed on 8th line of therapy. CrCl was 9.0 ml/min. Labs at progression: KLC 40.62 mg/L, K/L ratio 5.83, M protein 1500 mg/dl. Started on Tal 7/23/24, at usual prescribed dose. Received Dexamethasone for grade 2 ICANS with resolution within 48 hours. Has maintained weight. Skin irritation improved with ammonium lactate. Achieved a partial response (PR). TTFR 1 month. She had improved CrCl 16.2 ml/min. Patient 4:77 y/o M with Lambda light chain MM progressed on 5th line of therapy. CrCl was 19 ml/min. Labs at progression: 3.07 mg/dl, LLC 13,765 mg/L, L/K ratio 17,206, Cytoreduced with 3 cycles of VD-PACE, then started on Tec 12/9/24, at usual prescribed dose. No CRS or ICANS. Achieved a VGPR. TTFR 1 month. He had improved CrCl 33 ml/min. Progressed after 5 cycles and started on Tal 4/22/25 with PR after Cycle 1. Patient 5: 74 y/o M with IgG Kappa MM progressed on 3rd line of therapy. CrCl was 19 ml/min. Labs at progression: KLC 4,106 mg/L, K/L ratio 2,976. Started on Tal 4/7/25 at usual prescribed dose. No CRS or ICANS. Achieved a PR. TTFR 1 month. He had improved CrCl 30 ml/min. **Conclusions:** Tec and Tal seem to be well tolerated in RRMM patients with CrCl <40 ml/min without added toxicities. Patients with RRMM with renal insufficiency should not be excluded from getting Bispecifics.

PA-025

Monitoring and Management of CMV and other Viral Reactivations with Bispecific Antibodies (BsAbs) for Patients with Relapsed and Refractory Multiple Myeloma (RRMM)

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Introduction: CMV and other viral reactivations are reported with BsAbs in patients with RRMM. Despite this there are no clear guidelines on the monitoring or management of viral reactivation whilst on treatment leading to variations in practice. We therefore analysed our data to help inform practice. **Methods:** This was a retrospective data collection from patients who completed ≥1 cycle of Teclistamab, Elranatamab or Talquetamab between Jan 2022–May 2025. Viral load was measured in blood by PCR at clinical discretion. Overall survival (OS) was estimated using Kaplan-Meier methods. **Results:** 99 patients (median age 65yrs (44–79)) received Teclistamab (48%), Elranatamab (34%) or Talquetamab (17%) at a median of 5 prior lines (0–11). Median duration of treatment was 6 months (1–40), with a median follow up of 11 months (2–40). 50% received G-CSF, 50% received IVIg replacement (of which 14% started prior to BsAb), at any point. Baseline CMV IgG serology was performed in

78% of patients: 55% positive, 45% negative. 56% patients had >1 CMV PCR test during treatment, 19% 1 PCR, 25% not tested. For BCMA BsAbs, 60 (73%) patients had CMV PCR tests of which 24 (40%) patients were positive at any point during treatment (all those tested were baseline IgG+), peaking at a median of 2.5 cycles. 54% had a peak viral load (VL) below the limit of quantification (BLQ) and 16% reactivated ≥1 other virus besides CMV. There were no clear cases of CMV end organ disease, although 2 patients received CMV treatment for possible disease. Management of asymptomatic CMV PCR positivity was variable. 3 interrupted treatment (median peak VL 57,980 IU/ml (range 4,452–72,992) for a median 97 days (66–146) with reduction of CMV VL whilst maintaining MM response. 21 patients continued BsAb treatment (peak VL 62% BLQ; 29% <1,000; 9% >1,000), with either maintenance of low levels, or spontaneous reductions in CMV titres, despite on-going treatment (peak VL range: BLQ-24,087, median: BLQ). 15/21 (71%) had a subsequent CMV PCR test which was also positive. None developed CMV disease. At the time of first CMV positivity, BsAb administration was given Q1W: 14, Q2W: 5, Q4W: 2. The likelihood of developing CMV reactivation was unrelated to age, number of prior lines, baseline lymphocyte count, nadir lymphocyte count, prior T cell immunotherapy status, nadir IgG level or use of IVIG. Other viral reactivations were identified by blood PCR but generally asymptomatic: adenovirus (2), EBV (8), parvovirus (1 case, symptomatic). 17% of Talquetamab patients had viral reactivation (2 CMV (both BLQ), 1 EBV), all were asymptomatic. OS was not affected by CMV reactivation: median 30 m for CMV PCR+ and not reached for CMV PCR - p = 0.5585. **Conclusions:** CMV reactivation is common with BCMA BsAbs and occurred early in treatment. Regular blood PCR monitoring for CMV IgG+ patients may be useful as interruption of treatment reduces viral loads, limiting the need for antiviral treatment. CMV disease in our data was rare as were other viral reactivations.

PA-026

Evaluation of Sequential Absolute Lymphocyte Count (ALC) in Patients with Relapsed Multiple Myeloma (RRMM) with Cranial Nerve Palsies (CNPs) Post Ciltacabtagene-Autoleucel (cilta-cel)

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Introduction: Cilta-cel is an FDA-approved CAR T-cell therapy targeting BCMA, for patients with RRMM after at least one prior therapy including a PI and IMID, or after four prior therapies including a PI, IMID, and CD38 antibody. Approval was based on the Cartitude 1 and 4 studies showing strong efficacy (Martin et al., 2023; San Miguel et al., 2023). Neurotoxicity occurs in up to 20% of patients, including ICANS and delayed effects like movement/neurocognitive toxicities (MNTs) and CNPs. MNTs are linked to high CAR T-cell expansion, measured by max ALC (Cohen et al., 2022), but factors associated with CNPs remain unclear. We aim to study baseline features and sequential ALC in these patients. **Methods:** We retrospectively reviewed the baseline characteristics of patients who received cilta-cel in our institution and developed CNPs (n = 14), compared to control cohort (n = 67). We examined sequential ALCs from day of cilta-cel infusion to day +30 and compared to a control cohort (n = 38), matched by age, gender, presence of extramedullary or high-risk disease, high marrow burden (≥50%), and ferritin >400 at time of lymphodepletion. Max ALC, days to max ALC, max ALC slope (change in ALC/time) and ALC D7 to max ALC slope (Max ALC - Day +7 ALC/ Day max ALC −7) were calculated for all patients with CNP and matched controls. **Results:** Between May 2022 and October 2024, 140 patients received cilta-cel, with 14 (10%) developing CNPs at a median of 17.5 days (range 14–32) post-infusion. Six patients had >1 CN involved, and CN 7 (n = 11) was the most common. Treatments included steroids with or without IVIG. CNPs resolved in 71.4% of cases, with a median time to recovery of 61 days (range 23–201). Patients with CNPs were older, had fewer prior LOT, higher max C-reactive protein value and more infections ($p < 0.05$ for all). There were no differences in the incidence of CRS or ICANS. Median time to max ALC was 12 days (range, 10–30) in both cohorts, but max ALC was higher in the CNP cohort when compared to matched control cohort (4.98 vs 2.36, p = 0.011). Similarly, the max ALC slope and ALCD7 to max ALC slope were higher in the CNP cohort vs the matched control cohort. (2.92 vs 1.36, p = 0.009 and 1.09 vs 0.43, p = 0.011, respectively). **Conclusions:** This study identified characteristics associated to increased risk of development of CNP post cilta-cel and showed that increased max CRP and max ALC were associated with higher risk to develop this complication. Intervention with suppressive dexamethasone in patients who exhibit ALC over 3 or CRP over 12, in an attempt to prevent CNP post cilta-cel, is ongoing and updated results will be presented.

PA-027

Linvoseltamab (LINVO) Monotherapy in Patients (pts) with Newly Diagnosed (ND) Multiple Myeloma (MM): Initial Dose-Escalation Results from the Window of Opportunity LINKER-MM4 Trial

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Introduction: LINVO, a B-cell maturation antigen (BCMA) × CD3 bispecific antibody, achieved an overall response rate (ORR) of 71% (complete response [CR] or better [≥CR] 52%) at the 200 mg dose in pts with relapsed/refractory (RR) MM. Pts with NDMM are likely to have more intact T-cell fitness than pts with RRMM, supporting study of LINVO in NDMM. We report safety and preliminary efficacy of LINVO monotherapy dose escalation in pts with NDMM in the open-label Phase (Ph) 1/2 LINKER-MM4 study (NCT05828511). **Methods:** Adults with previously untreated, symptomatic MM who were autologous stem cell transplantation (ASCT) eligible (TE) or ineligible (TIE) were enrolled. TE pts received LINVO induction then ASCT and LINVO consolidation; TIE pts received LINVO monotherapy until disease progression. Initial dose-escalation (Ph1A) and -expansion (Ph1B) data will inform the recommended Ph2 dose. Ph1A included modified step-up dosing (1 mg on Cycle [C] 1 Day [D] 1, 4 mg on C1D4, 25 mg on C1D8) and evaluated three full doses (50, 100, 200 mg). Ph1 primary endpoints were incidences of dose-limiting toxicities (DLTs), treatment-emergent AEs (TEAEs) and AEs of special interest. Secondary endpoints included ORR and depth of response by International Myeloma Working Group criteria, duration of response (DOR), and progression-free survival (PFS). **Results:** By Feb 11, 2025, 12 pts had received LINVO (50 mg, n = 3; 100 mg, n = 4; 200 mg, n = 5) in Ph1A; 75% were TE. Median follow-up was 9.1 months (mo; range 1.6–12.9). Median age was 64.5 years (range 43–82); 67% were male, 50% White, 42% Black/African American; 67% had bone marrow plasmacytosis ≥50%, 8% extramedullary plasmacytomas, 50% sBCMA ≥400 ng/mL, 42% R-ISS II, and 50% high cytogenetic risk. No DLTs were observed. Among all pts, the most common TEAEs were increased alanine aminotransferase (any Grade [Gr], 67%; Gr 3–4, 17%) and aspartate aminotransferase (50%; all Gr 1–2; transient in all but one pt). The most common hematologic TEAE was neutropenia (50%; all Gr 3–4). CRS was reported in 33% of pts (all Gr 1). No ICANS events were reported. Infections occurred in 58% of pts (Gr 3–4, 25%). There were no treatment discontinuations due to TEAEs or TEAEs resulting in death. Investigator-assessed ORR was 83%; 75% achieved ≥VGPR and 58% ≥CR. Median time to response was 1.1 mo. Five of seven CRs occurred within 6 mo of treatment initiation. Five pts (200 mg, n = 3; 100 mg, n = 2) were MRD evaluable, and all were MRD negative at 10^{-6} by clonoSEQ. Median DOR and PFS were not reached. At 6 mo, all pts maintained their response and were progression free. LINVO pharmacokinetics in NDMM aligned with prior RRMM findings. **Conclusions:** LINVO monotherapy had a generally manageable safety profile across all doses tested in TE and TIE pts with NDMM. The ORR, CR rate, MRD-negativity rate, and response durability were promising, supporting ongoing assessment of LINVO monotherapy in the front-line setting.

PA-028

Development of Anti-AL Amyloidosis CAR Phagocyte Therapy

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Introduction: Current anti-plasma cells therapies for AL amyloidosis reduce new fibril formation but do not remove existing deposits, which continue to damage organs. CAEL-101(c11-1F4), a fibril-specific monoclonal antibody in Phase 3A/B trials, promotes amyloid clearance via phagocytosis. However, the use of anti-CD38 antibodies in AL amyloidosis treatment and the recent failure of Birtamimab raised concerns that antibody-dependent phagocytosis for amyloid clearance may be impaired by high serum levels of anti-CD38 antibodies competing for Fc receptor binding. To address this, we developed a first-in-class human CAR phagocyte therapy based on 11-1F4 that directly targets amyloid deposits, bypassing Fc competition and enhancing amyloid clearance. **Methods:** The anti-AL amyloid CAR lentiviral construct was designed to include 11-1F4 scFv and FcRγ signaling domain with GFP tag. Irrelevant CD19-CAR-GFP or empty G4S-GFP construct (with scFv deleted) were used as controls. Transduced RAW264.7 or human $CD34^+$ cells were sorted by GFP+ flow. Human CAR-phagocytes were then differentiated from the transduced $CD34^+$ cells using M-CSF. CAR-P phagocytic activity was assessed using pHrodo Red-labeled AL amyloid fibrils, visualized by fluorescence microscopy. For in vivo assay, Dylight 755-labeled Len fibrils (5 mg/mouse) and luciferase-expressing 11-1F4-CAR or control phagocytes (2×10^7 cells/mouse) were s.c. co-injected into NSG-SGM3 mice (N = 5/group). Amyloid clearance and CAR cell persistence were tracked using fluorescence and BLI. **Results:** 11-1F4-CAR–transduced RAW264.7 macrophages exhibited significantly enhanced phagocytic activity against λ6 Wil and κ4 Len amyloid fibrils compared to controls (****$P < 0.0001$). To support clinical translation and scalable

manufacturing, we utilized human CD34+ hematopoietic stem cells for lentiviral CAR-transduction and achieved a transduction rate of >90%. The cells were expanded ex vivo and then differentiated into CAR phagocytes with M-CSF. Flow cytometry analysis confirmed expression of characteristic phagocyte markers, including CD14, CD16, CD64, CD68, CD86, CD206, CD11c, and HLA-DR. In phagocytosis assays, CD34+-derived 11-1F4-CAR phagocytes showed significantly increased engulfment of λ6 Wil and κ4 Len fibrils compared to the controls (****P < 0.0001). For in vivo evaluation, Dylight 755-labeled Len fibrils were co-injected with luciferase-expressing CAR phagocytes into NSG-SGM3 mice. BLI imaging confirmed CAR phagocyte persistence for up to 5 weeks. Co-injection with 11-1F4-CAR phagocytes significantly accelerated amyloid clearance compared to controls (*P < 0.05), reducing the median clearance time from 7.1 days (control) to 4.8 days, supporting their therapeutic potential. **Conclusions:** We developed the first-in-class anti-AL amyloidosis CAR phagocytes using CD34+ cells and confirmed their amyloid-targeting activities both in vitro and in vivo. By bypassing serum IgG Fc competition, CAR phagocytes represent a promising novel cell therapy for AL amyloidosis.

PA-029

Long Term Follow-Up of Zevor-Cel in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: Zevorcabtagene autoleucel (zevor-cel) is a B-cell maturation antigen (BCMA) targeting, fully human, autologous, chimeric antigen receptor (CAR) T-cell therapy which has been approved in China since 2024 for the treatment of patients with relapsed or refractory multiple myeloma (RRMM). Herein, we present the updated results from Phase 1b of LUMMICAR STUDY 1 evaluating the safety and efficacy of zevor-cel in 14 patients. **Methods:** This was a single-arm, open-label study conducted at five sites in China (NCT03975907). Patients with RRMM who had received ≥ 3 prior regimens including a proteasome inhibitor and an immunomodulatory agent with an eastern cooperative oncology group (ECOG) score of 0 or 1 were enrolled. Zevor-cel was administered as a single infusion of 100 × 106 or 150 × 106 CAR+ T cells. **Results:** Between July 23, 2019 and July 10, 2020, 14 patients (50% male) with a median age of 54 years (range:34, 62), received a single infusion of zevor-cel (100 × 106 CAR+ T cells in 3 patients, 150 × 106 CAR+ T cells in 11 patients). As of February 22, 2025, the median follow-up duration was 53.3 months (range:14.8, 63.5). Thirteen (92.9%) patients experienced cytokine release syndrome all at grade 1 or 2. There were no reports of immune effector cell-associated neurotoxicity syndrome, delayed neurotoxicities or other delayed AEs on the study. Three patients died at month 42.5, 32.6 and 48.5, respectively; none were related to zevor-cel. The overall response rate was 100% (95% CI; 76.8, 100.0) with 11 (78.6%) patients achieving complete response (CR) or stringent complete response (sCR), 2 (14.3%) achieving very good partial response and 1 (7.1%) achieving partial response. All patients who achieved CR or better were minimal residual disease (MRD) negative at 10^{-5} threshold. One patient remained in sCR at 59.3 months in the study. The median PFS was 25.8 (95% CI; 14.88, 46.72) months. The PFS rate at 36 and 48 months were 41.7% and 15.6%, respectively. The median duration of response was 24.9 (95% CI; 14.03, 45.86) months. The proportion of patients with a response lasting ≥36 months and ≥48 months were 41.7% and 15.6%, respectively. The median overall survival (OS) was not reached. The proportion of patients surviving at 24, 36, 48 and 60 months after infusion were 100%, 92.3%, 84.6% and 76.9%, respectively. **Conclusions:** At approximately 5 years of follow-up, zevor-cel demonstrates manageable safety profile while eliciting deep and durable responses in RRMM patients.

PA-030

Health Care Contact Days After Standard of Care (SOC) B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor T-Cell Therapy (CAR T) for Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: CAR T offers deep responses along with a maintenance free treatment option for patients with RRMM. Due to these reasons, CAR T is often considered a "one-and-done" regimen for RRMM. Nevertheless, CAR T administration can be associated with significant time burden both pre-infusion (apheresis, bridging, lymphodepletion) and post-infusion (close clinical follow up, infections, monitoring CAR T related toxicities). **Methods:** We retrospectively reviewed consecutive patients with RRMM treated with standard of care (SOC) BCMA-directed CAR T at our institution between August 1, 2021, and January 31, 2024. Our primary endpoint was the number of Days Alive and Outside of

physical Health care contact through the first 100 days from CAR T infusion (DAOH100). All patients received CAR T in the inpatient setting. We categorized days with physical health care contact as inpatient days (index hospitalization for CAR T infusion and readmissions), clinic visits, radiologic study visits (X-ray, CT, MRI, PET, ultrasound scans), invasive procedures (biopsy, lumbar puncture, bronchoscopy, endoscopy), and infusions (blood transfusions, IVIG, G-CSF, other supportive care). We then compared the impact of patient, disease, and treatment characteristics on DAOH100 using the Wilcoxon rank sum test. **Results:** A total of 101 patients with a median of 5 (range 4–14) prior lines of therapy were included. Overall, 44 (44%) received idecabtagene vicleucel (ide-cel) and 57 (56%) received clitacabtagene autoleucel (cilta-cel). The 100-day progression free survival was 87% (95% CI: 81–94%) and overall survival was 93% (95% CI: 88–98%). Overall, 76% patients had cytokine release syndrome (CRS, 28% ≥ grade 2, 7% ≥ grade 3), 26% had immune effector cell associated neurotoxicity syndrome (ICANS, 9% ≥ grade 2, 5% ≥ grade 3). There was no significant difference in the CRS (70% vs 81%, p = 0.33) and ICANS (30% vs 21%, p = 0.45) rates between ide-cel and cilta-cel. The median DAOH100 was 79 days (range 0–87). Days with physical health care contact were predominantly driven by the index hospitalization for CAR T infusion (median 11 contact days, range 7–61), followed by post CAR T clinic visits (median 6 contact days, range 0–26). An ECOG performance status of ≥ 2 (vs 0–1, median 72 vs 79.5 days) and occurrence of ICANS (median 75.5 vs 79 days) were significantly associated with inferior DAOH100, with occurrence of ≥ grade 2 CRS (76 vs 79 days) demonstrating a trend towards inferior DAOH100. The median DAOH100 did not differ based on the CAR T product administered (77 vs 79 days for ide-cel vs cilta-cel, p = 0.28), age ≥ 75 years (vs <75 years, 77 vs 79 days, p = 0.92), and number of prior lines (4 vs ≥ 5, 80 vs 76.5 days, p = 0.32). **Conclusions:** During the first 100 days after CAR T infusion, patients spent around 20 days with physical health care contact. These data are helpful in counseling patients about post CAR T care and follow up.

PA-031

Safety, Efficacy and Health After Teclistamab (SEHAT Study) in Patients with Relapsed and Refractory Multiple Myeloma; A Multicentric Real World Indian Experience

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Introduction: Teclistamab is a bispecific antibody targeting B-cell maturation antigen (BCMA), with established efficacy in relapsed and refractory multiple myeloma (RRMM). Introduced in India in September 2023, its real-world performance in Indian patients remains largely unexplored. Given the distinct differences from Western populations, such as socioeconomic disparities, higher infection burden, and variations in healthcare infrastructure, gathering real-world evidence in this context is crucial. This study aims to evaluate the safety, efficacy, and clinical outcomes of teclistamab in Indian RRMM patients. **Methods:** This ongoing ambi-spective cohort study includes 32 patients with RRMM who received teclistamab across eight centers in India between Sep 2023 and May 2025. Data were collected using a standardized questionnaire covering demographic details, prior therapies, teclistamab administration and dosing patterns, treatment response, pre-treatment evaluations, infection-related events, use of intravenous immunoglobulin (IvIg), adverse events, and survival outcomes. The collected data were analyzed using statistical software to assess clinical outcomes and identify relevant trends. **Results:** Of the enrolled patients, 56.25% were male and 43.75% female, with 76.19% diagnosed with RRMM and 23.81% with secondary plasma cell leukemia. The mean age was 66.4 years. High-risk disease, as per ISS and R-ISS criteria, was predominant. Cytogenetic analysis showed that while most patients lacked abnormalities, the most common findings among those with positive cytogenetics were gain(1q) at baseline and del(17/17p) at relapse. Prior exposure to daratumumab was reported in 78.12%, and 46.88% had received autologous stem cell transplant. Most had received three (37.04%) or five (25.93%) prior lines of therapy. Teclistamab was administered for a mean duration of 3.78 months, with an average of 7.78 weekly doses. Prophylactic tocilizumab was used in 96.43% of patients. To optimize cost, vial sharing was common (81.25%), with unused doses refrigerated if not shared (72.42%). IvIg prophylaxis was given to 65.62% before and 84.38% during treatment, typically at an IgG cut-off of 400 mg/dL. Pre-treatment vaccination was performed in 69.23%, with PCV13 and Shingrix given in 94.44% of those vaccinated. Infections occurred in 40.62% of patients, predominantly gram-negative sepsis (72.73%). Serious adverse events were reported in 73.33% of patients, leading to dose modification in 50% and treatment discontinuation in 14.29%. Post-treatment relapse occurred in 6.90% and refractoriness in 4.35%. At data cut-off, 42.86% had achieved a complete response, while 16.13% had died. **Conclusions:** This early real-world analysis demonstrates that teclistamab shows acceptable safety and promising efficacy in Indian patients with RRMM. These results offer important insights into its use in resource-constrained and infection-prone settings, highlighting practical strategies like prophylactic interventions and cost optimization.

PA-032

Immune Correlates of Response to T-Cell Engaging Bispecific Antibody Treatments in Multiple Myeloma

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Introduction: Bispecific antibodies (BsAbs) are a promising therapy for patients with relapsed or refractory multiple myeloma (RRMM). Three BsAbs—BCMA-directed teclistamab and elranatamab, and GPRC5D-directed talquetamab—are FDA approved. Responders typically present with higher absolute lymphocyte counts (ALC) and preserved CD4 and CD8 T-cell function, whereas non-responders may have lymphopenia or dysfunctional T-cell profiles. Prior studies suggest higher proportions of $CD4^+$ cells may predict more durable response to BCMA-directed BsAbs. We evaluated whether dynamic changes in lymphocyte subsets during early BsAb treatment correlate with clinical response **Methods:** We retrospectively reviewed a patient cohort with RRMM who received BsAb therapy at a single academic center. Baseline ALC, CD4%, and CD8% were recorded alongside clinical characteristics. Dynamic changes in ALC and T-cell subsets were assessed at three pre-specified timepoints: pre-treatment (T0), post-step-up/after one cycle (T1), and after two or three cycles (T2). We calculated changes (Δ) in ALC, CD4%/ALC, and CD8%/ALC between timepoints and assessed their association with clinical response using Student's t-test. Statistical analysis was performed using Python 3.12.9 with SciPy 1.15.3. **Results:** Of 31 patients (19 M/12 F, median age 69 y), 23 received BCMA-targeting agents (teclistamab 19, elranatamab 4) and 8 received GPRC5D-targeting talquetamab. Patients had a median of six prior LOT (3–11); 10 had prior BsAb, and 15 had prior ASCT. 13 had extramedullary disease. At T0, median CD4 was 319 cells/μL (18–927), CD8 was 395 cells/μL (13–2760), ALC was 1.0 cells/μL (0–3.8). ΔALC between timepoints did not correlate with response. Baseline-to-post-cycle-1 ΔCD4%/ALC correlated with response for BCMA-directed BsAbs ($p = 0.007$) and the combined cohort ($p = 0.006$); no significant correlations were seen at the later interval. Similarly, baseline-to-post-cycle-1 ΔCD8%/ALC correlated with response in the overall cohort ($p = 0.0007$) and in BCMA-treated patients ($p = 0.0005$). Post-cycle-1 to cycle-2/3 ΔCD8%/ALC showed no significant association with response. Baseline-to-cycle-2/3 ΔCD8%/ALC was significant for the overall cohort ($p = 0.0009$). **Conclusions:** Our findings suggest early increases in peripheral CD4+ and CD8+ T-cell percentages correlate with improved response to BsAb therapy in RRMM. The strongest associations were seen with CD8% changes from pre-treatment to post-step-up and to post-cycle 2 or 3. Baseline CD8% alone did not correlate with response, highlighting the assessment of dynamic immune changes over static pre-treatment measures only. Peripheral CD4+ and CD8+ T-cell monitoring needs to be evaluated further as a biomarker of BsAb response. Larger prospective studies are needed to validate these findings and explore mechanistic underpinnings, given limitations of our sample size, particularly in the GPRC5D cohort. Follow-up will clarify whether these immune shifts predict durable, late responses.

PA-033

Reshaping Treatments: Insights from the BiTAL Study on Talquetamab in Relapsed Refractory Multiple Myeloma

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Introduction: Multiple myeloma (MM) stands as one of the leading hematological malignancies, characterized by a relentless course of relapses despite available therapeutic options. Among the high-risk patient population are those who are triple-class exposed relapsed refractory multiple myeloma (TCE RRMM). The recent introduction of bispecific antibodies, particularly talquetamab (TAL), represents a promising new avenue. Approved in Europe in August 2023, TAL was made accessible to adult patients (pts) via pre-approval access programs (PAA) in Spain after reviewing for program eligibility based on specified PAA treatment guidelines. **Methods:** This ongoing, retrospective, observational study encompasses pts data collected from 64 Spanish centers covering a chart review period from September 2024 to March 2025. The study included adult pts with TCE RRMM who initiated TAL monotherapy within the PAA programs, between November 22–24. Key eligibility criteria mandated pts to have received their initial dose of TAL at least 30 days before study commencement and to have provided informed consent. Pts demographics, treatment history, and clinical outcomes were systematically analyzed. **Results:** A total of 148 pts met the criteria for analysis at the data cut-off. The median age of the participants was 66.5 years, with 71 (48.0%) females. Median number of prior lines to TAL was 4.0 (1–9). All pts were triple-class exposed, and 70.9% were triple refractory. Mean time to follow-up was 11.1 months, and the mean duration of TAL was 8.2 months. The ORR was 78.4%, with 24.8% pts achieving complete responses

or better (>CR), and 60.8% with a very good partial response or better (>VGPR). According to the biweekly initial dosage regimen, the ORR was 81.3%, 25.2% of pts achieved >CR, and 63.6% >VGPR. Pts experienced a mean PFS and overall survival (OS) of 11.56 and 17.59 months, respectively. In the biweekly initial dosage regimen group, pts mean PFS and OS were 12.15 and 18.21 months, respectively. Adverse events (AE) characteristic of GPRC5D T-cell redirection therapy were skin-related events (71.6%), CRS (59.5%), infection (52.0%), dysgeusia (46.6%), nail-related events (41.2%), weight loss (10.1%), and ICANS (8.1%). Concerning pts who permanently discontinued treatment (N = 84), 50.0% discontinued treatment primarily due to disease progression or lack of response, and only a minimal percentage (6.0%) discontinued as a result of AE. **Conclusions:** The preliminary findings from the BiTAL study highlight the effectiveness and safety profile of TAL in the treatment of this complex TCE RRMM pts, demonstrating encouraging depth of response. Observed PFS and OS outcomes support long-term benefit, while the safety profile and low discontinuation rate due to AEs reinforces the treatment's tolerability in this heavily pre-treated population.

PA-034

One-Time Ex-Vivo Conditioning of CAR-T Cells with a Novel Metabolic Modulator

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Introduction: Metabolism is altered during tumor progression in both tumor cells and immune cells, including T cells, contributing to immunosuppression in the tumor microenvironment. These metabolic changes highlight the importance of targeting metabolic enzymes to enhance the efficacies of tumor immunotherapy. We previously identified that carnitine palmitoyltransferase 1A (CPT1A), which is known as a rate limiting enzyme in fatty acid oxidation (FAO), has a moonlight enzymatic activity as lysing succinyltransferase (KSTase). Our studies in cancer metabolism reveal that CPT1A can directly succinylate fatty acid synthase (FASN) to maintain its stability in cells, thereby promoting de novo lipogenesis (DNL). Based on these findings, we first developed a novel small molecule inhibitor against the KSTase activity of CPT1A (KSTi) that inhibits FASN succinylation in-vitro. Subsequently, we developed a prodrug of KSTi to allow for improved targeted drug delivery that also decreases FASN succinylation and expression leading to reduced intracellular levels of palmitate (PA) without affecting FAO. **Methods:** Since DNL and saturated fatty acid accumulation have been reported to impair T cell function while FAO supports the longevity of T cells, we hypothesized if KSTi prodrug that decreases FASN while sparing FAO would affect any CART cell function. To test this hypothesis, we conditioned anti-BCMA CAR-T cells with KSTi prodrug on the last day of manufacturing and performed in vitro cytotoxicity analysis of these ex-vivo conditioned anti-BCMA CAR-T cells against myeloma cells. We also measured their cytokine production and metabolite levels using flow cytometry and mass spectrometry, respectively. Finally, we evaluated their in vivo efficacy in myeloma cell line xenograft models in which 2.5 × 10^5 myeloma OPM2 cells were intravenously injected into NSG mice followed by another intravenous injection of 1.5 × 10^5 ex-vivo conditioned anti-BCMA CAR-T cells 21 days after OPM2 cell injection. Myeloma disease progression was assessed by monitoring for signs of paralysis. **Results:** KSTi prodrug treatment decreases total PA levels in anti-BCMA CAR-T cells while increasing the intracellular levels of TNF-α and IFN-γ and more importantly, one-time ex-vivo conditioning of CART cells with KSTi prodrug significantly increases their efficacy and durability against myeloma cells in vitro and in mice. The median survival rate for the group of mice with anti-BCMA CAR-T cells alone was 50 days after CAR-T cell injection while that with ex-vivo conditioned anti-BCMA CAR-T cells had not yet been reached at 80 days. **Conclusions:** These results support our hypothesis that KSTase activity of CPT1A is a novel druggable driver of lipogenesis that can be exploited to improve the efficacy and durability of anti-BCMA CAR-T cells against myeloma.

PA-035

Clinical Outcomes after Teclistamab Failure in Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab (Tec) is a BCMAxCD3 bispecific antibody approved for triple-class exposed (TCE) relapsed or refractory multiple myeloma (RRMM) after ≥3 prior lines of therapy (LOT). The optimal management of patients who relapse after teclistamab remains undefined. This is the first comprehensive study to characterize relapse patterns, salvage treatments and outcomes in RRMM patients progressing after Tec. **Methods:** We retrospectively analyzed 191 patients treated with Tec, 60 on clinical trials (Feb 2019–Feb 2023) and 131 commercially (Dec 2022–Apr 2024). Data cutoff was Mar 2025. Outcomes were comparable across cohorts, so analyses were pooled. Among Tec relapsed or refractory patients, we assessed disease characteristics, relapse types, salvage regimens, and outcomes. Treatment refractoriness was defined as less than partial response (< PR) after 2 treatment cycles. Progression was defined per 2016 IMWG criteria. Median follow-up from first salvage was 21.7 months (95% CI: 20.3–NE). **Results:** 109 patients (57%)

progressed after Tec, including 41 (68%) in the trial cohort and 68 (52%) in the commercial cohort. Of these, 52 (33 trial, 19 commercial) completed at least 1 full Tec cycle and received systemic salvage therapy and were included in this analysis. Median prior LOT was 6 (IQR 5–8.5); all were TCE, 83% were penta-exposed, and 21% had prior BCMA therapy (ide-cel: 7, belantamab: 4). Relapse types were biochemical (69%), end-organ damage (CRAB, 12%), and extramedullary disease (EMD, 19%). Notably, 50% of CRAB and 67% of EMD relapses were oligo- or non-secretory (defined as M-spike <0.5 g/dL and involved free light-chain <100 mg/L). Median overall survival from first salvage (OS2) was 11.3 months (95% CI: 7.3–14.2); median duration of response (DOR) was 3.2 months (95% CI: 1.9–5.7). The overall response rate (≥PR) to first salvage was 35%. Response rates and durability varied by regimen, with higher DOR observed in patients receiving novel agents such as talquetamab, other BCMA-directed therapies, or clinical trials. Achieving ≥PR to salvage therapy was associated with longer OS2 (HR: 0.3, P = 0.006) and DOR (HR: 0.1, P < 0.001). Early relapse (<6 months) predicted inferior OS2 (HR: 2, P = 0.04). Other factors —including frailty (IWMG simplified frailty score), cytogenetic risk, penta-exposure, Tec refractoriness, and CRAB/EMD relapse—were not significantly associated with OS2 or DOR. In penta-exposed patients who progressed after Tec, the use of novel immunotherapies (CAR-T, BiTEs, ADCs) in salvage regimens was linked to prolonged DOR (HR: 0.4, P = 0.04), though not OS2. **Conclusions:** This is the first real-world analysis of patients with RRMM who progressed after Tec. Prognosis is poor, especially with early Tec relapse (<6 months). While no standard salvage exists, novel immunotherapies may offer improved disease control. These findings provide a key benchmark in a setting with limited prospective data.

PA-036

Effectiveness, Safety and Clinical use of Teclistamab in Patients with Triple-Class-Exposed Multiple Myeloma. Data from the Danish ABC-Study

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Introduction: This study reports the real-world effectiveness, safety, and clinical use of teclistamab in Denmark following its reimbursement in February 2024 as standard of care (SOC) for triple-class-exposed (TCE) relapsed/refractory multiple myeloma (RRMM). Teclistamab is a BCMA-targeted bispecific antibody (BsAb), approved based on the MajesTEC-1 trial. We present real-world data from the first year of clinical use. **Methods:** In this ongoing, retrospective, multicenter study, myeloma specialists from all Danish healthcare regions reviewed patient charts of all TCE RRMM patients treated with SOC teclistamab during its first year of availability. Data collected included baseline demographics, prior lines of therapy (pLOT), response rates, progression-free survival (PFS), duration of response (DOR), overall survival (OS), adverse events (AEs), and clinical use patterns. The study was conducted in collaboration with Johnson & Johnson and GSK provided financial support. **Results:** Ninety patients received teclistamab between February 2024 and February 2025. Median follow-up was 8 (IQR 4–11) months. Median age at treatment initiation (T0) was 71 years; 51% were male. Median number of pLOT was 4, and median time since diagnosis was 6 years. High-risk FISH [t(4;14), t(14;16), or del17p] was present in 37% of patients. Performance status was 0–1 in 92%, and 26% had extramedullary disease. Most patients (99%) were TCE; 80% were triple-class refractory; 10% were refractory to GPRC5D BsAbs, and 72% had undergone autologous transplant.Overall response rate (ORR) was 61%, with 54% of patients achieving ≥VGPR. Fourteen percent had unmeasurable disease at T0 and were not evaluable for response. Median PFS was not reached; at 12 months 56% remained progression-free. Estimated 12-month DOR and OS were 77% and 67%, respectively. All patients were hospitalized for step-up dosing, and 48% were treated with one dose of prophylactic tocilizumab during teclistamab step-up. Eighty-five percent of patients received immunoglobulin substitution while on treatment with teclistamab. Most frequent AEs were cytokine release syndrome (CRS; 38% grade 1–2, none ≥grade 3) and infections. Sixty percent experienced infections; 25% were ≥ grade 3, including two grade 5 infections. Most common infections were upper respiratory and pulmonary. Dosing intervals were extended in 55% of patients, deviating from the labeled regimen, after a median of 3 months. The most common extension was dosing every two weeks, with 29% of cases attributed to infections. **Conclusions:** In this real-world cohort of elderly, heavily pretreated RRMM patients, teclistamab showed clinical effectiveness consistent with MajesTEC-1. No new safety signals were identified; however, infections were common. Most patients received immunoglobulin substitution while on treatment with teclistamab.

Teclistamab dosing intervals were frequently modified, often due to infections.

PA-037

Real World Accelerated Step-Up Dosing of Teclistamab and Talquetamab in the Outpatient Setting is Feasible and Associated with Low Incidence of Cytokine Release Syndrome

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Introduction: Teclistamab (Tec) and Talquetamab (Talq) are T-cell redirecting bispecific antibodies (BsAb) for the treatment of relapsed-refractory multiple myeloma (RRMM). We instituted an accelerated step-up dosing (aSUD) schedule in the outpatient setting as described in the FDA prescribing information, wherein BsAb are given every 48 hours if no evidence of cytokine release syndrome (CRS) or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). This is the first study to describe the outcomes of an aSUD BsAb regimen as an outpatient (OP). **Methods:** We conducted a retrospective cohort study of patients with RRMM who received Tec or Talq under this protocol from May 1, 2024, to May 30, 2025. Salient exclusion criteria included bone marrow involvement >60% and ECOG >2. BsAb were administered every 48 hours if there was no CRS or ICANS with daily evaluation in the OP clinic. Patients were educated to take acetaminophen and dexamethasone (dex) for fever without any other co-morbid symptoms, and were admitted if fever did not resolve after 1–4 hours. The primary endpoint is the incidence of CRS and ICANS. The secondary endpoint is the incidence of hospitalization. **Results:** A total of 30 patients started OP aSUD; 15 patients received ≥1 Tec dose and 15 patients received ≥1 Talq dose. Median age was 68.5 yrs (35–89). Patients received a median of 4 prior lines of therapy, 8 patients (26.7%) had prior CAR T-cell therapy, and 5 patients (16.7%) previously received another BsAb (Tec). Eleven patients (36.7%) developed CRS (Gr 1 n = 10, Gr 2 n = 1) and none developed any grade ICANS. Seven patients (23.3%) developed CRS following SUD1, 6 (20%) following SUD2, 3 (10%) following SUD3 (Talq), and 1 (3.3%) following SUD4 (Talq). Among the 11 patients with CRS, 5 patients were completely managed OP. Four patients (13.3%) were admitted for CRS while 2 patients developed CRS during hospitalization for tumor lysis and suspected infection, respectively. Five patients (16.7%) received tocilizumab for CRS treatment. Ten admissions were prevented with OP management of CRS with acetaminophen/dex out of 17 individual CRS events. **Conclusions:** To our knowledge, this is the first real-world report describing an aSUD protocol for Tec and Talq in the outpatient setting. The low CRS rates in this study are comparable to those previously published by Puttkamer and colleagues who utilized a standard step-up schedule OP model. The low incidence of CRS without neurologic toxicity suggests that an OP aSUD with daily monitoring and escalation of care for toxicity management is safe and reduces health care resource utilization. Including tocilizumab prophylaxis prior to SUD1 may further reduce the risk of CRS and could enable a completely outpatient delivery without the need for intense monitoring.

PA-038

Optimizing the use of Chimeric Antigen Receptor T-Cell (CART) Therapy for Relapsed/Refractory Myeloma

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Introduction: Chimeric Antigen Receptor T-cell (CAR-T) therapies have changed the treatment landscape of relapsed and/or refractory myeloma (RRMM), with two commercially available anti-BCMA CAR-T now approved in early relapse. The optimal use and choice of construct is still debatable, and here we describe our institutional experience to optimize the use and indication. **Methods:** 248 patients received 253 CAR-T therapies targeting BCMA from 2/2018 until 3/2025 at Winship Cancer Institute of Emory University. 60 (23.7%) were administered on trial and were excluded from analysis. Demographic and clinical characteristics and outcomes data were obtained from our institutional review board-approved myeloma database and with manual abstraction. Responses and progression were evaluated per International Myeloma Working Group Uniform Response Criteria. The median follow-up for the entire cohort for PFS was 10.5 months (Ide-cel and Cilta-cel was 25.2 vs 8.1 months) and for OS was 12.45 months (26.3 vs 8.1 months). **Results:** 193 patients received commercial constructs: 29% Ide-cel and 71% Cilta-cel. The median age is 65.4 (range, 29–86). 57% are male and 38.3% are black. Most patients (74.6%) received ≥4 PLOT including 97% with prior transplant. Only 9.4% of this cohort previously received prior BCMA therapy. The ORR and ≥VGPR rates are 77.8% and 72.2% for Ide-cel, and 88.3% and 83% for Cilta-cel, respectively. The ORR and ≥VGPR rates for patients with ≥4 PLOT for Ide-cel vs Cilta-cel are 77.1% vs 88.1% and 70.8% vs 82.1%, respectively (p = NS). The median PFS for patients treated with Ide-cel was 46.3 months while that for Cilta-cel was NR, due to shorter follow up (16-month PFS 86.7%). For those with ≥4 PLOT, estimated 16-month PFS is 59% vs 83% for Ide-cel vs Cilta-cel. The 2-year OS rate for patients treated with Ide-cel vs Cilta-cel was 72% vs 76% (p = NS).

For those with ≥4 PLOT, 2-year OS rate for patients treated with Ide-cel vs Cilta-cel was 71% vs 73% (p = NS). All grade CRS was higher in Ide-cel vs Cilta-cel (82% vs 66% p = 0.031), though no statistically significant difference in grade 2 or higher CRS. All grade neurotoxicity was higher in Ide-cel vs Cilta-cel (28% vs 17% p = 0.093), including grade 2 or higher (12.5% vs 2.9%, p = NS). **Conclusions:** Though earlier administration of both BCMA CAR-T cell therapies is becoming increasingly common, these data demonstrate impressive efficacy in both late relapse and real world setting as compared to clinical trial data. This improvement might be attributable to improved bridging therapies available at this time, as well as careful patient selection. Of note, early Ide-cel use prior to Cilta-cel approval was often administered to patients with significant tumor burden potentially explaining the increased CRS and neurotoxicity. This data suggests prolonged responses and excellent outcomes in the right patient population.

PA-039

Differential Impact of BCMA (TNFRSF17) Extracellular Domain Mutations on in vitro Potency of Elranatamab versus Teclistamab

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Introduction: BCMA (B cell maturation antigen) is a surface protein expressed by malignant plasma cells in multiple myeloma (MM). Elranatamab (elra) and teclistamab (tec) are bispecific BCMAxCD3 T cell engagers (TCEs) commercially approved for treating relapsed/refractory MM (RRMM) patients. BCMAxCD3 TCEs mediate tumor killing by binding to T cells via CD3 and tumor cells via BCMA. BCMA mutations (BCMAmuts) may represent potential resistance mechanisms in some RRMM patients progressing on BCMA TCEs. In a small cohort of such patients (n = 11), R27P, P33S, and P34del mutations were identified in patients progressing on elra, and S30del and P34del mutations were identified in patients progressing on tec (Lee et al, 2023). R27P, S30del, and P34del were reported to decrease the potency of select BCMA TCEs in vitro. Here, we performed in vitro studies to compare the impact of these BCMAmuts on elra and tec binding and tumor killing potency. **Methods:** AlphaFold modeling was performed to predict elra's parental anti-BCMA Fab binding to BCMAmuts. For all in vitro work, commercial grade elra and tec were used. Binding affinity to recombinant BCMAmut proteins was evaluated via surface plasmon resonance (SPR). HEK-293 cell lines were engineered to express wild type (WT) BCMA or individual BCMAmuts. Binding was assessed by flow cytometry. Co-culture assays were run with BCMAmut HEK cells, healthy donor CD3+ T cells, and BCMAxCD3 TCEs to evaluate killing potency (CellTiterGlo) and T cell activation (flow cytometry). **Results:** AlphaFold models predicted S30del and P33S would not influence elra binding, while R27P and P34del might reduce binding due to structural changes. SPR-derived measurements confirmed the AlphaFold predictions and showed decreased binding affinity for both elra and tec to R27P and P34del. Both elra and tec cell binding and cytotoxicity were decreased by R27P and P34del. Neither elra nor tec binding or cytotoxicity was decreased by P33S. S30del minimally impacted elra binding affinity (KD 0.168 nM, 4-fold weaker than to WT BCMA), while tec binding affinity was substantially reduced (KD 145 nM, 711-fold weaker than to WT BCMA). Correspondingly, elra T cell mediated killing with associated T cell activation was maintained toward S30del, while tec activity was severely diminished. **Conclusions:** These in vitro results suggest BCMAmuts may differentially impact BCMAxCD3 TCE activity, although the clinical relevance remains uncertain. Not all mutations may impact TCE potency, such as P33S (germline). Preclinically, elra T cell activation and killing potency was similar to or higher than tec. As preclinical binding affinity and killing potency is maintained, elra may have increased activity for patients harboring the S30del mutation. Further understanding mutation prevalence may inform if various BCMAxCD3 TCEs select for specific mutations, which could inform optimal treatment sequencing and selection, although these results must be clinically validated.

PA-040

Overcoming Resistance in CD44-Overexpressing Myeloma through Combination Therapy with ATRA, Bortezomib, and NK Cells

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Introduction: CD44, a surface glycoprotein, is often highly expressed in patients with poor treatment response and advanced disease stages across numerous studies. This study aims to investigate the prognostic impact of CD44 overexpression in multiple myeloma (MM) patients, and investigates the therapeutic impact of combining NK cell therapy with all-trans retinoic acid (ATRA) and bortezomib in CD44-overexpressing myeloma cell lines. **Methods:** Clinical data from the CoMMpass database were analyzed to assess survival outcomes associated with CD44 expression. NK cells were expanded from healthy donors using K562-OX40L-mbIL18/21 feeder cells and IL-2/IL-15. Functional assays were performed using CD44-high myeloma cell lines treated with ATRA and bortezomib, individually and in combination with NK cells. Changes in CD44 expression, β-catenin levels, and downstream effectors (NF-κB, MMP2/9) were examined via western blot and qPCR. NK cell activation markers and cytotoxicity were assessed by flow cytometry. **Results:** CD44 overexpression was significantly associated with worse overall survival in MM patients (P < 0.0001), including those in R-ISS I and III stages. In addition, CD44 expression was associated with myeloma cell proliferation, migration and invasion, which is mediated through

the downregulation of NF-κB, MMP2, and MMP9 in myeloma cell lines. In vitro, the combination of ATRA and bortezomib significantly downregulated CD44 and β-catenin levels, reduced MM cell proliferation, migration, and invasion, and enhanced susceptibility to NK cell-mediated lysis. This was accompanied by upregulation of activation ligands (MICA/B, FAS, TRAILR2) and adhesion molecules (ICAM1), suggesting improved NK-target cell interaction. NK cells alone not sufficient to kill myeloma cells overexpressing CD44; however, cytotoxicity was significantly increased when NK cells were combined with ATRA and bortezomib against CD44 overexpression myeloma cells at all E:T ratios. **Conclusions:** Our findings highlight CD44 as a poor prognostic marker and a viable therapeutic target in MM. The combination of ATRA and bortezomib effectively sensitizes CD44 overexpression myeloma cells to NK cell-mediated cytotoxicity. This strategy may offer a novel approach to improving NK cell-based immunotherapy in high-risk MM patients.

PA-041

Enhanced Persistence and Antitumor Activity of IL-15–Armored Anti-BCMA CAR NK Cells in Myeloma Mouse Model

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Introduction: Chimeric Antigen Receptor (CAR) Natural Killer (NK) cell therapy has emerged as a promising approach in cancer immunotherapy. However, its clinical efficacy remains constrained by challenges such as inefficient gene transfer, suboptimal in vitro expansion, and limited proliferation and persistence in vivo. Interleukin-15 (IL-15) is known to enhance NK cell proliferation and cytotoxicity. In this study, we investigated the persistence and therapeutic efficacy of genetically engineered NK cells transduced with a lentiviral vector encoding an anti-B-cell maturation antigen (BCMA) CAR construct incorporating IL-15. **Methods:** CAR NK cell cytotoxicity was evaluated using CD107a degranulation and lactate dehydrogenase (LDH) release assays. Long-term cytotoxic effects were assessed by monitoring target cell confluence over time in co-culture systems. IL-15 concentrations in the culture supernatant were quantified via ELISA. The in vivo antitumor efficacy of IL-15–expressing BCMA CAR NK cells was assessed in an MM.1s-Fluc xenograft mouse model. **Results:** Anti-BCMA–IL-15 CAR NK cells were successfully generated, demonstrating a purity of 96.9%, fold expansion ranging from 53.99 to 67.20, and a transduction efficiency of 21.6%. In short-term (4-hour) cytotoxicity assays, IL-15–armored CAR NK cells displayed comparable cytotoxicity to BCMA CAR NK cells lacking IL-15. However, in long-term co-culture experiments, IL-15–armored CAR NK cells maintained superior and sustained cytotoxic activity across multiple BCMA-positive myeloma cell lines. Culture supernatants from the BCMA–IL-15 group exhibited elevated IL-15 levels (10.58–11.02 pg/mL) relative to BCMA-only and mock-transduced controls (1.51–1.96 pg/mL). The vector copy number per cell ranged from 2.15 to 2.50. In vivo, BCMA-IL-15 CAR NK cells exhibited the most potent and durable antitumor activity, as evidenced by significantly reduced bioluminescence signals in MM.1s-Fluc xenograft mice. While both BCMA and IL-15 CAR NK cells initially suppressed tumor growth, only the BCMA-IL-15 CAR NK group sustained tumor control up to day 44. This group also demonstrated the longest survival and no significant weight loss, indicating effective and well-tolerated therapy. **Conclusions:** In conclusion, IL-15–armored anti-BCMA CAR NK cells show enhanced long-term persistence and cytotoxicity in myeloma mouse model. These findings support the potential of IL-15–armored CAR NK cells as a promising therapeutic candidate for the treatment of multiple myeloma.

PA-042

Peak Absolute Lymphocyte Count as a Biomarker for CAR T-Cell Expansion is Associated with Non-ICANS Neurotoxicities Following Ciltacabtagene Autoleucel

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Introduction: Ciltacabtagene autoleucel (cilta-cel) is an effective, FDA approved chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma (RRMM). Cilta-cel is associated with delayed neurotoxicities which are distinct from immune effector cell-associated neurotoxicity syndrome (ICANS) observed following CAR T-cell infusion. These non-ICANS neurotoxicities (NIN) include but are not limited to cranial nerve palsies (CNP), movement and neurocognitive toxicities (MNT), Guillain-Barré syndrome (GBS), peripheral neuropathy (PN), and altered cognition or personality. Predisposing risk factors for NIN are unknown though peak absolute lymphocyte count (pALC) after infusion may be associated with developing NIN. **Methods:** Retrospective review of patients with RRMM treated with commercial, standard of care (SOC) cilta-cel at a single-center between July 21, 2022 and October 31, 2024. Patient baseline characteristics, outcomes, and NINs were collected. NINs included CNP, MNT, GBS, PN, cognitive changes,

or other neurologic symptoms occurring after CAR T-cell infusion, judged distinct from ICANS by the treating clinician and consulting neurologist. **Results:** In total, 109 patients treated with SOC cilta-cel were included. At a median follow-up of 13 months, 12 (11.0%) patients had a NIN, including 5 patients with ≥2 NIN. Overall, 21 NINs were reported, including 13 CNPs (10 CNVII, 2 CNVI, 1 CNIII), 2 MNTs, 2 GBSs, 2 delayed/prolonged ICANS, 1 PN, and 1 patient with major personality change. Median time to NIN was 21 days for patients who had a NIN. A pALC of 3.2 × 103/μL was determined, using maximally selected Wilcoxon rank statistics, as a significant risk factor for developing NIN. In a univariable analysis, baseline characteristics, including age, sex, race, tumor burden, high-risk cytogenetics, presence of clonal hematopoiesis, steroid exposure, and estimated cumulative fludarabine exposure, were not associated with an increased risk of NIN. In both univariable and multivariable analyses, pALC>3.2 × 103/μL was associated with a significantly increased risk of NIN ($p < 0.0001$). Median time to pALC was 12 days after CAR T-cell infusion. Of patients with pALC≤3.2 × 103/μL, 0/77 (0.0%) developed NIN compared to 12/32 (37.5%) patients with pALC>3.2 × 103/μL. A pALC>3.2 vs ≤3.2 × 103/μL was not associated with significant differences in progression-free survival (PFS) or overall survival (OS). **Conclusions:** NINs occurred in 11% of patients treated with cilta-cel with a median symptom onset of 21 days. Peak ALC was associated with NIN and pALC>3.2 × 103/μL may identify patients at risk of developing NIN. Peak ALC>3.2 × 103/μL was not associated with longer PFS or OS. Thus, interventions to maintain pALC≤3.2 × 103/μL may mitigate the risk of NIN without negatively impacting treatment outcomes. T-cell phenotyping analysis via flow cytometry and single-cell transcriptomics from patient peripheral blood samples is ongoing and will be presented at the meeting.

PA-043

Anti-BCMA-CAR-IL15 Natural Killer Cells Prevent Multiple Myeloma Growth in the Bone Marrow but Allow Later Emergence of Extramedullary Disease

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Introduction: Multiple myeloma (MM) is an aggressive blood cancer arising from plasma cells. The B cell maturation antigen (BCMA) has been established as an effective therapeutic target on plasma cells, with BCMA-targeted chimeric antigen receptor T cell (α-BCMA-CAR-T) immunotherapies currently providing life-saving treatment for MM patients. Unfortunately, severe toxicities along with the high cost and complexity of autologous CAR-T manufacturing remain important limitations. Novel research is underway to use CAR-expressing natural killer (NK) cells as an allogeneic CAR-T alternative. Clinical trials are currently utilizing α-CD19-CAR-NK cells to treat lymphoma, showing the potential for an "off-shelf-immunotherapy" with minimal side effects, but studies have yet to evaluate long-term CAR-NK efficacy against MM. **Methods:** NK cells were isolated, expanded via feeder-cell stimulation, and engineered to express α-BCMA-CAR with or without human IL-15 co-expression using lentiviral vectors. In vitro effector function of α-BCMA-CAR-expressing NK cells were assessed by co-incubation with MM cell lines. IFNγ and CD107a cytokine production are measured as a sign of function while cytotoxicity was assessed using the IncuCyte live-cell assay. Lastly, the long-term persistence and therapeutic potential of α-BCMA-CAR-IL15 NK cells were evaluated in a luciferase-expressing MM-xenograft mouse model. **Results:** α-BCMA-CAR NK cells have enhanced cytokine production and cytotoxicity against BCMA-high MM cells compared to untransduced NK cells, with IL-15 co-expression required for CAR-NK persistence in low cytokine media conditions. When injected into NSG mice, both α-BCMA-CAR and IL-15 expression were required for persistent restriction of MM growth in the blood, spleen and bone marrow. Interestingly, despite near complete and sustained elimination of MM in hematopoietic tissues, long-term assessment of mice treated with α-BCMA-CAR-IL15 NK cells revealed the emergence of extramedullary disease (EMD) in the form of nodal BCMA-positive MM plasmacytomas. **Conclusions:** Our study showcases α-BCMA-CAR-IL15 NK cell therapy as a potent anti-MM therapeutic, achieving sustained MM elimination from the bone marrow and greatly extending survival in a MM-xenograft model. However, α-BCMA-CAR-IL15 NK cells appeared ineffective at eliminating extramedullary disease. EMD is strongly associated with poor prognosis in MM patients. The relevance of this animal model in replicating EMD observed in patients is currently under investigation. By demonstrating the strengths and weaknesses of α-BCMA-CAR-IL15 cells, we hope this study could help direct the use of such therapies in clinical trials and provide a valuable pre-clinical MM model for developing interventions for aggressive MM-EMD.

PA-044

Real-World Treatment Patterns Associated With Elranatamab Among Patients With Relapsed/Refractory Multiple Myeloma: The ALTITUDE-2 Study

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Introduction: Elranatamab (ELRA) is a humanized bispecific antibody that targets both B-cell maturation antigen (BCMA)-

expressing multiple myeloma (MM) cells and CD3-expressing T-cells. ELRA is currently approved for the treatment of relapsed/refractory MM (RRMM) in several countries. Data on the efficacy and safety of ELRA has been published from the registrational MagnetisMM-3 trial (NCT04649359), an open-label, multicenter, non-randomized, phase 2 study. However, data on the usage of ELRA in the real world is limited. **Methods:** ALTITUDE-2 (EUPAS1000000293) is an ongoing, non-interventional database study designed to assess real-world treatment patterns and other outcomes among United States patients with RRMM treated with ELRA. The data source was the Medicare Fee-For-Service (FFS) dataset (December 2024 data cut), which represents 100% of the claims for all Medicare FFS beneficiaries including demographics and inpatient, outpatient, and prescription drug claims. All adult (≥18 years) patients with at least one claim for ELRA, and who met other inclusion and exclusion criteria (e.g., ≥180 days and ≥30 days of continuous closed-claim enrollment pre- and post-index, respectively), were included in the analyses. The first ELRA claim represented the index date. This interim analysis descriptively reported the treatment patterns of ELRA separately for the step-up dosing period ("SUD period"; Index to Day 8), maintenance period 1 ("MP1"; Day 9 to Day 168, where per label QW is expected), and maintenance period 2 ("MP2"; Day 169+, where per label Q2W is expected, depending on patient response). **Results:** N = 237 patients treated with ELRA were included (median age = 74 years, interquartile range [IQR] = 69–79 years; 56% female, 72% White, 15% Black) with a median follow-up time of 4.4 months (IQR = 2.0–8.2 months). The median time from diagnosis to starting ELRA was 67 months (IQR = 42–98 months). 62% of patients were penta-drug exposed and 23% had a prior commercial BCMA-directed therapy (CAR T-cell therapy or belantamab, with 19% having a prior CAR T-cell therapy). There were 241 claims of ELRA during MP1 (Days 9–168 post-index). The median number of days between administrations was 7 (Q1 = 7, Q3 = 13 days), with approximately a quarter of administrations already occurring on a Q2W cadence during this period. There were 62 claims of ELRA in MP2 (Days 169+ post-index). The median number of days between administrations was 14 (Q1 = 14, Q3 = 28 days), with approximately 25% of administrations occurring on a monthly (Q4W) cadence. **Conclusions:** Patients treated with ELRA in the real-world were heavily pre-treated, and prior exposure to BCMA-directed therapy was common. During MP1 and MP2, real-world treatment patterns suggest less frequent administration of ELRA compared with the label.

PA-045

Elranatamab Fixed Dosing: The Optimal Dosing Strategy for Safety, Efficacy, and Convenience Across Body Weights

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Introduction: Bispecific T-cell engagers (TCEs) are a promising modality for cancer treatment, and evaluation of dosing strategies including utilization of body weight (BW)–based versus fixed dosing is essential to ensure optimal therapeutic outcomes. Elranatamab is a bispecific TCE that targets B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells. Elranatamab is approved for the treatment of adult patients (pts) with relapsed/refractory multiple myeloma (RRMM). Here, we provide data evaluating the impact of BW on the pharmacokinetics (PK), safety, and efficacy of elranatamab, supporting the approved fixed dosing strategy. **Methods:** Data from the phase 2 MagnetisMM-3 trial (NCT04649359) were used to evaluate the impact of BW on the PK, safety, and efficacy of elranatamab. This trial comprised 2 cohorts: Cohort A included pts who had not previously received BCMA-directed therapy and Cohort B included pts who had received prior BCMA-directed therapies. All pts received a 76-mg fixed dose of subcutaneous elranatamab after a 2-step priming dose regimen (12 mg on day 1; 32 mg on day 4). Blood samples were collected from MagnetisMM-3 trial pts for PK analysis. The PK, safety, and efficacy were assessed using the 20th percentile of BW as a cutoff (ie "low BW" is ≤20th percentile and "high BW" is >20th percentile of BW). **Results:** A total of 187 pts (both cohorts) were enrolled in MagnetisMM-3. The median (range) baseline BW was 71.8 kg (36.5–159.6 kg). The 20th percentile of BW was 60.3 kg. In the pts receiving both step-up doses (n = 183), median (range) BW in the low (n = 37) and high (n = 146) BW groups was 54.9 kg (36.5–60.3 kg) and 76.4 kg (61–159.6 kg), respectively. Baseline characteristics were balanced between groups. Elranatamab pre-dose concentrations were similar between the low and high BW groups. There were no clinically relevant differences in the safety profiles between the low and high BW groups (n = 183). The overall incidence of adverse events (AEs, both 100%), Grade 3/4 AEs (62.2% vs 71.2%), serious AEs (70.3% vs 76.7%), and discontinuations due to AEs (24.3% vs 28.1%) were similar between the low and high BW groups. The overall response rate (50% vs 64%) and complete response rate (34.6% vs 38.2%) were comparable between low and high BW groups. The Kaplan-Meier (KM) curves for progression-free survival overlapped between groups (P = 0.65). The median duration of response was not reached in either group with overlapping KM curves (P = 0.74). **Conclusions:** Concerns with flat dosing include the potential for overdosing pts with lower BW and underdosing individuals with higher BW. However, this study provides evidence that fixed dosing of elranatamab is effective and demonstrated a consistent and manageable safety profile across a broad range of BWs. There is no significant impact of BW on the PK, safety, or efficacy of elranatamab. These findings support the approved fixed dosing of elranatamab in pts with RRMM.

PA-046

Efficacy and Safety of Less Frequent Dosing With Elranatamab (ELRA) in Patients With Relapsed or Refractory Multiple Myeloma (RRMM): A US Subgroup Analysis from MagnetisMM-3

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Introduction: The ongoing phase 2 MagnetisMM-3 (NCT04649359) study demonstrated efficacy and safety of ELRA in patients (pts) with RRMM and no prior BCMA-directed therapy (Cohort A). With a median follow-up of 33.9 mo, ORR was 61.0%, median DOR was not reached, median PFS was 17.2 mo, and median OS was 24.6 mo. Here we report results for the subgroup of pts enrolled in MagnetisMM-3 in the US. **Methods:** Eligible pts had RRMM with disease refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 antibody. Pts were given subcutaneous ELRA as step-up priming doses followed by 76 mg QW for 6 cycles. Pts given QW dosing for ≥6 cycles who achieved partial response or better lasting ≥2 mo were transitioned to Q2W dosing and to Q4W after ≥6 cycles of Q2W dosing. The subgroup of pts within Cohort A enrolled in the US (n = 47) was analyzed. At data cutoff (March 10, 2025 [≈38 mo after last pt first dose]), median follow-up was 39.6 mo (95% CI, 38.7–41.5; estimated by reverse Kaplan–Meier). **Results:** Pts in the US subgroup had a median of 5 prior lines of therapy (range, 2–22); 93.6% were triple-class refractory, and 46.8% were penta-drug refractory. Eight (17.0%) pts were Black or African American. ORR (95% CI) by Blinded Independent Central Review was 66.0% (50.7–79.1); 42.6% of pts achieved complete response (CR) or better. Median (range) time to response was 1.08 mo (0.95–7.36), and median time to CR or better was 4.76 mo (1.22–12.75). Median duration of response (95% CI) was 40.8 mo (24.0-not estimable [NE]). Median (95% CI) PFS and OS were 27.3 mo (4.3–NE) and 43.6 mo (14.9–NE), respectively. Median DOR and OS were after 38 mo and potentially not yet mature. Any grade [G] and G3/4 treatment-emergent adverse events were reported in 100% and 78.7% pts, respectively. Infections (any G, G3/4, G5) were reported in 70.2%, 42.6%, and 0.0%, respectively; 51.1% received Ig replacement. Anti-viral, anti-pneumocystis jirovecii pneumonia, anti-bacterial, and anti-fungal prophylaxis were received by 80.9%, 23.4%, 14.9%, and 8.5% of pts, respectively. The rate of cytokine release syndrome (CRS) was 61.7% (G1, 34.0%; G2, 27.7%; G≥3, 0.0%). Immune effector cell-associated neurotoxicity syndrome was reported in 8.5% of pts (G1, 4.3%; G2, 4.3%; G≥3, 0.0%). 22 pts switched from QW to Q2W, and 8 pts further switched from Q2W to Q4W dosing. **Conclusions:** Pts with RRMM in MagnetisMM-3 Cohort A, including the US subgroup, were heavily pretreated. Consistent with overall Cohort A data, ELRA induced deep, durable responses in the US subgroup, with a mPFS of 27.3 mo. CRS was G1 and G2 only. Infections were consistent with what was observed in the overall study population; infection prophylaxis including Ig replacement are recommended.

PA-047

Melphalan-Induced Enrichment of TP53-Mutant CHIP as a Risk Factor for Subsequent CAR-T Related Myeloid Neoplasms in Multiple Myeloma

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Introduction: CAR-T cell therapy has shown remarkable efficacy in multiple myeloma (MM), but concerns are emerging about an increased risk of secondary myeloid neoplasms (t-MN), potentially linked to the intrinsically high prevalence of clonal hematopoiesis of indeterminate potential (CHIP, ~22%) in MM patients (pts). Most importantly, the interplay between CAR-T induced effects on pre-existing CHIP, including a hyperinflammatory hematopoietic niche, and the mutagenic impact of prior therapy (e.g. melphalan, lenalidomide) remains poorly understood. **Methods:** To better characterize melphalan as a potential driver of CAR-T associated leukemia in MM, we here employed CRISPR-Cas/ sleeping beauty technologies to study melphalan-induced effects on TP53-mutant CHIP clones in THP-1 cell line models. The impact of CAR-T related inflammation was studied by ex vivo pt-derived models using the CoSeedis® platform. **Results:** This study leverages on a prior report from our group which described the accelerated onset of post-CAR-T t-MN in a cohort of n = 10 heavily pretreated MM pts (all lenalidomide-exposed, median of 2 (1–4) prior ASCTs). WGS on BMMCs from these pts was positive for the melphalan-associated SBS-MM1 signature, thereby providing clinical evidence that enrichment of CHIP may in part be related to prior ASCT. Consequently, we conducted competition assays on TP53-mutant THP-1 models with and without melphalan using different wildtype

(WT):knock-out (KO) ratios. In monoculture, TP53-KO clones showed relative resistance to melphalan compared to WT with an IC50 shift of 1.4–2.1 µM. Interestingly, KO clones had a baseline survival disadvantage in drug-free co-culture, which was reversed upon melphalan exposure, with KO clones rapidly outcompeting WT, and reaching a clonal dominance of >90% after 14 days of treatment; these effects being consistent for different seeding ratios. Upon melphalan withdrawal, recovery of WT cells was observed, while a re-introduction of melphalan again selected for KO clones. This data points towards selection as a key driver for how melphalan contributes to t-MN pathogenesis. To investigate CAR-T as a pathogenic second hit potentially leading to the accelerated expansion of CHIP, we next mimicked CAR-T hyperinflammation using ex vivo models and BMMCs from known CHIP carriers. Preliminary data on these primary samples indicate a ~6 fold increase in clonal expansion as determined by VAF quantification after 14 days for HS-5 co- vs. monocultures. Further investigations on the additional impact of CRS-associated cytokines are ongoing and will be presented at the meeting. **Conclusions:** While the link between t-MN and CAR-T therapy remains unclear, our data suggest melphalan-driven selection of TP53-mutant CHIP as an early leukemogenic event predisposing to subsequent CAR-T-related cytopenia and t-MN. These findings support earlier use of CAR-T to mitigate secondary leukemia risk, particularly in pts with known high-risk TP53CHIP variants.

PA-048

Preclinical Analysis of Ciltacabtagene Autoleucel Combination Strategies with T Cell Bispecifics and Daratumumab to Support Optimization of Clinical Benefit in Myeloma Patients

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Introduction: Ciltacabtagene autoleucel (Cilta-cel) is a multiple myeloma (MM) specific CAR-T cell therapy targeting BCMA. Teclistamab (Tec), and talquetamab (Tal) are MM directed T cell bispecifics (BsAbs) targeting BCMA and GPRC5D, respectively. All three therapies are designed to harness the anti-tumor activity of T cells. Yet, little is known about their use in concert and/or their preferred sequencing to maximize therapeutic benefit. Likewise, little data exist exploring the impact of daratumumab (Dara), a monoclonal antibody targeting CD38, on the efficacy of Cilta-cel. Our work aims to characterize underlying mechanistic interactions between these therapies to potentially inform on their optimal clinical utilization as we push towards regimens with curative intent in MM. **Methods:** We used an in vitro model where healthy donor T cells were exposed to MM cells with either Tec, Tal, or Dara, before or concurrently with research-grade Cilta-cel. See figure legends for details. **Results:** BsAbs induced downregulation of CD28 on T cells and up-regulation of markers associated with T cell exhaustion. Downstream assays using these BsAb pre-exposed T cells revealed diminished expansion and reduced transduction efficiency during the generation of research grade Cilta-cel, and a reduced capacity of the derived CAR-T products to kill MM cells in a serial cytotoxicity assay. Tec and Tal produced similar results, suggesting this effect is BMCA and GPRC5D target agnostic. These data may explain why MM patients with prior BCMA BsAbs had lower response rates and shorter duration of response to BCMA CAR-T. Interestingly, when BsAbs were concurrently added with research-grade Cilta-cel to MM cells, enhanced cytotoxicity synergistically. We also observed increased levels of activation and proliferation of the CAR negative T cells present in the co-culture, along with increased expression of FAS and ICAM-1 on the tumor cells. Finally, addition of Dara, also synergistically enhanced the in vitro cytotoxicity of research-grade Cilta-cel against MM cells. In contrast to BsAbs, Dara was shown to limit the overall expansion of research grade Cilta-cel. However, immunophenotyping data showed that the remaining CAR-T cells exhibited a reduction in frequency of exhausted T cells and CD38+ Tregs, potentially indicating improved T cell fitness. **Conclusions:** These preliminary data support careful consideration of the timing of apheresis with respect to treatment with BsAbs, to preserve T cell fitness. They also suggest that Tec, Tal and Dara, may have an important role in bridging and maintenance strategies to enhance the cytotoxic activity of Cilta-cel, if labeling indications permit. Furthermore, these agents may potentially optimize reduced Cilta-cel cytotoxicity resulting from previous BsAb exposure. Ultimately, mechanisms unraveled by this study may help guide trial designs and the development of novel therapeutic regimens, although more investigation will be required.

PA-049

Linvoseltamab in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) in the LINKER-MM1 Study: Longer Follow-up and Subgroup Analyses

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Introduction: In pts with triple-class exposed RRMM, linvoseltamab (BCMA×CD3 bispecific antibody) demonstrated high response rates, with early responses that deepened over time, and a generally manageable safety profile. Here we report longer-term follow-up of pts receiving the EMA-approved 200 mg dose, including subgroup efficacy analyses by risk status and prior treatment, in the Phase (Ph) 1/2 LINKER-MM1 study (NCT03761108). **Methods:** In Ph2, pts received linvoseltamab IV QW through Week 14, then Q2W. Ph2 200 mg pts with ≥VGPR and ≥24 weeks of treatment switched to Q4W dosing. Ph2 primary endpoint was objective response rate (ORR) by IRC. Efficacy was assessed in prespecified subgroups defined by age, ISS stage, cytogenetic risk, baseline (BL) sBCMA concentration, BMPC %, EMP, and disease refractoriness; efficacy by prior treatment was analyzed post hoc. **Results:** This analysis included 117 pts: median age, 70 yrs (range 37–91); ISS III, 18%; high-risk cytogenetics, 39%; median sBCMA, 377 ng/mL (165–909); median BMPC, 23% (1–100); EMP, 16%; ≥penta-refractory, 29%. As of Jul 23, 2024, median duration of follow-up was 21.3 mos. In the overall 200 mg cohort, ORR was 71% (≥CR, 52%) and median duration of response was 29.4 mos (95% CI: 20.0−not evaluable [NE]). Median progression-free survival was not reached (17.3 mos−NE) and median overall survival was 31.4 mos (23.8−NE). From Ph2, 58/105 (55%) pts transitioned to Q4W dosing at ≥24 weeks of treatment. For these 58 pts, total median treatment duration was 12.8 mos, and 43 remained in response after transition. Among 27 pts with VGPR at transition, 19 (70%) later achieved ≥CR. Response rates were high across subgroups of the overall 200 mg cohort, including by age (≥75 yrs, ORR 71%; ≥65−<75 yrs, 76%; <65 yrs, 66%), ISS stage (I, 73%; II, 71%; III, 62%), cytogenetic risk (high, 67%; standard, 73%), BL sBCMA (≥400 ng/mL, 57%; < 400 ng/mL, 83%), BL BMPC (≥50%, 50%; >0−<50%, 79%), and BL EMP (EMP+, 53%; EMP−, 74%), and in pts with penta-refractory disease (68%). ORR was 72% (64/89) in pts with ≥4 prior LoT and 70% (7/10) in pts with prior anti-BCMA antibody-drug conjugate (belantamab mafodotin) exposure. Time-to-event outcomes by subgroup will be presented. Treatment-emergent AEs (TEAEs) occurred in all pts (Grade [Gr] ≥3, 88%). No new safety signals were observed. In total, 21% of pts discontinued due to TEAEs. The most common TEAEs were CRS (any Gr 46%), neutropenia (44%), diarrhea (42%), anemia, and cough (both 40%). Infections occurred in 75% (Gr 3–4 37%) of pts, with rate decreasing after 6 mos of treatment (0–<3 mos: any Gr 52%/Gr 3–4 21%; 3–<6 mos: 49%/22%; 6–<9 mos: 37%/6%; 9–<21 mos [in each 3-mo period]: 23–37%/0–8%). **Conclusions:** This longer-term analysis showed that linvoseltamab 200 mg induced high rates of deep, durable response and prolonged survival in pts with RRMM, including those with heavily pretreated and high-risk disease, while maintaining a generally manageable and consistent safety profile.

PA-050

Comparative Efficacy of Iinvoseltamab versus Idecabtagene Vicleucel and Ciltacabtagene Autoleucel in Triple-Class Exposed Relapsed/Refractory Multiple Myeloma: A Matching-Adjusted Indirect Comparison

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Introduction: Direct comparisons of anti–B-cell maturation antigen (BCMA) bispecific antibodies and chimeric antigen receptor T cell (CAR-T) therapies are lacking in triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). We used matching-adjusted indirect comparisons (MAICs) to compare linvoseltamab (linvo) with idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), using intention-to-treat (ITT: enrolled, apheresed, bridging therapy if applicable) and modified ITT (mITT: infused) populations from CAR-T trials. **Methods:** Patient (pt)-level data from LINKER-MM1 (linvo; ITT/mITT 117 pts; data cut-off [DCO] 7/24; median follow-up [mFU] 21.3 months [mos]) and published data from KarMMa (ide-cel; ITT 149, mITT 137; DCO 12/23; mFU 63.6 mos) and CARTITUDE-1 (cilta-cel; ITT 113, mITT 97; DCO 10/22; mFU 33.4 mos) were used. To align

with CAR-T trial eligibility, LINKER-MM1 pts with prior BCMA antibody–drug conjugates (all analyses) and pts not refractory to their last line (ide-cel analyses only) were excluded. Unavailable ITT data for CAR-T trials were imputed from mITT populations. Outcome definitions were harmonized where possible. LINKER-MM1 pts were weighted to match each CAR-T trial on pre-specified key prognostic factors. Outcomes included objective response rate (ORR), very good partial response or better (≥VGPR) and complete response or better (≥CR) rates, duration of response (DOR), progression-free (PFS) and overall survival (OS). **Results:** After matching, vs ide-cel ITT (effective sample size [ESS] 43.7), linvo had significantly higher ≥CR rate (OR 1.83, 95% CI 1.12–3.01), similar ≥VGPR rate (OR 0.93, 0.57–1.51), and significantly longer DOR (HR 0.21, 0.10–0.44) and PFS (HR 0.52, 0.29–0.91). Although not significant, linvo had lower ORR (OR 0.67, 0.40–1.15) and longer OS (HR 0.77, 0.44–1.35). Results vs ide-cel mITT (43.9) were similar to those in the ITT, with significantly lower ORR and numerically lower ≥VGPR and higher ≥CR rates with linvo. Vs cilta-cel ITT (52.8), linvo had significantly lower ORR (OR 0.41, 0.22–0.76) and ≥VGPR (OR 0.37, 0.21–0.66) and ≥CR rates (OR 0.40, 0.24–0.66), but longer DOR (HR 0.46, 0.22–0.95). PFS was similar (HR 1.08, 0.62–1.91) and, though not significant, OS was shorter (HR 1.27, 0.71–2.25). Results vs cilta-cel mITT (57.6) were similar, with numerically longer DOR and shorter PFS with linvo. **Conclusions:** Linvo showed significantly higher ≥CR rate and longer DOR and PFS, and numerically longer OS vs ide-cel in the ITT population, and numerically lower ORR and similar ≥VGPR rate. Vs cilta-cel ITT, linvo showed significantly longer DOR and similar PFS despite significantly lower response rates and numerically shorter OS. Although outcomes improved in the CAR-T mITT populations and MAIC results were broadly consistent, the impact of bridging therapy on these comparisons remains unclear. These findings suggest linvo has the potential to offer a clinically meaningful, off-the-shelf alternative to CAR-T therapies in TCE RRMM.

PA-051

Initial Results of a Phase 2 Study to Evaluate Elranatamab (elran) Post-Idecabtagene Vicleucel (ide-cel) Consolidation (EPIC) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Ide-cel demonstrated a median PFS of 8.8 months with deeper responses (≥CR) associated with a longer median PFS of 19 months in the phase 2 KarMMa trial. There is an opportunity to improve the depth and durability of responses with ide-cel. Our hypothesis is that elra consolidation 100 days after ide-cel could re-invigorate polyclonal T cell responses against BCMA-positive MM cells at a point when both cytopenias after CAR-T are commonly resolved and the CAR T-cell population has decreased substantially. The EPIC phase 2 study (NCT06138275) in pts with RRMM who have received ide-cel aims to investigate fixed duration elra as a consolidation therapy (tx) to improve PFS by deepening disease response. We present initial results from the EPIC study. **Methods:** This single-arm, non-randomized, prospective phase 2 study (NCT06138275) evaluates elra as consolidative tx in pts ≥18 years with RRMM after ≥2 lines of tx who received ide-cel as standard of care. Pts received fixed duration elra consolidation from Day +100 up to +160 after ide-cel infusion (elra schedule, C1–2: D1, D4 (C1 only), D8, D15, D22; C3–6: D1, D15). IVIG was recommended for serum IgG <400 mg/dL; HSV/VZV and PJP prophylaxis were required. The primary objective is to evaluate the PFS of elra consolidation in RRMM after tx with ide-cel. Key secondary objectives were to evaluate safety, CR/sCR, DOR, MRD-negative conversion rate, time to MRD-negativity, and rate of sustained MRD-negativity of ≥6 or ≥12 months. Data cutoff date was 5/19/2025. **Results:** To date, 12 pts have been enrolled with 3 in screening; 6 pts have completed elra consolidation. Median follow-up was 7 months. Median age was 71 (range 48–82), 50% were female, and 25% had high-risk cytogenetics (del[17p], t[4;14], or t[14;16]). Pts had a median of 3 (range 2–6) prior lines pre-ide-cel. Median number of days between ide-cel and elra was 113 days (range 91–158). Five pts received step-up dosing as an outpatient. One pt has had disease progression with an isolated plasmacytoma (329 days post ide-cel; 219 days after start of elra consolidation) requiring radiation tx without any systemic tx. All are currently alive. Disease response post-ide-cel were: 4 sCR, 2 VGPR, and 6 PR and for the 6 pts who have completed elra were: sCR 5/6 and VGPR 1/6. Five of 6 pts who had completed elra with available MRD were all uMRD6 with MRD conversion in 3/6 pts from uMRD positive to uMRD6. CRS occurred in 42% of pts (5 events in 5 pts, all grade [G] 1). No ICANS occurred. Neutropenia G ≥3 was observed in 4 pts (33%) and anemia G ≥3 in 1 pt (8%) with no G ≥3 thrombocytopenia. Six pts (50%) experienced G ≥3 AEs without attribution (febrile neutropenia [FN], n = 1; lung infection, n = 1, hypertension, n = 1; hypophosphatemia, n = 1; neutropenia, n = 3) and 1 pt was hospitalized (n = 1, FN). Enrollment is ongoing. **Conclusions:** Early data suggests that elra consolidation after standard of care ide-cel is feasible and may deepen MRD negativity in pts with RRMM. Updated data will be presented.

PA-052

BCMA CAR-T Cells Capable of IL-6-Neutralization Bifunctionally Reduce Cytokine Release Syndrome and IL-6-driven Myeloma Growth in Preclinical Models

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Introduction: The widespread adoption of BCMA-directed CAR-T cells for relapsed multiple myeloma (MM), especially in outpatient and community settings, is limited due to inflammatory toxicity concerns, including cytokine release syndrome (CRS). We therefore seek to develop CAR-T cells that can modulate the signalling involved in CRS to improve the therapeutic window of CAR-T cell therapy. **Methods:** We developed single domain antibody (sdAb)-based BCMA CAR constructs (sdBCMA.BBz) and generated CAR-T cells using lentiviral vectors and healthy donor T-cells. We performed in vitro testing of cytotoxicity, cytokine release, proliferation, and repetitive stimulation against human cell lines, and in vivo with OPM2 xenografts in NSG mice. We then developed membrane-bound versus secreted versions of a sdAb that neutralizes IL-6 and incorporated this into the lead sdBCMA.BBz CAR construct. These underwent the same in vitro and in vivo assessment as above. We also developed an in vitro tri-culture system with CAR-T cells, tumour cells, and monocyte-derived macrophages, to model CRS cytokine production. Finally, we tested our sdIL-6 neutralizing domains against IL6-dependent MM cell lines. **Results:** CAR-T cells generated from healthy donor T-cells carrying anti-BCMA sdAb's with varying affinities, or control binders derived from ide-cel and cilta-cel, were tested using co-culture experiments with MM target cell lines. These in vitro studies confirmed that all sdBCMA.BBz CAR-T cells effectively lysed MM targets, released inflammatory cytokines, and proliferated. Effective disease control was demonstrated in NSG mice bearing OPM2 tumours with our sdAb-based CARs, comparable to our mimics of clinically approved CAR-T cells. We synthesized an anti-human IL-6 sdAb and show effective binding with an EC50 of 0.84 nM in a direct binding assay, and an IC50 of 2.8 nM in a competitive binding assay with the native IL-6 receptor. We show effective clearance of exogenous IL-6 in culture supernatants, as well as clearance of macrophage-derived IL-6 in tri-cultures incorporating CAR-T cells, OPM2 or MM1S tumour cells, and monocyte-derived macrophages. We also show that this IL-6 binder can slow the growth of IL-6-dependent cell lines, ANBL-6 and INA-6. In NSG mice with OPM2 tumours, we demonstrate equivalent survival with CAR-T cells incorporating the IL-6-neutralizing domains. **Conclusions:** We show that our sdAb-based CAR T-cells are functional in vitro and in vivo. We further show that our IL-6-neutralizing CAR-T cells can clear macrophage-derived IL-6 derived in vitro, the major source of IL-6 in CAR-T cell-related CRS. We show that this IL-6 binder can impede the growth of IL-6 dependent cell lines, highlighting microenvironment-derived IL-6 as a potential therapeutic enhancement. The assessment of these CAR-T cells in humanized mouse models of MM is on-going. Taken together, we show a CAR-T cell product that can neutralize IL-6, which underlies the pathophysiology of CRS and is a key myeloma growth-promoting cytokine.

PA-054

Outcomes of Patients with Multiple Myeloma Post-BCMA Directed Treatment: An Australian Perspective

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Introduction: BCMA-directed therapies - including CAR-T cells, bispecific antibodies and antibody drug conjugates - have demonstrated high initial response rates in patients with relapsed/refractory multiple myeloma (RRMM). However, most patients eventually relapse. There are limited data on outcomes following disease recurrence after BCMA-directed therapy in an Australian cohort. **Methods:** Using the Myeloma and Related Disease Registry (MRDR), we retrospectively analysed Australian patients who received BCMA-directed therapy up to 17 March 2025 and subsequently developed progressive disease (PD) as defined by the IMWG response criteria. The commencement of first salvage therapy following progression after BCMA therapy was considered the index date. Overall survival (OS) was defined as the time from index date to death, and progression free survival (PFS) as the time from index date to the earliest of progression or death. Disease responses to salvage treatments were assessed by the treating physician or delegate according to IMWG criteria. All analyses were performed using Stata/BE 18.0. **Results:** We identified 40 patients who commenced first salvage therapy following progression after BCMA-directed therapy. Of these, 29 (73%) were male. Median age at diagnosis, and index therapy was 62.1 years, and 68.5 years respectively. High risk cytogenetics were present in 22.2% (6/27) of patients and 14.3% (3/21) had R-ISS stage 3 disease. All patients were triple-class refractory and 32.5% (13/40) were penta-drug refractory. Median line of treatment at index therapy was 5 (range 2–13). The median OS from

commencement of post-BCMA salvage therapy was 10.5 months (95% CI: 5.6–23.9). Half of the patients received a proteasome inhibitor and/or immunomodulatory drug as salvage therapy. Anti CD38 antibody-based regimens were used in 10 patients (25%). Among the 25 patients with response data available, the overall response rate to first salvage regimen was 44% (11/25), with a median PFS of 5.3 months (95% CI: 3.0–11.7 months). **Conclusions:** Patients with RRMM who progress after BCMA-directed therapy have limited prognosis, although some can achieve deep responses. Further research is needed to identify optimal treatment pathways for this rapidly increasing cohort of myeloma patients.

PA-055

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-056

CAC-MM-001: Anti-BCMA CAR-T Therapy Followed by Autologous Stem Cell Transplantation and Second CAR-T (CART-ASCT-CART2) in Newly Diagnosed Multiple Myeloma Patients with P53 Gene Abnormalities

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Introduction: Multiple myeloma (MM) patients with P53 gene abnormalities have poor outcomes and often relapse early after standard treatments. BCMA-targeted CAR-T therapy has shown promise in the high-risk group. CAC-MM-001 (NCT05850286) is the first trial to evaluate a sequential CART-ASCT-CART2 strategy in newly diagnosed MM with P53 abnormalities. **Methods:** Transplant-eligible patients with P53 gene abnormalities, defined as del(17p) by FISH or P53 mutation by sequencing, were enrolled. After induction therapy, patients will receive a first infusion of BCMA-directed CAR-T cells. Subsequently, 3 cycles of consolidation therapy were administered. Patients then undergo high-dose melphalan conditioning followed by ASCT on day 1 and a second CAR-T infusion on day 3. Maintenance is started after 3 months post-transplant. **Results:** As of April 2025, 11 patients who completed the full CART-ASCT-CART2 regimen. 11 patients had del(17p), of which 3 patients with concurrent P53 mutations. The median age was 55 years (range 40–60), 6 male, 5 patients with t (4;14), 3 with gain(1q), 4 ISS stage III, 3 EMB. The median time from diagnosis to first infusion was 164 days (range 111–280). After first CAR-T infusion, 54.5% (6/11) experienced CRS (9.1% grade 2, 45.5% grade 1) and fully recovered. 6 patients received corticosteroids, and 2 received tocilizumab. The median time to onset of CRS was 3 days (range, 1–6), with a median duration of 6 days (range, 2–7). Hematologic toxicities included neutropenia in 100% (81.8% grade 3/4), anemia in 90.9% (9.1% grade 3) and thrombocytopenia in 45.5% (9.1% grade 4). All patients achieved hematologic recovery, with a median time of 18 days (range, 4–57) for ANC ($\geq 1.5 \times 10^9$/L) and 4 days (range, 2–44) for PLT ($\geq 100 \times 10^9$/L). After ASCT and the second CAR-T infusion, CRS occurred in 4/11 (36.4%) patients (9.1% grade 2, 27.3% grade 1). One patient received both corticosteroids and tocilizumab. No cases of ICANS were observed. After ASCT, hematologic reconstitution was achieved in a median of 17 days (range, 13–28) for ANC ($\geq 0.5 \times 10^9$/L) and 12 days (range, 8–50) for PLT ($\geq 20 \times 10^9$/L). Two patients received stem cell boost due to delayed hematopoietic recovery. No treatment-related deaths occurred. At a median follow-up of 279 days (range, 168–602) post-first CAR-T, 63.6% (7/11) of patients achieved CR with MRD negativity. Among the 11 patients who received the second CAR-T infusion, the CR and MRD negativity rate reached 90.1% (10/11). The median duration of MRD negativity was 255 days (range, 140–523). One patient experienced disease progression, which had biallelic

inactivation of the P53 gene. **Conclusions:** Preliminary results from this trial suggest that CART-ASCT-CART2 has a favourable safety profile in NDMM patients with P53 gene abnormalities. Although the follow-up time is relatively limited, high rates of CR and MRD negativity has been observed. We expect to see further deepening depth of response and durable MRD negativity with longer follow-up.

PA-057

Outcomes of Outpatient Step-up Dosing (SUD) of Teclistamab and Talquetamab in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Findings from a Large Network of Community Practices in the USA

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Introduction: Teclistamab (Tec) and talquetamab (Tal), two first-in-class bispecific T-cell engaging antibodies approved for the treatment of RRMM, should be initiated using SUD in an inpatient (IP) setting to mitigate the risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), per US label. However, to reduce IP healthcare resource utilization and improve patient (pt) experience, outpatient (OP) [OP SUD with acetaminophen or dexamethasone for Grade 1 CRS, or hospitalization for Grade 2+ CRS] and hybrid (HY) SUD [OP SUD with 48 h IP observation] is also being implemented. This real-world study evaluated the outcomes in pts with RRMM initiating Tec or Tal with SUD in OP, HY, and IP settings. **Methods:** This was a retrospective, observational, three-cohort (SUD in IP, OP, and HY settings) study of pts with RRMM (≥18 years) from a large network of community oncology practices in the US. Anonymized data on clinical characteristics, adverse events (AEs), and treatment history for pts initiating Tec (from Oct 2022) or Tal (from Aug 2023) were extracted till Feb 2025 from EMR for the first 14 days of SUD. Descriptive results were analysed for all cohorts. **Results:** This study included 120 pts with RRMM (OP: Tec = 13, Tal = 10; IP: Tec = 42, Tal = 12; HY: Tec = 29, Tal = 14), of which 48%, 40%, and 31% were aged ≥75 years in the OP, HY, and IP cohorts, respectively. Among the OP, IP, and HY cohorts, 9%, 13%, and 28% of pts were Black; 9%, 19%, and 17% had ECOG scores of ≥2; and 26%, 33%, and 28% had high-risk cytogenetics (t(4; 14); t (14; 16); del17p), respectively. Most pts were penta-drug exposed (OP = 70%, IP = 80%, HY = 81%). Tec and Tal pts had 4 median prior lines of therapy (PL) in OP, 4 and 5 PLs in IP, and 4 and 6 PLs in HY, respectively. More pts in IP (24%) and HY (33%) cohorts had prior exposure to T-cell redirecting therapy than the OP cohort (9%). The most frequent OP SUD schedule was 1–3–5 (62%) for pts receiving Tec. Most Tal pts followed biweekly dosing (80%). The 14-day CRS rates were comparable across cohorts (OP = 61%, IP = 50%, HY = 63%); the highest grade (G) of CRS was 2 (OP = 22%, IP = 7%, HY = 37%). Pts received tocilizumab for the treatment of CRS (OP = 13%, IP = 17%, HY = 56%). No pts discontinued treatment due to CRS. All OP Tec and Tal pts successfully completed SUD, with G2 CRS patients needing 4 days (median) of hospitalization. The 14-day frequency of ICANS was low (OP: G2 = 4%, IP: G1 = 2%, G2 = 2%, G4 = 2%, HY: G1 = 9%, G2 = 2%, unknown = 2%). Pts received steroids for the treatment of ICANS (OP = 0%, IP = 4%, HY = 14%). No pts were hospitalized due to ICANS. One pt from HY cohort discontinued treatment due to ICANS. Most OP pts completed SUD without the need for hospitalization (70%). **Conclusions:** In community oncology practices, OP SUD showed comparable rates and severity of CRS and ICANS as IP/HY SUD. OP SUD of Tec or Tal is feasible and can be safely managed in heavily pre-treated pts with some requiring hospitalization for G2 CRS.

PA-058

Real-World Safety Outcomes and Healthcare Resource Utilization (HCRU) During Outpatient, Inpatient, and Hybrid Step-up Dosing (SUD) of Teclistamab (Tec) and Talquetamab (Tal): A Chart Review Study

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Introduction: Traditionally, SUD of Tec and Tal for relapsed/refractory multiple myeloma (RRMM) has been conducted in inpatient (IP) settings to manage cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). SUD is increasingly administered outpatient (OP) to expand patient (pt) access and reduce HCRU. This real-world study describes the safety outcomes and hospitalizations of Tec or Tal pts receiving SUD in OP, IP, and hybrid (mixed OP/IP) settings. **Methods:** This study used data from a medical record review of RRMM pts receiving Tec or Tal post-FDA approval across a consortium of US sites. Pts were categorized by intended SUD setting: OP, IP, or hybrid. Pt characteristics, safety outcomes, and hospitalizations were described for each cohort. **Results:** The OP, IP, and hybrid cohorts had 21 (Tec: 17; Tal: 4), 132 (Tec: 93; Tal: 39),

and 68 (Tec: 36; Tal: 32) pts, respectively. Median age at treatment initiation for OP pts was 75.0 years (IP: 68.8 years; hybrid: 66.5 years); OP pts were 66.7% White and 28.6% Black (IP: 82.6% and 14.4%; hybrid: 75.0% and 16.2%). Of OP pts, 23.8% had ECOG score ≥2 (IP: 38.6%; hybrid: 26.4%) and 28.6% had high-risk cytogenetics (IP: 54.5%; hybrid: 55.9%). The OP cohort received a median of 4 prior lines of treatment (IP: 6; hybrid: 5). All but 1 IP pt completed all SUD doses. During SUD, 33.3% of OP pts had CRS (IP: 59.8%; hybrid: 55.9%), with no grade 3+ events for OP and hybrid pts and only 4 (3.0%) IP pts reaching grade 3. ICANS occurred in 11.4% of the IP cohort and 7.4% of the hybrid cohort, with no events among OP pts. From SUD completion to 30 days post-treatment initiation, no OP pts experienced CRS or ICANS, but 1 additional grade 2 CRS event was reported in IP and hybrid cohorts each as well as 1 ICANS event in the hybrid cohort. In IP and hybrid cohorts, 47.7% and 30.9% of pts received tocilizumab to treat CRS, respectively; no OP pt was treated with tocilizumab. Two-thirds (66.7%) of OP pts received steroids during SUD (IP: 47.7%; hybrid: 73.5%) with 14.3% for CRS management (IP: 15.9%; hybrid: 19.1%), and 4.8% for other neurotoxicity event management (IP: 7.6%; hybrid: 4.4%). In the OP cohort, 2 pts (9.5%) required hospitalization. Median length of stay (LOS) per hospitalization was shortest among OP pts (2 days), followed by hybrid (2.3 days) and IP pts (8 days). The number of days hospitalized per pt was 0.2 days per OP pt vs 9.2 days per IP pt which is a 97.9% reduction in LOS for OP pts. **Conclusions:** In this real-world study of Tec and Tal pts, while OP pts were older than IP and hybrid pts, they had lower risk disease. These differing pt profiles and numerically lower rates of CRS and ICANS among OP pts (CRS mainly grade 1/2) highlight the importance of appropriate pt selection for OP SUD. SUD initiation in OP settings reduced HCRU compared to hybrid or IP. These findings demonstrate OP and hybrid SUD models are feasible, can be safely implemented, and resource-sparing with appropriate pt selection.

PA-059

A Phase 2 Study Measuring MRD Negativity after Talquetamab and Teclistamab Consolidation in Sequence As Part of First Line Treatment in Transplant Eligible Multiple Myeloma Patients (TALTEC)

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Introduction: Increasing minimal residual disease (MRD) negativity and search for possibly cure remain the goals of research efforts in multiple myeloma (MM) treatment. This study will evaluate the efficacy and tolerability of talquetamab and teclistamab in sequence, as consolidation after first line standard induction treatment in newly diagnosed multiple myeloma (NDMM) patients. **Methods:** In this open-label, multicenter phase 2 study, we enroll 50 NDMM patients eligible for high-dose therapy. Patients are treated with 6 cycles of daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd) with stem cell collection. This is followed by 6 cycles of talquetamab and 6 cycles of teclistamab in sequence. In follow up phase participants may receive standard of care with autologous stem cell transplantation (ASCT) and lenalidomide maintenance or only lenalidomide maintenance. Treatment response is assessed according to International Myeloma Working Group (IMWG) criteria. MRD is evaluated by next generation sequencing (NGS) and [18F] fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) at protocol-defined time-points. Participants' health related quality of life (QoL) and general well-being are captured using three patient reported outcome measures: PRO-CTCAE, EORTC-QLQ-C30 and FACT-Cog. Primary endpoint is to determine MRD negative complete response rate at a sensitivity level of 10–6 measured by NGS and FDG PET-CT after talquetamab and teclistamab consolidation therapy. Key secondary endpoints are to evaluate the proportion of participants achieving MRD negativity (10^{-6}) after induction treatment, conversion from positive MRD to negative MRD (10^{-6}) after talquetamab consolidation, conversion from positive MRD to negative MRD (10^{-6}) after teclistamab consolidation, and sustained MRD negativity.Exploratory endpoints are to describe migration,

clonal expansion and functional transition of T-cells, epigenetic changes of T-cell exhaustion, methylation status of resistant MM cells, and detect proteomic signatures from MRD positive and MRD negative patients by mass-spectrometry. **Results:** The TALTEC study opened in June 2024 and is currently enrolling the patients. 49 patients out of sample size of 50 patients were enrolled in the study as of 30-May-2025. Futher information about baseline characteristics will be provided in the presentation. **Conclusions:** TALTEC is an important study to evaluate the potential of sequencing two first in class T -cell redirectors talquetamab and teclistamab as consolidation after D-VRd induction as an alternative treatment option to high-dose melphalan and ASCT through improved MRD negativity. The study is conducted by North Estonia Medical Centre Foundation and Nordic Myeloma Study Group in collaboration and with the financial support from Janssen Pharmaceutica NV, a member of the Johnson & Johnson group of companies and with additional funding from Central Norway Health Region (EU CT 2023-508212-38-00; ClinicalTrial.gov NCT06505369).

PA-060

Phase 2 Study of Talquetamab (Tal) + Teclistamab (Tec) in Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM) and Extramedullary Disease (EMD): RedirecTT-1

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Introduction: Tal (anti-GPRC5D) and Tec (anti-BCMA) are bispecific antibodies (BsAbs) approved as monotherapies for triple-class exposed (TCE) RRMM. In pts with EMD, ORR was 41–48% with Tal and 36% with Tec alone. We report the efficacy and safety of Tal + Tec in pts with EMD in the phase 2 RedirecTT-1 EMD cohort (NCT04586426). **Methods:** Pts had TCE RRMM and EMD (≥1 nonradiated soft tissue plasmacytoma noncontiguous with bone ≥2 cm in 1 dimension with or without paraskeletal plasmacytomas). Nonsecretory/oligosecretory disease permitted. Prior CAR-T (≤20% of pts) and non-BCMA/-GPRC5D BsAb therapy permitted. Pts received Tal 0.8 mg/kg Q2W + Tec 3.0 mg/kg Q2W, with step-up doses; pts could switch to Q4W dosing at investigator's discretion after cycle 6 or after cycle 4 with confirmed ≥VGPR. Response was assessed by IRC per IMWG criteria; EMD response was assessed by PET-CT scans. **Results:** As of March 2025, 90 pts received Tal + Tec (median follow-up 12.6 mo [range 0.5–19.5]). Median age 65 yrs; 22% had high-risk cytogenetics, 39% had nonsecretory/oligosecretory disease, and median number of plasmacytomas noncontiguous with bone was 2 (range 1–14). Median prior LOT was 4: 84% triple-class refractory, 36% penta-drug refractory, 20% prior anti-BCMA CAR-T therapy, and 9% prior BsAbs. ORR (95% CI) was 79% (69.0–86.8), with ≥CR 52%; ORR was 83% (58.6–96.4; n = 15/18) in anti-BCMA CAR-T–exposed pts and 75% (34.9–96.8; n = 6/8) in BsAb-exposed pts. 9-mo DOR, PFS, and OS were 75%, 64%, and 80%, respectively. Most responders (>90%) deepened or maintained response after switching to Q4W dosing. Grade (gr) 3/4 AEs occurred in 78 (87%) pts. CRS occurred in 70 (78%) pts (all gr 1/2). ICANS occurred in 11 (12%) pts (gr 3, 1%; gr 4, 1%; gr 5, 0%). Neutropenia was the most common gr 3/4 AE (n = 56, 62%). Taste changes (n = 71, 79%), skin (n = 62, 69%), and nail (n = 50, 56%) were all gr 1/2, and rash (n = 26, 29%) was mostly gr 1/2. Infections occurred in 71 (79%) pts (gr 3/4, 37%); 88% of gr 3/4 infections occurred within the first 6 mo. 63 (70%) pts had posttreatment hypogammaglobulinemia. 78 (87%) pts received ≥1 dose of intravenous IgG. 8 (9%) pts discontinued Tal + Tec due to AEs; 5 due to gr 5 AEs (COVID-19 pneumonia, Klebsiella sepsis, aspiration, respiratory failure, euthanasia) and 3 due to non–gr 5 AEs. 2 pts discontinued Tal only due to non–gr 5 AEs. No pts discontinued Tec only. 10 pts had gr 5 AEs (5 infections); 5 were drug related. **Conclusions:** With 90 pts, the phase 2 cohort of RedirecTT-1 is the largest dedicated EMD study to date. Tal + Tec led to a high ORR and deep, durable responses; efficacy exceeded standard therapies, including BsAbs alone, and was comparable to CAR-T in pts with RRMM with EMD. No new safety signals were identified, including no exacerbated Tal or Tec AEs. These data highlight the clinical benefit of dual antigen targeting with the combination of Tal + Tec in pts with EMD, a population with high disease burden and significant unmet need.

PA-061

Updated Comparative Effectiveness of Talquetamab vs Real-World Physician's Choice of Treatment in Patients With Triple-Class Exposed Relapsed/Refractory Multiple Myeloma

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Introduction: Talquetamab (Tal) is the first G protein–coupled receptor class C group 5 member D-targeting bispecific antibody approved for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) based on results from the MonumenTAL-1 study (NCT03399799/NCT04634552). The nationwide Flatiron Health database is a collection of clinical data derived from deidentified electronic health records that characterizes real-world physician's choice of treatment (RWPC) in patients (pts) with TCE RRMM. Previous indirect comparisons showed superior efficacy outcomes with Tal vs RWPC in pts with TCE RRMM. We report an updated adjusted comparison of Tal vs RWPC in pts with TCE RRMM with longer follow-up in the MonumenTAL-1 study. **Methods:** Individual pt-level data from MonumenTAL-1 were included for pts who received subcutaneous Tal 0.4 mg/kg weekly (QW; n = 143) or 0.8 mg/kg every other week (Q2W; n = 154) using a data cut-off of September 2024; median follow-up was 38.2 (QW) and 31.2 (Q2W) months. An external control arm was created from the deidentified database (as of October 2024) for pts who met key MonumenTAL-1 eligibility criteria (N = 629 with 1169 eligible lines of therapy). A base case and fully adjusted model adjusted for baseline prognostic variables using inverse probability of treatment weighting. Baseline covariate balance after adjustment was assessed using standardized mean differences (SMDs). Outcomes assessed were progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT). A weighted Cox proportional hazards model estimated hazard ratios (HRs) and 95% CIs, and a weighted Kaplan-Meier method estimated median time-to-event outcomes. Sensitivity analyses evaluated the impact of alternative statistical methods and variable adjustment. **Results:** After reweighting, baseline characteristics were balanced between the RWPC and Tal cohorts, with all SMDs <0.1. In the base case model, pts receiving Tal QW had significantly superior outcomes vs RWPC, with longer PFS (HR 0.66 [95% CI 0.53–0.82]; P < 0.001; median 7.5 vs 4.8 months), longer OS (HR 0.56 [0.42–0.74]; P < 0.001; median 34.0 vs 16.5 months), and longer TTNT (HR 0.57 [0.47–0.69]; P < 0.001; median 9.1 vs 5.1 months). Similarly, pts receiving Tal Q2W had significantly superior outcomes vs RWPC, with longer PFS (HR 0.54 [0.44–0.68]; P < 0.001; median 11.2 vs 4.7 months), longer OS (HR 0.42 [0.31–0.57]; P < 0.001; median not reached vs 15.8 months), and longer TTNT (HR 0.49 [0.40–0.60]; P < 0.001; median 11.8 vs 5.1 months). Results were generally consistent in the full model and across sensitivity analyses. **Conclusions:** Results from the MonumenTAL-1 study continued to demonstrate superior effectiveness of Tal, especially with the Q2W dosing schedule vs RWPC, highlighting its clinical benefit and further supporting Tal as a compelling treatment for pts with TCE RRMM.

PA-062

Serologic Immunity to Measles, Mumps, and Rubella in Multiple Myeloma Patients Following Cellular Therapy: A Descriptive Analysis

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Introduction: Multiple myeloma is a malignant neoplasm of plasma cells that accounts for approximately 10% of all hematologic cancers. Patients with multiple myeloma (MM) are at heightened risk for infectious complications, particularly following intensive therapies such as autologous stem cell transplantation (ASCT) or chimeric antigen receptor (CAR) T-cell therapy. While immunity to measles, mumps, and rubella (MMR) may diminish post-treatment, real-world data on post-therapy serologic immunity remains limited. This study aims to characterize MMR immunity in multiple myeloma patients post-ASCT amid heightened risk from recent U.S. measles outbreaks. **Methods:** We conducted a retrospective descriptive analysis of multiple myeloma patients who underwent autologous stem cell transplantation (ASCT) as upfront consolidation, with at least 12 months post-ASCT. Measles, mumps, and rubella (MMR) IgG titers were measured during routine follow-up and standardized: measles and mumps IgG <5 IU/mL were set to 0 and capped at 300 IU/mL; rubella <10 IU/mL was set to 0 with no upper cap. Patients were classified as immune with titer thresholds of measles ≥16.5 IU/mL, mumps ≥11 IU/mL, and rubella ≥10 IU/mL. Median titers were calculated overall and by immune status. Patients receiving IVIG within 8 weeks of titer measurement were excluded. Comparisons were made across clinical subgroups, including response status, maintenance therapy, and CMV status. **Results:** 50 patients seen in our myeloma clinic between March and May of 2025 were included. Overall, 12/50 (24% of patients) were non-immune to all three viruses. Individually, 33.3% lacked immunity to measles, 35.8% to rubella, and 70.4% to mumps. Immune patients had higher median MMR titers compared to non-immune for measles [142.5 (18.5–300) vs 0 (0–10.6) IU/mL, p < 0.0001], rubella [42.45 (10–509) vs 0 (0–0), p < 0.0001], and mumps [35.5 (12.7–283) vs 0 (0–10.4), p < 0.0001]. Non-immune cohort demonstrated longer median time from ASCT to titer assessment, with statistical significance only for mumps: measles (63 vs 53.5 months, p = 0.4135), rubella (59 vs 52.5, p = 0.5512), and

mumps (63 vs 37.5, p = 0.0027). Among immune patients, immunity to measles (62.5% CR, 58.8% VGPR 40% PR) and rubella (58.8% VGPR, 56.25% CR, 50% PR) was highest in VGPR and CR groups, while mumps immunity was uniformly low (37.5% CR, 26.5% VGPR, 10% PR). Use of maintenance therapy was associated with non-significant higher measles and rubella titers, and no difference in mumps while CMV positivity correlated with non-significant higher titers for measles, mumps, and lower for rubella. **Conclusions:** A substantial proportion of MM patients lack protective serologic immunity to one or more components of the MMR vaccine following cellular therapy. These findings underscore the importance of routine post-treatment serologic surveillance and may inform revaccination strategies to optimize infection prevention in this immunocompromised population.

PA-064

Linvoseltamab (LINVO) + Carfilzomib (CFZ) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Initial Results from the LINKER-MM2 Trial

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Introduction: LINVO, a human BCMA×CD3 bispecific antibody, demonstrated high efficacy and a generally manageable safety profile in pts with triple-class exposed (TCE) RRMM. Combination treatment (tx) with CFZ, a potent 2nd-generation proteasome inhibitor (PI), may provide additive or synergistic activity. We report safety and preliminary efficacy from the dose-finding portion in the LINVO + CFZ cohort of the Phase 1b LINKER-MM2 trial (NCT05137054). **Methods:** Eligible pts were aged ≥18 years with RRMM that progressed after ≥3 lines of therapy (LoT), or ≥2 LoT if TCE or double-class refractory (immunomodulatory drug + PI). Prior CFZ was allowed if previously tolerated and ≥6 months had elapsed since last exposure. CFZ-refractory pts were allowed during dose finding. Tx began with LINVO alone (Cycle [C] 0) as two step-up doses (5 mg, 25 mg) and three full doses (dose level [DL] 1: 100 mg; DL1b: 150 mg; DL2: 200 mg) before initiation of CFZ (20/56 mg/m2 on Days 1, 2, 8, 9, 15, 16) at C1. LINVO was given once weekly (QW) in C1–4, and once every 2 weeks thereafter. CFZ dosing could be switched to QW after C2. Dexamethasone premedication was given at C0–1. Primary endpoints were dose-limiting toxicities (DLTs) and tx-emergent adverse events (TEAEs). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). **Results:** As of 7 Mar, 2025, 23 pts were treated at DL1 (n = 12), DL1b (n = 6), or DL2 (n = 5). All pts had received ≥1 PI and 52% were refractory to ≥1 PI. Median number of prior LoT was 3 (range 2–6), including 91% of pts with TCE and 43% with triple-class refractory disease. Median age was 70 years (range 53–83), 48% were male, 4% had ISS stage III at study entry, 17% had high-risk cytogenetics, and 22% had sBCMA ≥400 ng/mL. Median duration of follow-up was 22.3 (DL1), 13.2 (DL1b), and 5.6 months (DL2), with 42%, 83% and 80% of pts still receiving tx, respectively. The most common TEAEs were neutropenia (any Grade [Gr] 61%; Gr 3–4 52%), cytokine release syndrome (61%; 0%), thrombocytopenia (52%; 30%), and diarrhea (52%; 4%). One pt experienced ICANS (Gr 1). Infections were reported in 91% of pts (Gr ≥3 43%). One DLT was observed at DL1, Gr 4 thrombocytopenia during tumor lysis syndrome, which was fully resolved and tx resumed at the same dose. Among evaluable pts, ORR was 91% at DL1 (10/11; very good partial response or better [≥VGPR] rate 91%), 100% at DL1b (5/5; ≥VGPR rate 100%), and 80% at DL2 (3/5; ≥VGPR rate 60%); 5/7 minimal residual disease (MRD)-evaluable pts were MRD negative (10^{-5} threshold). DOR rate was 87% (95% CI 56–97) and PFS rate was 83% (95% CI 55–94) at 12 months. **Conclusions:** In pts with heavily pretreated RRMM and prior PI exposure, LINVO + CFZ induced a high rate of deep and durable responses with a safety profile generally consistent with that expected based on the individual drug profiles. These preliminary data support continued development of LINVO + CFZ for the tx of pts with heavily pre-treated RRMM.

PA-065

Real-World Outcomes of Equecabtagene Autoleucel, the First Fully Human BCMA-Targeted CAR-T Therapy, in 150 Patients with Multiple Myeloma (MM): A Multicenter Experience from China

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Introduction: Equecabtagene Autoleucel (Eque-cel), a fully human BCMA-targeted CAR-T therapy, received NMPA approval in June 2023 for adults with relapsed/refractory multiple myeloma (RRMM) after ≥3 prior therapies. Building on the FUMANBA-1 trial's demonstration of durable efficacy and safety in heavily pretreated RRMM, this study presents the first post-approval real-world analysis of Eque-cel in China, offering clinical insights for its use. **Methods:** We conducted analysis on data from 150 patients who received infusion therapy across 48 centers between June 2023 and August 31, 2024.All patients received a single infusion of Eque-cel at the dose of 1.0 × 106 CAR-T cells/kg. Responses were evaluated per IMWG criteria, and the ORR was defined as at least ≥PR. **Results:** All 150 patients underwent leukapheresis followed by Eque-cel infusion. Median age was 60 years (range: 35–78), with 33.3% aged ≥65. Disease characteristics included high-risk cytogenetics (71.3%, 107/150), plasma cell leukemia (12.7%, 19/150), extramedullary myeloma (52.7%, 79/150), and CNS involvement (10%, 15/150). The median prior therapy lines were 3 (range:1–9), with 78.6% (118/150) triple-class exposed, 40.7% (61/150) penta-exposed, 82% (123/150) anti-CD38 antibody-treated, and 53.3% (80/150) with prior ASCT (including 7 with prior second ASCT). The CAR-HEMATOTOX classifier stratified 82 patients into low- (n = 12) and high-risk (n = 70) groups. In the efficacy-evaluable population (n = 137; excluding 10 deaths, 1 lost to follow-up, and 2 missing data), the overall response rate (ORR) was 98.5% (135/137), with 73% (100/137) achieving complete response (CR) or better. Among 90 patients with ≥CR and MRD data, 97.8% (88/90) were MRD-negative. In the EMM subgroup, ORR was 98.6% vs 98.4% in non-EMM, with ≥CR rates 70.8% and 75.4% respectively. The CR rates showed significant variation between treatment lines, with early-line therapy achieving 81.3% CR vs 65.1% CR in late-line settings. Patients without high-risk cytogenetics had a higher ≥CR rate (77.8% vs 73.5%). In the low-risk CAR-HEMATOTOX group, the ≥CR rate was 91.7% vs 73.4% in the high-risk group. In the available dataset, CRS occurred in 90.7% (136/150). Most cases were Grade 1 or 2, while higher - severity cases were more prevalent in high - risk patients. ICANS was 10.7% (16/150), with 4% experienced ≥ Grade 3. In the CAR-HEMATOTOX low-risk group, hematologic recovery was by Day 28, while the high-risk group had prolonged cytopenias and longer hospital stays. **Conclusions:** Eque-cel, China's first fully human BCMA-targeted CAR-T therapy, demonstrated high efficacy in 137 evaluable patients. Despite high-risk features including EMM (52.7%), PCL(12.7%), and CNS infiltration (10%), outcomes aligned with the pivotal FUMANBA-1 trial. Safety profiles showed predominantly low-grade CRS and limited but severe ICANS. These findings confirm Eque-cel as an effective therapy with manageable

safety, though extended follow-up is needed to assess survival benefits and optimize strategies.

PA-066

Kinetic Characteristics of T Cells in CAR-T Therapy for Multiple Myeloma: A Real-World Analysis

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Introduction: Chimeric Antigen Receptor T-cell (CAR-T) therapy has shown remarkable efficacy in treating hematologic malignancies in recent years. However, the long-term functional dynamics, mechanisms of exhaustion, and impact on the immune microenvironment of CAR-T cells remain insufficiently explored, particularly in real-world settings. This multicenter study investigates the kinetic profiles of T cells in patients with multiple myeloma treated with a fully human CAR-T cell therapy, equecabtagene autoleucel. We focus on the temporal evolution of differentiation subsets, exhaustion markers, and senescence phenotypes to provide a theoretical foundation for optimizing CAR-T therapy strategies. **Methods:** This study included patients receiving eque-cel infusion at the First Affiliated Hospital of Zhejiang University and other centers from August 2023 to April 2025. Post-infusion CAR-T cell proportion, exhaustion, and senescence were assessed in subsets of patients. Differentiation subsets (central and effector memory) were analyzed among CD4+ and CD8+ CAR-T cells. Immune checkpoint expression (PD-1, TIGIT, TIM-3, LAG-3) and senescence markers (CD27−, CD28−, CD57+) were measured. Linear regression assessed associations between indices and time, reporting β coefficients, P-values, and adjusted R^2. Nonlinear trends were evaluated using generalized additive models, with significance set at $P < 0.05$. **Results:** Of 30 patients, 40% were male (12/30), median age was 62 years (range: 49–77), 67% had IgG-type myeloma, 50% had high-risk cytogenetics, and 53% had extramedullary disease. Median follow-up was 161 days (range: 12–507). Data included multiple time points for senescence, exhaustion, and differentiation analysis (total 6,814 entries)-with over 80% collected within 50 days post-infusion. CAR-T persistence reached 391 days. Significant temporal trends ($P < 0.05$) were observed in most parameters. Notably, CD27− CD8+ CAR-T proportions remained stable ($P = 0.766$), whereas endogenous CD27− CD8+ T cells increased ($P = 0.004$), suggesting engineered CAR-Ts sustain vitality while endogenous T cells are more prone to senescence. Differentiation analysis revealed endogenous effector memory CD8+ T cells expanded early but declined over time, while central memory CD8 + CAR-T cells increased at later stages. Exhaustion markers, especially PD-1, showed an initial rise then decline in both CAR-T and endogenous T cells. In contrast, TIGIT and TIM-3 expression did not change significantly, possibly due to limited late-stage samples. **Conclusions:** This study sheds light on the dynamic evolution of T cells following CAR-T cell infusion in patients with multiple myeloma, offering valuable insights for refining CAR-T therapy strategies. However, further validation of differences across analytical models is required. Expanding the sample size and extending follow-up duration are essential to confirm these findings and enhance their clinical relevance.

PA-067

Infections in Patients (Pts) with Multiple Myeloma (Mm) Treated with BCMA-Directed CAR T Cell Therapies and Bispecific Antibodies: Analysis of the FDA Adverse Event Reporting System (FAERS)

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Introduction: Novel B-cell maturation antigen (BCMA)-directed therapies including chimeric antigen receptor (CAR) T cells (idecabtagene vicleucel [ide-cel], ciltacabtagene autoleucel [cilta-cel]) and bispecific antibodies (teclistamab, elranatamab) have emerged as effective treatments for MM. FAERS is a real-world (RW) post-marketing safety surveillance database capturing adverse events (AEs) reported to the US FDA for all marketed drugs and biologics across a broad population. We assessed RW infection-related AEs in pts receiving BCMA-directed CAR T cells and bispecific antibodies using FAERS. **Methods:** We used FAERS to capture infections and infection-related non-relapse mortality (NRM) and hospitalizations from case report forms (CRFs) in pts with MM where ide-cel, cilta-cel, teclistamab, or elranatamab were identified as drugs of interest. Infection-related NRM was defined as deaths excluding any from progressive MM with further filtering for infections.

Infection-related hospitalization was defined similarly. The primary analysis used all CRFs from Q1 2021 to Q4 2024, the latest FAERS quarterly release. To adjust for differences in follow-up duration between treatments after market approval, we conducted sensitivity analyses by restricting the CRF analysis time to 2 y post-market approval for each drug. Reporting odds ratios (ROR) were used to identify differences between treatments; a ROR >1 indicates the event was reported more frequently for the comparator than ide-cel. **Results:** Overall, 4809 AE reports in MM were associated with ide-cel (n = 689), teclistamab (n = 1732), elranatamab (n = 363), and cilta-cel (n = 2025). In disproportionality analyses (ROR [95% CI]), a significantly higher frequency of infection reports was associated with teclistamab (3.81 [2.51–5.77]), elranatamab (5.67 [3.53–9.10]), and cilta-cel (1.78 [1.16–2.73]) vs ide-cel. Results were similar in sensitivity analyses. Teclistamab (ROR, 4.02 [95% CI, 1.43–11.32]) and elranatamab (ROR, 5.57 [95% CI, 1.76–17.65]) had a significantly higher frequency of infection-related NRM reports than ide-cel. Results were comparable between ide-cel and cilta-cel (ROR, 1.01 [95% CI, 0.33–3.12]). Similar findings were observed for infection-related hospitalizations (teclistamab: ROR, 3.44 [95% CI, 2.03–5.83]; elranatamab: ROR, 5.65 [95% CI 3.14–10.19]; and (cilta-cel: ROR, 1.53 [95% CI, 0.88–2.65]). **Conclusions:** FAERS provides long-term follow-up data of drug safety, offering insights beyond pts meeting clinical trial criteria and providing greater statistical power to identify and understand observed toxicities. This retrospective analysis showed a favorable RW safety profile for ide-cel vs other BCMA-directed therapies in terms of infections and infection-related NRMs and hospitalizations. This highlights the importance of integrating safety profiles into treatment decisions to optimize outcomes and reduce risks, especially infection-related burden and mortality in pts with MM who are immunocompromised or have other comorbidities.

PA-068

Impact of Neighborhood-Level Disadvantage, Travel Distance, and Travel Time on Clinical Outcomes of Multiple Myeloma (MM) Patients Treated with Standard of Care (SOC) Idecabtagene Vicleucel (IDE-CEL)

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Introduction: Ide-cel, the first CAR T cell therapy approved for MM, shows notable responses and improved survival. Despite racial, ethnic, and socioeconomic disparities in MM incidence and outcomes, impacts of place of residence and neighborhood-level socioeconomic factors on outcomes of MM patients (pts) treated with CAR T cell therapy are mostly unknown. Here we look at effects of neighborhood-level disadvantage and travel distance (TD)/time on outcomes of MM pts treated with SOC ide-cel. **Methods:** Pts with MM who underwent leukapheresis by May 31, 2024, and received ide-cel at Moffitt Cancer Center were included. The main exposure was Area Deprivation Index (ADI), a composite measure of 17 neighborhood-level disadvantage metrics. Higher ADI percentiles denote more disadvantaged areas. TD/time from pts' homes to Moffitt were calculated using Google Directions API (driving mode). Differences in pt characteristics and clinical outcomes examined by ADI and TD/time were categorized using the upper quartile as the cut-point. **Results:** Of 183 MM pts treated with ide-cel, most were male (55%), non-Hispanic White (69%), and aged >60 y (75%). Safety and responses were aligned with previous data. Median follow-up was 12.4 mo (range 0.1–38.4). Median ADI was 42 (range 1–96) and 38% of pts lived in neighborhoods more disadvantaged than the national average (ADI >50). Baseline clinical characteristics showed that pts living in more disadvantaged neighborhoods (ADI ≥59.5, n = 47) were younger (67 vs 69 y; P = 0.09), had fewer prior therapies (5 vs 6; P = 0.04), and were more likely to have had prior autologous stem cell transplant (81% vs 61%; P = 0.01) and extramedullary disease (28% vs 15%; P = 0.06) vs pts in less disadvantaged neighborhoods (ADI <59.5, n = 136). Post infusion, pts with high vs low ADI had higher peak C-reactive protein levels (11.3 vs 7.7 mg/dL; P = 0.07). Clinical outcomes by ADI were similar, except non-relapse mortality (NRM), which was higher in pts living in more disadvantaged neighborhoods (13% vs 4%; P = 0.06), mainly due to infections in both groups. Among in-state pts (n = 178), median TD was 76.2 miles (range 2.3–452.2) and median travel time (TT) was 79 min (range 7–396). A total of 32% (n = 52) of pts traveled >100 miles, and 28% traveled >2 h for CAR T cell therapy. Pts with a longer TD (≥136 miles) were more likely to have high-risk cytogenetics (54% vs 29%; P = 0.005) and prior B-cell maturation antigen therapy (22% vs 9%; P = 0.03); no other differences in pt characteristics/clinical outcomes by TD were noted. Findings were similar for TT. Pts from more disadvantaged neighborhoods had shorter TTs (54 vs 83 min; P = 0.001) and TDs (46.2 vs 80.8 miles; P < 0.001). **Conclusions:** In these MM pts treated with SOC ide-cel, most lived in less disadvantaged neighborhoods yet faced significant travel burdens. Longer TD for most pts, and increased NRM in pts living in more disadvantaged neighborhoods highlights the need to address systemic barriers to improve CAR T cell therapy access and outcomes.

PA-069

Integrating Real-world Evidence to Augment Crossover Adjustment in KarMMa-3: A Case Study in Relapsed/Refractory Multiple Myeloma

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Introduction: KarMMa-3 (NCT03651128) is a phase 3 randomized controlled trial evaluating idecabtagene vicleucel (ide-cel) versus standard of care (SoC) in patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). Evaluating overall survival (OS) benefits in KarMMa-3 is challenging, given that 56% of patients randomized to the SoC arm crossed over to ide-cel following disease progression (unadjusted OS hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.73–1.40). Two-stage estimation methods were used to estimate OS benefits adjusted for crossover (HR, 0.72; 95% CI, 0.49–1.01), but this adjustment was limited by the small number of patients who did not crossover. We aimed to estimate the OS benefit of ide-cel versus SoC in KarMMa-3 by using real-world SoC evidence from the COTA Vantage database to inform a more precise crossover adjustment model. **Methods:** Crossover adjustment was performed using real-world data to determine what post-progression survival (PPS) would have looked like in KarMMa-3 SoC patients had they not crossed over to ide-cel. First, PPS data from a TCE RRMM cohort in the COTA database (November 2015 to March 2021) were aligned with KarMMa-3 (April 2023 cutoff) based on key trial inclusion criteria. Next, COTA PPS data were combined with KarMMa-3 SoC PPS via dynamic borrowing (ie, incorporated in a way that allows more influence when the external data closely resemble the trial population and less when they differ) to estimate the impact of crossover while controlling for confounders. This estimated impact of crossover was then used to adjust OS times in KarMMa-3. Finally, a stratified Cox proportional hazards model was fitted to the adjusted KarMMa-3 OS times to estimate HRs comparing ide-cel versus SoC in KarMMa-3 patients. Separate analyses were performed for the KarMMa-3 intention-to-treat (ITT) population and modified-ITT (mITT) population (patients who received their initial assigned treatment). **Results:** Following crossover adjustment, ide-cel improved OS versus SoC (HR, 0.67; 95% CI, 0.49–0.93) for the KarMMa-3 ITT population (ide-cel, N = 254; SoC, N = 132). An OS benefit of ide-cel versus SoC was also observed in the mITT population after crossover adjustment (HR, 0.50; 95% CI, 0.35–0.70) (ide-cel, N = 225; SoC, N = 126). Crossover adjustment was based on data from KarMMa-3 patients, with PPS information borrowed from 471 COTA patients, and adjusted for age, number of prior lines of therapy, cytogenetic risk profile, triple-class refractory status, tumor burden, time to progression on last regimen, time since diagnosis, hemoglobin level, prior stem cell transplantation, race, sex, Eastern Cooperative Oncology Group score, and lactate dehydrogenase level. **Conclusions:** Leveraging real-world SoC data allowed for a more efficient and precise estimation of crossover-adjusted OS in KarMMa-3. Findings from this analysis further support the significant and clinically meaningful OS benefit of ide-cel over SoC in patients with RRMM.

PA-070

An Evaluation of Overall Survival Between B-cell Maturation Antigen Chimeric Antigen Receptor T cell Therapies and Bispecific Antibodies for the Treatment of Relapsed/Refractory Multiple Myeloma

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Introduction: B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T cell therapies (idecabtagene vicleucel [ide-cel] and ciltacabtagene autoleucel [cilta-cel]) and bispecific antibodies (teclistamab and elranatamab) have not been directly or indirectly compared in a methodologically robust manner. Previous indirect comparisons between CAR T cell therapies were unanchored, did not incorporate randomized controlled trial (RCT) evidence, and did not adjust for crossover in KarMMa-3 overall survival (OS). This study aimed to compare OS across BCMA CAR T cell therapies and bispecific antibodies for the treatment of patients with relapsed/refractory multiple myeloma (RRMM). **Methods:** Objective 1: Individual-level patient data (IPD) for ide-cel were pooled across KarMMa (phase 2), KarMMa-2 (phase 2), and KarMMa-3 (phase 3; ≥4 prior lines) to form triple-class exposed (TCE) and triple-class refractory (TCR) cohorts. The ide-cel TCE cohort was compared with aggregate data (AD) for teclistamab 1.5 mg/kg population (phase 2 MajesTEC-1; 100% TCE), and the ide-cel TCR cohort was

compared with AD for elranatamab cohort A (MagnetisMM-3; 100% TCR). Unanchored matching-adjusted indirect comparisons (MAICs) were performed adjusting for prespecified 9 to 11 prognostic factors and/or effect modifiers across analyses, targeting each external trial. Objective 2: IPD from KarMMa-3 (intent-to-treat [ITT] population) was compared with AD from cilta-cel (phase 3 CARTITUDE-4; ITT population) using an anchored MAIC to target a population similar to CARTITUDE-4, assuming that standard of care (SoC) between the RCTs was comparable. OS from KarMMa-3 was adjusted for crossover using the 2-stage estimation. Seven prespecified effect modifiers were adjusted for in the analysis. **Results:** For the interclass unanchored MAICs, 368 pooled ide-cel TCE patients were compared with 165 teclistamab patients (effective sample size [ESS] 235), and 272 pooled ide-cel TCR patients were compared with 123 elranatamab patients (ESS 142). Ide-cel was associated with improved OS versus teclistamab (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.44–0.80) and elranatamab (HR, 0.58; 95% CI, 0.39–0.86). For the intraclass anchored MAIC, 254 ide-cel and 132 SoC patients from KarMMa-3 were compared with 208 cilta-cel and 211 SoC patients from CARTITUDE-4, resulting in an ESS of 73 (48 for ide-cel and 25 for SoC). Ide-cel and cilta-cel had comparable OS benefits (HR, 1.07; 95% CI, 0.41–2.81), with wide CIs. This analysis reflects the first anchored comparison of ide-cel and cilta-cel incorporating RCT evidence and crossover adjustment. **Conclusions:** This analysis demonstrates that ide-cel provides a clinically meaningful improvement in OS for patients with RRMM compared with teclistamab and elranatamab (BCMA-directed antibodies) and offers comparable survival outcomes to cilta-cel (BCMA-directed CAR T cell therapy).

PA-071

Real-World Safety and Efficacy of BCMA Bispecific Antibodies in Relapsed and Refractory Light Chain Amyloidosis

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Introduction: Light Chain (AL) Amyloidosis is a protein processing disorder resulting in misfolded kappa or lambda light chains that deposit into healthy tissue leading to organ dysfunction. Amyloid production is shut down by achieving hematologic complete response (hCR) with anti-plasma cell therapy. With rapid hCR both overall survival (OS) and major organ deterioration progression free survival (MOD-PFS) improve. The current standard of care for newly diagnosed AL Amyloidosis is Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone with a hCR rate of 59.5% with median time to hCR of 67.5 days. There are two FDA approved B-cell maturation antigen (BCMA) bispecific antibodies (BiAbs) for the treatment of relapsed refractory multiple myeloma (RRMM) after 4+ lines of therapy, Teclistimab and Elranatamab. Both with an overall response rate (ORR) of ~61% in highly pre-treated MM. Studies are accessing safety and efficacy in newly diagnosed MM (NDMM) as combinations with other myeloma drug classes and as a maintenance regimen after ASCT. However, there is limited safety and efficacy regarding BCMA bispecific antibodies in AL Amyloidosis. **Methods:** Within our institution we identified 11 patients with RR AL Amyloidosis who received either Teclistimab or Elranatamab. We reviewed the charts for patient demographics, disease characteristics, treatment history and details regarding adverse events and response to BCMA BiAbs. **Results:** Of the 11 patients, median age 73 (60–80), 55% were female, 6 with cardiac involvement (1 with Mayo Stage IIIB, 4 with Mayo Stage IIIA), 7 with renal involvement, median plasma cell bone marrow involvement at diagnosis was 20% (4–94%), two cases with dual diagnosis with myeloma. One patient was not included in the safety and efficacy analysis due to disease related death during step-up dosing. Based on the ten patients included there was a 100% ORR, with 70% achieving a hCR, 30% VGPR. Median time to first response was 0.6 months (0.4–0.9). 4 of the 6 patients with cardiac amyloid had evidence of organ recovery with steady reduction in NT-pro-BNP. The data has not matured to determine DOR or any survival analyses; however, one patient has a DOR in hCR for >20 months. All patients received PJP prophylaxis. Two reports of grade 3 neutropenia with upper respiratory infection, both supported with IVIG and G-CSF. Three patients discontinued therapy after achieving hCR and maintain excellent disease control off treatment. **Conclusions:** In RR AL Amyloidosis we report an impressive ORR, hCR rate and time to hCR with a favorable safety profile. In AL Amyloidosis, there is an unmet need to improve both the hCR rate and time to hCR, especially those with advanced organ damage. Clinical trials to assess safety and efficacy for the use of BCMA BiAbs in AL Amyloidosis, specifically newly diagnosed, are essential in improving clinical outcomes. Studies will also need to address the best duration of therapy, a continued vs fixed course.

PA-072

Optimizing CAR-T Therapy in Multiple Myeloma: Outpatient Reinfusion of Cesnicabtagene Autoleucel (ARI0002 h)

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Introduction: Cesnicabtagene autoleucel (ARI0002 h) is a fully academic, autologous, humanized, 4-1BB-based second-generation CAR T-cell therapy targeting BCMA for relapsed/refractory multiple myeloma (RRMM). After 3 months from the initial infusion, patients with sustained response and no severe complications may receive a second infusion of 3×10^6 CAR-T cells/kg. Lymphodepletion (LD) is required only if circulating CAR-T cells are undetectable. We evaluated efficacy, safety and logistical feasibility of an outpatient booster dose supported by a structured at-home (AH) care program. **Methods:** This retrospective study included 22 RRMM patients who had received initial ARI0002 h infusion and met clinical/logistical criteria for outpatient reinfusion, between September 2023 and December 2024. Eligibility included ECOG≤2, no active infection or severe organ comorbidities and availability of a trained 24-hour caregiver. AH protocol included pre-infusion education, caregiver training, home monitoring tools, and 24/7 specialized hematology support unit. Home LD was administered as needed. Vital signs and immune effector cell-associated encephalopathy score were monitored by nursing staff via telephone every 12 hours, with lab tests on days 1 and 3 post-infusion. CAR-T persistence was assessed via qPCR and clinical responses by IMWG criteria. **Results:** Median age was 63 years (range, 49–75). Most patients (95.4%) had MM, and one had AL amyloidosis. At baseline, 80% had ISS II/III, 63.1% high-risk cytogenetics and 23.8% extramedullary disease. All patients had received ≥2 prior therapies, 31.8% were triple-refractory and 18.2% penta-refractory. Before first CART infusion, bridging therapy was used in 77.2%, mainly cyclophosphamide-based regimens (41.1%). LD was administered in 40.9% before reinfusion. AH follow-up was 4 days (range, 3–4) for those not requiring LD, and 10 days for those needing LD. No patients developed cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome or macrophage activation syndrome after booster infusion. CAR-T re-expansion was observed in 72.7% of patients, more frequently in LD recipients (88.9% vs. 61.5%, p = 0.157). By day 100 post-booster, 77.8% achieved at least VGPR, and 54.6% reached CR. Five patients (22.7%) showed deepened responses post-booster: 2 patients in partial response achieved CR, and 3 patients improved to VGPR. Eighteen patients (81.1%) remain in response, while only 4 patients (18.2%) experienced disease progression after a median of 7 months (IQR 6–10). No patient required hospitalization within 45 days of booster; no treatment-related secondary malignancies have been reported. **Conclusions:** Outpatient second administration of ARI0002 h within a structured AH care model is safe, feasible, and effective in RRMM. This approach enables outpatient care while optimizing hospital resources. Second infusions enhanced depth of response and maintained CAR-T activity, providing a promising strategy to optimize long-term disease control in RRMM.

PA-073

Linvoseltamab (LINVO) in Frail Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): A Subgroup Analysis of the LINKER-MM1 Study

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Introduction: Bispecific antibodies (bsAbs) are a significant advancement for certain pts with MM. Frailty is known to be a key indicator of pt prognosis and impacts the efficacy and toxicities of MM therapy. Currently, data are limited on how frailty impacts outcomes for pts treated with bsAbs. In LINKER-MM1 (NCT03761108) LINVO, a human BCMA×CD3 bsAb approved in the EU, showed high response rates with a generally manageable safety profile in pts with RRMM. We report efficacy and safety from LINKER-MM1 based on frailty status. **Methods:** Pts with triple-class exposed RRMM received LINVO IV QW through Week 14–16 (step-up dosing in Week 1–2), then Q2W. Phase 2 pts who had ≥VGPR and received ≥24 weeks of LINVO 200 mg switched to Q4W dosing. Frailty was evaluated post hoc using three different indices: ECOG Proxy Frailty (ECOG-PF) score, International Myeloma Working Group Frailty Proxy (IMWG-FP), and Patient-Reported Frailty Phenotype (PRFP) measure (Facon et al. Leukemia 2020; Murugappan et al. J Geriatr Oncol 2024). Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and tx-emergent AEs (TEAEs) were assessed by frailty status per IMWG-FP and PRFP. **Results:** As of 23 July, 2024, 117 pts were enrolled into the 200 mg cohorts (median [m] follow-up: 21.3 months [mo]). There was variation among the different scores in classifying patients as frail. By IMWG-FP, 32 frail and 77 non-frail; and by PRFP, 24 frail and 89 non-frail. Differences in baseline characteristics were seen among frail and non-frail pts across all indices. For example, frail vs non-frail pts were older by IMWG-FP (m 75 vs 65 years), but not PRFP (68 vs 71 years); a greater proportion of frail vs non-frail pts had ECOG PS 1 (IMWG-FP: 91 vs 66%; PRFP: 88 vs 70%) and higher tumor burden (sBCMA ≥400 ng/mL; IMWG-FP: 66 vs 36%; PRFP: 54 vs 42%). Responses were generally high among frail and non-frail pts; ORRs in frail and non-frail pts were 66% and 73% by IMWG-FP and 63% and 73% by PRFP, respectively. mPFS (95% CI) for frail vs non-frail pts by IMWG-FP was not reached (NR; 3.3 mo–non-evaluable [NE]) vs NR (17.3 mo–NE); and by PRFP, 17.3 mo (11.8–NE) vs NR (19.7 mo–NE). mOS (95% CI) for frail vs non-frail pts by IMWG-FP was 27.8 mo (13.0–NE) vs NR (23.8 mo–NE); and by PRFP, 23.8 mo (13.0–NE) vs NR (31.4 mo–NE). Grade 3/4 TEAEs were consistent across frail and non-frail pts

(IMWG-FP: 75% and 73%, respectively; PRFP: 71% and 74%, respectively). Grade 3/4 CRS, ICANS, and infections in frail and non-frail pts ranged 0–4.2%, 1.1–8.3%, and 35–42%, respectively, across frailty measures. **Conclusions:** Overall, efficacy and safety of LINVO 200 mg was consistent in frail and non-frail pts, with high responses, durable OS/PFS, and a generally manageable safety profile regardless of frailty status index. These results suggest that frail, older adults can be treated with LINVO with a similar risk-benefit profile to non-frail patients. Efficacy and safety per ECOG-PF score will be presented at the meeting.

PA-074

Circulating Plasma Cells Evaluation Before and After CAR T-cell Therapy as a Dynamic Factor for Response Assessment

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Introduction: Recently, an increasing number of studies evaluated the presence of circulating tumor plasma cells (CTC) as a potential biomarker of aggressive disease. In our single-center observational study we evaluated the presence of CTC as a dynamic factor before and after CAR T-cells infusion in order to define a potential role in predicting response to the therapy. Additionally, we evaluate the persistence of CAR T-cells in the peripheral blood at the same fixed timepoints to underline a possible correlation. **Methods:** Between December 2024 and May 2025 nine patients underwent lymphocyte apheresis and received CAR T-cell therapy with Idecabtagene vicleucel (Ide-Cel). We plan to evaluate CTC using flow cytometry (FC) in the peripheral blood before infusion, at day +30, +60, +90, +180 and +360 after infusion; similarly we evaluate the persistence of CAR T-cells in the peripheral blood at day +6, +30, +60, +90, +180 and +360 after infusion. Regarding CTC, the analysis was made using two-tube single-platform (sensitivity 4×10^{-6}). The first tube allowed to select and quantify the absolute count of plasma cells (PC) and identify those with abnormal phenotype. Thereafter, PC were identified by CD38/CD138 gate (CD38+/CD138+) and pathologic PC by specific expression at diagnosis. Similarly, a second tube with intracellular antibody combination was performed to assess and confirm the CTC clonality. The threshold for CTC detection was defined as 20 PC events out of 5.000.000 events analyzed. Multiple Myeloma serological response was evaluated as for IMWG response criteria. **Results:** We analyzed eight out of nine patients; one patient was excluded from the analysis for early death before day +30 after infusion. In all eight patients analyzed (100%) CTC were detected by FC at baseline. Median follow-up was 77 days after infusion, the best ORR was 87.5% (37.5% RP, 50% VGPR), one patient (12.5%) showed progressive disease (PD) at day +90. In all 7 patients that reached a response, we could observe a significative reduction of CPC as compared to baseline (median 79.5%, range 32.65%–100%); in 2 patients (25%) in VGPR we could observe a disappearance of CPC (values <20 PC events out of 5.000.000 events analyzed). Regarding the patient that showed PD an increase in CPC on day +90 was seen after an initial reduction on day +30 and +60. Regarding the persistence of CAR T-cells on peripheral blood, we could observe significative values at day +30 after infusion (median 14.8%, range 0.75%–58.5%); the only patient with CAR T-cells <1% was the one that shows disease progression at day +90. **Conclusions:** In conclusion, our preliminary data on this group of patients shows favorable results regarding the evaluation of CTC using flow cytometry as a dynamic factor to determine and confirm response to the therapy; a longer follow-up and a larger group of patients and analysis are needed to confirm this trend and to correlate CTC and CAR T-cells persistence.

PA-075

Macrophage Activation Syndrome-Like in Multiple Myeloma Patients Treated with the Academic Bcma-Directed Car-T Ari0002h: Genomic Insights and Clinical Implications

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy targeting B-cell maturation antigen (BCMA) has revolutionized multiple myeloma treatment (MM). However, managing its immune-mediated adverse events, particularly macrophage activation syndrome-like (MAS-like), remains challenging due to underreporting. **Methods:** This multicentre, retrospective, analytical study

evaluated MM patients treated with the anti-BCMA academic product ARI0002 h. The definition of MAS-like was based on the University of California San Francisco (UCSF) consensus criteria: [1] ferritin rise ≥100 mg/L/h within 24 hours and [2] fibrinogen <150 mg/dL or LDH >2 times the upper limit of normal or histopathological diagnosis. The primary endpoints included analysis of baseline characteristics, identification of predictive factors, and assessment of the impact on survival based on the development of MAS-like. **Results:** Among the 80 patients analysed, 12 (15%) met the UCSF criteria for MAS-like events. These patients exhibited a higher International Staging System (ISS) score at enrolment (ISS III: 54.5% vs. 15.2%; p = 0.006), elevated serum monoclonal component levels (31.3 g/L vs. 6.8 g/L; p = 0.004), both of which demonstrated independent predictive value for MAS-like, and a higher prevalence of extramedullary disease (41.7% vs. 16.2%; p = 0.05). In the genetic analysis, variants affecting perforin-related pathways—including mutations in the PRF1 and UNC13D genes—were identified in 16.7% of patients presenting with MAS-like. This syndrome typically began approximately 9 days after infusion, with a rise in ferritin, followed by LDH (median 11.5 days) and hypofibrinogenemia (median 14 days). One-third of patients met all three criteria, and all exhibited hypertriglyceridemia, hypertransaminasemia, and ≥2 cytopenias. Histopathological examination was positive in 5 out of 8 evaluated patients. Patients who developed MAS-like had a poorer response (complete response: 25% vs. 68%; p = 0.008) and shorter median progression-free survival (PFS) and overall survival (OS) (7 months vs. 21.4 months and 18 months vs. not reached, respectively; p = 0.004). Furthermore, patients who met all three UCSF criteria, compared to those who met only two, showed a poorer response (VGPR or better: 25% vs. 100%; p = 0.04), as well as shorter PFS (5.5 months vs. 11.8 months; p = 0.01) and OS (7.8 months vs. 21.5 months; p = 0.01). **Conclusions:** MAS-like is associated with poorer responses and reduced PFS and OS, especially in patients meeting all three UCSF criteria: elevated ferritin, hypofibrinogenemia and increased LDH. High tumour burden, including elevated monoclonal component, high ISS and extramedullary disease, seems to contribute to MAS-like development.

PA-076

Long-term Follow-Up of a Phase 1 Study of Arlocabtagene Autoleucel (arlo-cel; BMS-986393) in Patients With Heavily Pretreated Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Arlo-cel is a chimeric antigen receptor (CAR) T-cell therapy targeting G protein-coupled receptor class C group 5 member D (GPRC5D), a validated target in RRMM. Previously reported results (23Aug2024 cutoff) from this multicohort, dose escalation phase 1 study (NCT04674813) in pts with RRMM demonstrated deep, durable responses across doses, including the 150 × 106 dose, which was identified as the recommended phase 2 dose (RP2D) currently being used in the ongoing phase 2 QUINTESSENTIAL study. Herein we report the longer-term follow up of this phase 1 study for the 75 × 106 and the 150 × 106 cohorts – the 2 dose-expansion cohorts with patients that have not yet reached end-of-study follow up. The 25 × 106, 300 × 106, and 450 × 106 dose cohorts have completed follow up and were previously reported. **Methods:** We enrolled pts with RRMM who received ≥3 prior lines of treatment, including a PI, an IMiD™, and anti-CD38 therapy. Following lymphodepletion, arlo-cel was administered as a single infusion of 25 × 106–450 × 106 CAR+ T-cells. The primary objective was to demonstrate safety; secondary objectives included to demonstrate clinical activity (assessed per IMWG Uniform Response Criteria) and describe pharmacokinetics. The data cutoff date was 4April2025. **Results:** Of 86 enrolled pts, 84 (98%) received arlo-cel, of whom 24 received the 75 × 106 dose and 26 who received the 150 × 106 dose. Baseline characteristics were similar across dose levels. Median age was 63 years, 51% were male, and 44% had high-risk cytogenetics; pts had a median of 5 prior regimens. In these 2 cohorts, respectively, treatment-related grade G3/4 AEs were 75% and 69%. Cytokine release syndrome (CRS) rates were 75% and 88%, and 1 patient in each cohort experienced G1 immune effector cell-associated neurotoxicity syndrome (ICANS). CRS events were all G1/2 and resolved; both ICANS events resolved. Rates of on-target/off-tumor (OTOT) nail, skin and oral TEAEs were similar at the 2 dose levels; all were G1/2.Median follow up for efficacy evaluable pts in the 75 × 106 and 150 × 106 cohorts was 19.9 mo (range, 3.8–27.5) and 24.0 mo (range, 4.6–25.8), respectively. Efficacy outcomes were similar, including overall response rate (92% vs 91%), complete response rate (58% vs 43%), and median (95% CI) duration of response (16.4 mo [11.1, NA] vs 13.6 mo [5.3, NA]). Additionally, for these two dose cohorts, similarities were observed in clearance of sBCMA and in MRD negative CR rates (46% vs 41%). **Conclusions:** Maturing data from the phase 1 study demonstrate a safety profile consistent with previous disclosures and deep and durable responses following a single infusion of arlo-cel. These data, demonstrating comparable efficacy between 75 × 106 and 150 × 106 doses of arlo-cel, suggest that both doses have a favorable benefit-risk profile in RRMM.

PA-077

Trial in Progress: QUINTESSENTIAL—A Phase 2 Study of Arlocabtagene Autoleucel (arlo-cel) in Triple- and Quad-Class Exposed Patients With Relapsed and Refractory Multiple Myeloma (RRMM)

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Introduction: Limited treatment options exist for patients (pts) with RRMM who are triple-class exposed (TCEx: immunomodulatory drugs [IMiD], anti-CD38 antibodies, and proteasome inhibitors [PI]) and quad-class exposed (QCEx: IMiD, anti-CD38 antibodies, PI, and B-cell maturation antigen [BCMA]-targeted therapy). To address this unmet need, new treatment options are needed for late-line populations, which will continue to grow with more QCEx pts due to the approval of BCMA-targeted therapies in earlier lines. G protein-coupled receptor class C group 5 member D (GPRC5D) is an orphan receptor expressed on plasma cells, with limited expression elsewhere, making it a promising therapeutic target for MM. Data from a phase 1 first-in-human study (NCT04674813) suggested that arlo-cel, a GPRC5D-directed autologous chimeric antigen receptor (CAR) T-cell therapy, is safe and efficacious in pts with TCEx RRMM, including pts who received prior BCMA-targeted therapy. At the recommended phase 2 dose (RP2D) of 150 × 106 CAR T-cells, overall response rate (ORR) was 91% (21/23), median progression-free survival (PFS) was 18.3 months, and median overall survival (OS) was not reached in those with ≥3 prior lines of therapy (pLOT) (Bal S et al. ASH 2024. Abstract 922). Here, we present the study design of QUINTESSENTIAL (NCT06297226), an open-label, multicenter, phase 2 study evaluating arlo-cel in pts with TCEx and QCEx RRMM. **Methods:** For analyses, enrollment is planned at 175 pts. Key inclusion criteria include age ≥18 years, confirmed diagnosis of MM as per International Myeloma Working Group (IMWG) criteria, ≥3 classes of MM treatment (including IMiD, PI, and anti-CD38), and ≥3 pLOT. Pts must also have documented disease progression (PD) during or after the most recent regimen as per IMWG, measurable disease, and an ECOG performance status of 0 or 1. Pts who previously received a GPRC5D-targeted therapy are excluded. After screening, pts will undergo leukapheresis followed by bridging therapy. Pts will then receive lymphodepleting chemotherapy followed by a single infusion of arlo-cel at the RP2D of 150 × 106 CAR T-cells (range: 120–180 × 106). The primary endpoint is ORR by IMWG response criteria per an independent review committee in pts who are QCEx and received ≥4 pLOT. Key secondary endpoints are ORR and complete response rate in all pts. Other secondary and exploratory endpoints include time to response, duration of response, PFS, OS, minimal residual disease-negative status, and safety. Pts will be followed for ≤5 years after the last pt receives arlo-cel, with a subsequent long-term follow-up study continuing for ≤15 years. **Results:** This is a trial in progress and will recruit at ~47 centers across the USA, Canada, and Japan. The first pt first visit was achieved on March 21, 2024. **Conclusions:** This phase 2 study will evaluate the efficacy and safety of arlo-cel in heavily pretreated pts with RRMM.

PA-078

Optimizing Post–Chimeric Antigen Receptor (CAR) T-Cell Monitoring: Evidence Across Idecabtagene Vicleucel (ide-cel) Pivotal Clinical Trials and Real-World Experience

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Introduction: CAR T-cell therapies, including B-cell maturation antigen–directed ide-cel, have shown remarkable efficacy in relapsed and refractory multiple myeloma (RRMM), though toxicities can occur. Here, we report incidence and timing of cytokine release syndrome (CRS) and neurotoxicity (NT) from clinical trials and real-world experience (RWE) of ide-cel to inform post-infusion safety monitoring requirements. **Methods:** Safety data were analyzed from patients (pts) with RRMM treated with ide-cel in 2 pivotal clinical trials and 1 RW registry. Pooled data from the phase 2 KarMMa (NCT03361748) and phase 3 KarMMa-3 (NCT03651128) trials comprised 349 pts who received ide-cel. RW data comprised 998 pts from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry who had ≥1 assessment after infusion of commercial ide-cel. Safety analyses included incidence, grade (G), onset and duration of CRS and NT after ide-cel infusion. **Results:** Pt characteristics were similar in the clinical trials and registry (median

age, 62 y and 66 y; males, 62% and 58%; median prior regimens, 4.0 and 6.0; high-risk cytogenetic abnormalities, 37% and 23% [though 47% not tested/unknown for CIBMTR]).Clinical trials: CRS occurred in 89% of pts (310/349; G3 at onset, 5.2%; no G4/5). Of those with CRS, 98% (304/310) had first onset ≤1 wk (median, 1 d) after infusion; median time to resolution from onset was 4 d. Of 1.9% (6/310) with CRS onset >1 wk (median, 13 d) after infusion, median time to resolution was 6.5 d. Investigator identified (ii) NT occurred in 40% of pts (139/349; G3 at onset, 1.1%; no G4/5). Of those with iiNT, 81% (112/139) had first onset ≤1 wk (median, 2 d) after infusion; median time to resolution from onset was 3 d. Of 19% (27/139) with iiNT onset >1 wk (median, 24 d) after infusion, median time to resolution was 7 d. Registry: CRS occurred in 84% of pts (834/998; G≥3 in those with G reported, 3.4%). Of pts with CRS and time to onset data, 96.6% (804/832) had first onset ≤1 wk (median, 2 d) after infusion; median time to resolution was 3 d. Of 3% (28/832) with CRS onset >1 wk (median, 48 d) after infusion, median time to resolution was 2 d. Immune effector cell associated neurotoxicity syndrome (ICANS) occurred in 31% of pts (313/998; G≥3 in those with G reported, 5.7%). Of those with ICANS and time to onset data, 82.7% (201/243) had first onset ≤1 wk (median, 2 d) after infusion; median time to resolution was 4 d. Of 17% (42/243) with ICANS onset >1 wk (median, 16.5 d) after infusion, median time to resolution was 4 d. **Conclusions:** Safety data from 1347 pts across ide-cel pivotal clinical trials and RWE demonstrate most cases of CRS and NT are low grade (G1/2) and occur within 1 wk of ide-cel infusion (median 1–2 d). For the pts with event onset >1 wk post-infusion, median time to resolution from onset was ≤7 d. These findings highlight the manageable safety profile of ide-cel, supporting a flexible monitoring period after 1-wk post–ide-cel infusion for patients with RRMM.

PA-079

Trial in Progress: QUINTESSENTIAL-2—A Phase 3 Study of Arlocabtagene Autoleucel Vs Standard of Care in Adult Patients With Relapsed and Refractory Multiple Myeloma (RRMM) Refractory to Lenalidomide

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Introduction: Despite advances in MM treatment, nearly all patients (pts) will relapse, highlighting the need for new drug classes to improve outcomes in RRMM. Further, MM refractory to lenalidomide, an immunomodulatory drug (IMiD) used in frontline and maintenance therapies, poses an additional challenge as the disease is less likely to respond to subsequent treatment. G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising therapeutic target for MM as the receptor is highly expressed on malignant plasma cells; it has little to no expression on non-plasma immune cells and limited expression elsewhere. Arlocabtagene autoleucel (arlo-cel) is a GPRC5D-directed autologous CAR T-cell therapy that has demonstrated safety and efficacy in pts with RRMM in a first-in-human phase 1 study. Following a single infusion of arlo-cel (150 × 106 CAR T-cells), overall response rate (ORR) was 96% (23/24) and 91% (21/23) in those with 1–3 and ≥3 prior lines of therapy (pLOT), respectively (Bal S, et al. ASH 2024. Abstracts 2069 and 922). We present the design of QUINTESSENTIAL-2 (NCT06615479), a randomized, open-label, multicenter, phase 3 confirmatory study comparing the efficacy and safety of arlo-cel versus standard of care (SOC) in adults with RRMM. **Methods:** Pts aged ≥18 y must have received 1–3 pLOT (may include a proteasome inhibitor, IMiD, and anti-CD38 antibody), be refractory to lenalidomide (progression on or within 60 days of completing therapy), and have confirmed MM diagnosis per International Myeloma Working Group criteria, measurable disease during screening, and ECOG performance status 0 or 1. Eligible pts will be randomized 1:1 to Arm-A or Arm-B. Pts randomized to Arm-A will receive a single infusion of arlo-cel, including leukapheresis within 3 days of randomization, bridging therapy of DPd (daratumumab, pomalidomide, dexamethasone) or Kd (carfilzomib, dexamethasone) per Investigator choice within 3 days of leukapheresis, and lymphodepleting chemotherapy prior to arlo-cel infusion. Pts randomized to Arm-B will receive SOC of DPd or Kd per Investigator choice, dosed per labeling. Primary endpoints are progression-free survival and minimal residual disease (MRD) negativity in complete response. Secondary endpoints include overall survival, ORR, MRD-negative status, complete response rate, time to response, duration of response, pharmacokinetics, patient-reported quality of life outcomes, and safety. Pts will be followed for ≤5 years after the last pt is randomized, with a subsequent long-term follow-up study (≤15 years post-infusion) for pts receiving arlo-cel. **Results:** This is a trial in progress and is expected to enroll 440 pts at over 100 sites globally. The first pt was enrolled in March 2025. **Conclusions:** This phase 3 study will compare the efficacy and safety of arlo-cel versus SOC in adult pts with RRMM who are refractory to lenalidomide.

PA-080

Arlocabtagene Autoleucel, a GPRC5D-Targeted CAR T-Cell Therapy for Patients With Relapsed/Refractory Multiple Myeloma: Updated Phase 1 Safety and Efficacy Results in Patients With 1–3 Prior Regimens

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Introduction: There is an urgent need for new therapeutic options with alternative targets or mechanisms of action for patients (pts) with relapsed and refractory multiple myeloma (RRMM). Arlocabtagene autoleucel (arlo-cel; CC-95266; BMS-986393) is a CAR T-cell therapy targeting GPRC5D that is being evaluated in the multicohort phase 1 trial (NCT04674813). We report updated safety and efficacy data for the cohort of pts with 1–3 prior lines of therapy. **Methods:** Pts had 1–3 prior anti-MM regimens, including a proteasome inhibitor and an immunomodulatory agent. Anti-CD38 therapy was not required; BCMA-directed therapies, including CAR T-cells, were allowed. After screening and leukapheresis (bridging therapy optional), pts received lymphodepleting chemotherapy followed by a single infusion of arlo-cel at the recommended phase 2 dose (RP2D, 150 × 106 CAR T-cells). The primary objective was safety; secondary objectives included clinical activity per IMWG Uniform Response Criteria and pharmacokinetics. **Results:** As of April 4, 2025, 31 pts had been enrolled and 100% received arlo-cel following successful manufacturing; 68% received optional bridging therapy. Median age was 62 y (range 31–78); 68% were male. Overall, 26% had high-risk cytogenetics (del[17p], t[4;14], and/or t[14;16]), 68% had 1q21 gain/amp, and 32% had extramedullary disease. Pts had a median of 2 prior regimens; 29% received 3 prior regimens. All 31 pts had a treatment-emergent (TE) adverse event (AE); 87% had grade (G) 3/4 TEAEs. No deaths were attributed to AEs. Treatment-related AEs occurred in 97% (48% G3/4). Cytokine release syndrome occurred in 84% (all G1/2 resolved); no pts had macrophage activation syndrome/hemophagocytic lymphohistiocytosis. Immune effector cell-associated neurotoxicity syndrome occurred in 10% (all G1/2 resolved). On-target/off-tumor nail, skin and oral TEAEs were reported in 39%, 42% and 42%, respectively (all G1/2). Other select neurotoxicity occurred in 6.5%: 1 pt with G2 gait disturbance and G2 ataxia and 1 pt with G1 gait disturbance (resolved) and G1 dysarthria. TE infections occurred in 55% (all G1/2).After a median 15.8 mo follow-up (range 3.8–21.5 mo) for 24 efficacy-evaluable pts, overall response rate was 96% and complete response (CR) rate was 63%; 15/24 responses were still ongoing. Median progression free survival (PFS) was not reached; 12-mo PFS rate was 74%. Of 16 pts with minimal residual disease (MRD) data, the MRD negative (10^{-5} depth) rate was 75%. **Conclusions:** A single administration of arlo-cel at the RP2D in pts with RRMM and 1–3 prior lines of therapy was well tolerated and led to a high response rate that deepened over time, with few early relapses after 15.8 mo median follow-up. The favorable benefit-risk profile for this dose and population was consistent with prior disclosures. Notably, frequency and grade of infections were improved over some BCMA-targeted therapies. These data support arlo-cel as a potential early-line treatment in RRMM.

PA-081

Consolidative Use of BCMA CAR-T Therapy in Relapsed/Refractory Myeloma — A Retrospective Evaluation

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Introduction: In initial trials of BCMA-CAR-T cells in heavily (≥4 lines) relapsed/refractory multiple myeloma (RRMM), most patients (pts) were refractory to their most recent regimen at time of apheresis. This approach (ie. waiting until pts are progressing before moving to CAR-T) can lead to difficulty controlling disease during manufacturing, undermining CAR-T clinical use. We hypothesized that using CAR-T cells as a planned consolidation strategy may lead to lower toxicity and improved long-term outcomes. **Methods:** We retrospectively reviewed all RRMM pts treated with commercial BCMA CAR-T cells (ide-cel and cilta-cel) at our institution from 6/2021 to 5/2024 (follow-up through 2/2025). Pts were considered to have CAR-T therapy as consolidation if their pre-apheresis therapy was identical to their bridging therapy, or if consolidation was clearly intended by chart review. Responses were determined by IMWG criteria. T-cell phenotyping at time of apheresis was performed by flow cytometry. **Results:** Among 158 treated patients (median follow-up 22.6 months), 83 received CAR-T as consolidation. Median prior lines in these pts was 6, with 76% triple-class refractory, 16% with prior BCMA therapy. Carfilzomib-based triplets were the most common pre-/post-apheresis therapy. At time of apheresis, 10% had PD, 39% SD, 35% PR, and 16% ≥VGPR. 53% received cilta-cel and 47% ide-cel. Post-CAR-T infusion, 83% achieved ≥VGPR (88% for cilta-cel and 77% ide-cel). Median PFS was not reached for cilta-

cel (18-month PFS: 83%) and was 16.5 months for ide-cel. OS at 18 months was 89% in cilta-cel and 82% in ide-cel pts. Grade ≥3 CRS was 3.6%, any grade ICANS 8.4%, and delayed neurotoxicity 6%. We then compared these pts to those who did not receive CAR-T as a consolidative approach (no-consolidation group, 75 pts). Clinical characteristics were comparable between groups. As expected, the no-consolidation group had poorer disease control at both apheresis and pre-lymphodepletion, and greater disease burden at apheresis. After CAR-T treatment, consolidation group pts had higher: ≥VGPR rates (83% vs 66%, p = 0.02), PFS (not reached vs 8 months. p < 0.01), and OS (cilta-cel subgroup only: OS 18 months 88% vs 70%, p = 0.02), and lower ICANS (8% vs 19%) and CRS≥G3 (3.6% vs 8%). No differences in delayed neurotoxicity were seen. In multivariate Cox regression, extramedullary disease, high-risk cytogenetics, ide-cel, and absence of consolidation intent were associated with inferior PFS. Pts in the no-consolidation group who responded to bridging still had inferior PFS compared to the consolidation group. **Conclusions:** Late-line RRMM pts moving to CAR-T cells as consolidation of their current line demonstrated higher CAR-T response rates, longer PFS and OS, and reduced severe toxicity, supporting the use of CAR-T as a consolidation strategy in RRMM. These findings should be confirmed prospectively. Comparative analyses of apheresis T-cell phenotypes will be presented at the meeting.

PA-082

Real-World Outcomes of Patients with Multiple Myeloma Who Received BCMA-Targeted Bispecific Antibodies in British-Columbia

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Introduction: Teclistamab and Elranatamab are bispecific antibodies targeting B-cell maturation antigen (BCMA), demonstrating high overall response rates (ORR) and durable responses in patients with relapsed and/or refractory multiple myeloma (RRMM), including those with triple-class exposure. **Methods:** We retrospectively analyzed clinical outcomes in 58 patients with RRMM who received compassionate access single-agent BCMA bispecific antibody in British-Columbia between May 2023 and April 2025, as per standard indication. Eligible patients had at least one month of follow-up post-therapy initiation. **Results:** Among the 58 patients, 56 (97%) received Teclistamab and 2 (3.4%) received Elranatamab. Two patients had prior BCMA-directed therapies (Cilta-Cel and/or Belantamab Mafodotin). Median number of prior lines was 4 (range:2–10). All patients were triple-class refractory and 43% were penta-refractory. 57 patients (98%) were refractory to their last line of treatment and 24% had failed to achieve at least a stable disease at any time. The median age was 67 years (range:41–84), 41% aged ≥70. High-risk cytogenetics. (IMWG 2009) were present in 26%, and 33% had extramedullary disease. With a median follow-up of 4.5 months (range:0.6–23.8), the ORR was 53%, including complete responses (CR) in 34%, very good partial responses (VGPR) in 9%, and partial responses (PR) in 10%. The estimated 12-month PFS for all patients was 37% (95%CI, 26–53%), with a median of 4.1 months (2.3-NR). The estimated 12-month OS was 53% (95%CI, 40–68%) with the median not reached (5.1-NR). The median duration of response (DOR) was not reached, with an estimated 12-month DOR rate of 69% (95% CI, 52–90%). Responders (≥PR) had significantly better outcomes than non-responders with median PFS not reached vs. 1.05 months (p < 0.001) and median OS not reached vs. 2.4 months(p < 0.0001). Patients who were exclusively triple-class refractory (n = 33) had higher ORR (67% vs. 36%, p = 0.02), longer mPFS (7.9 vs. 2.2 months, p = 0.04), and superior mOS (NR vs. 3.8 months, p = 0.01) compared to penta-refractory patients (n = 25). In responders, DOR was similar in both groups (estimated 12-month DOR of 72% vs. 63%, p = 0.66). Cytokine-release syndrome occurred in 68% (all ≤ grade 2). Immune effector cell associated neurotoxicity syndrome occurred in 9% (one grade 3). 48% had an infection. **Conclusions:** This data demonstrates the real-world effectiveness of BCMA-targeted bispecific therapy. In this heavily pretreated RRMM cohort, triple-class refractory patients derived significantly improved outcomes compared to those with penta-refractory disease, showing higher response rates and improved survival endpoints. However, when responses were achieved the disease control was comparable. These results highlight the importance of refractory status in predicting treatment outcome. Further, it supports the use of these therapies earlier in the treatment course to increase the proportion of responding patients and maximize clinical benefit.

PA-083

Talquetamab in Brazil: Initial Experience and Outcomes Within an Expanded Access Program

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Introduction: Talquetamab (TAL) was approved in Brazil in 2024. Prior to this approval, Brazilian Expanded Access Program (EAP) enabled access to TAL in 2023 for patients with prior exposure to the three main classes of therapies (IMiDs, proteasome inhibitors, and anti-CD38 antibodies). This report presents real-world outcomes from patients treated under this EAP. **Methods:** We conducted a retrospective study of Brazilian patients enrolled in the TAL EAP. The study assessed safety and efficacy for patients from 8 independent Brazilian oncology centers. Dose schedule (0.4 mg/kg weekly vs 0.8 mg/kg every other week) was determined by physician's choice. **Results:** Our cohort comprised 18 patients (12M, 6F), median age of 60.5 y (38–76), and median of 4 prior lines of therapy (2–8). All patients were triple-class exposed, with 94% of triple-class refractory. Notably, 33% (n = 6) had received belantamab mafodotin, and 17% (n = 3) had prior teclistamab exposure. Therefore, 50% of patients were BCMA-targeted therapies refractory as their last therapy. The TAL schedule was 0.8 mg/kg Q2W for all patients. The safety profile revealed CRS as the most frequent AE, occurring in 72% of patients (gr1:44%, gr2:23%, gr3:5%), leading to tocilizumab in 62% of cases and fully resolved. Neurotoxicity events were uncommon, with only 11% (n = 2) grade 1 ICANS, also resolved. Infections occurred in 49% of patients (gr1: 12%, gr2: 19%, gr3: 10%, gr4: 7% and 1 death due to COVID-19). We documented one case of late-onset ataxia and dysarthria after 9 months of TAL, requiring treatment discontinuation; remarkably, this patient remains in CR for nearly one year following therapy cessation. Characteristic GPRC5D-mediated toxicities were prevalent, including skin changes (78%; pruritus in 39%), dysgeusia (61%), weight loss in 67% of patients (gr1: 22%, gr2: 39%, and gr3: 6%), and nail abnormalities (78%). With a median follow-up of 12.4 months, talquetamab demonstrated efficacy in this refractory population. The overall response rate (ORR) was 67%, with 61% of patients achieving ≥VGPR. Median OS was 13 m, and median PFS differed significantly according to BCMA targeted-therapies refractoriness status: 9.2 months overall (5.6 m for BCMA-refractory vs 10.8 m for BCMA-naive patients). Median duration of response for responders (PR or better) was not reached. ORR among BCMA-naive was also significantly different compared to BCMA-refractory: 80% vs 50%, respectively. **Conclusions:** Our findings confirm the safety of talquetamab in heavily pretreated Brazilian patients. Notably, GPRC5D on-target/off-tumor effects were frequent, mostly low grade and manageable, consistent with published data. The patient with late-onset ataxia underscores the need for increased vigilance and further investigation into its pathogenesis and management. Responses were consistent with those reported in other studies, including MonumenTAL-1, further emphasizing the suboptimal outcomes for anti-BCMA-refractory patients and the significant unmet need for this population.

PA-084

Drivers of Primary Resistance to BCMA-targeted T Cell Redirected Therapies in High Tumor Burden

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Introduction: T cell engager (TCE) and CAR-T targeting BCMA have shown promising activity and efficacy in heavily pre-treated, relapsed/refractory multiple myeloma. Although deep responses can be achieved, most inevitably relapse. Patients with high tumor burden, or low effector-to-target ratio, are more resistant to these therapies. In addition to tumor debulking, novel strategies are needed to overcome primary resistance. We aimed to investigate in vitro and in vivo T cell intrinsic and extrinsic mechanisms of primary resistance in high tumor burden that mimics clinical conditions, using the immunocompetent Vk*MYC mouse model of MM. We tested three strategies to improve anti-BCMA mediated T cell activity: increasing TCE dose, increasing surface BCMA while reducing soluble BCMA with gamma-secretase inhibition (GSi), or boosting T cell function by combination with IMiDs. **Methods:** In vitro killing assays were performed using murine CAR-T cells (expressing human CRBN) and murine surrogate TCE, comparing low (high E:T) and high (low E:T) tumor burden. Cell killing and T cell activation parameters were quantified by flow cytometry. For in vivo studies, tumor bearing mice with low and high tumor burden were treated with TCE at two concentrations, −/+ GSi. We evaluated response, survival and T cell characteristics. **Results:** In vitro, we observed proportional decrease in TCE-mediated tumor killing as E:T ratio decreased (from 7:1 to 1:2), that was not associated with reduced T cell activation or imbalanced T cell:tumor proliferation. Adding GSi and increasing TCE was not sufficient to overcome high tumor burden. Reduced killing in vitro therefore results from tumor intrinsic mechanisms that require further exploration. Conversely, in vivo we found a proportional decrease in T cell activation as tumor burden increases, that was only transiently overcome by combination with IMiDs or by increased TCE + GSi, without improving OS. This suggests limited TCE engagement and highlights a more complex scenario in vivo that cannot be completely replicated in vitro. Regardless of tumor burden, CAR-T kill effectively at 72 h, consistent with clinically observed high response rates. Though, earlier timepoints (24–48 h) showed decreased function and expansion in high tumor burden. Surprisingly, at low E:T, POM inhibited CAR-T expansion and reduced antitumor effect, suggesting deleterious effects of hyperactivation. **Conclusions:** Lack of response to TCE in high tumor burden correlates with reduced T cell activation in vivo, but not in vitro, may be partly due to insufficient TCE needed for adequate T cell activation. Consistently, combination with IMiD or increasing TCE moderately improved responses, but only when combined with GSi. CAR-T activity is less dependent on tumor burden. Unexpectedly, IMiD did not improve CAR-T

function and at low E:T lead to decreased expansion and functional exhaustion, suggesting efforts to improve CAR-T efficacy should be directed to favor persistence, rather than activation.

PA-085

TRAIL-CD28 Armoring Enhances anti-BCMA CAR-T Cell Function and Overcomes Resistance in Multiple Myeloma

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Introduction: While BCMA-targeted CAR-T cell therapies have demonstrated encouraging response rates in multiple myeloma (MM), most patients eventually relapse. Our transcriptomic single cell analysis of patient samples treated with anti-BCMA CAR-T cells (Ide-cel) revealed that responders exhibited higher expression of genes encoding survival and activation-related proteins such BclxL, TRAIL, and CD28. Cognizant of the role of death receptor ligands in mediating activated T cells cytolytic activity, we here investigated whether TRAIL or TRAIL-CD28 chimeric construct armoring of anti-BCMA CAR-T cells enhanced their fitness and anti-tumoral activity. **Methods:** Single-cell RNA sequencing (CITE-seq, 10× Genomics) was used to analyze CAR-T cells from responders and non-responders to Ide-cel. CAR constructs with anti-BCMA scFv, 4-1BB and CD3z were cloned into the pLX307 lentiviral backbone, with variants co-expressing either TRAIL or a chimeric TRAIL-CD28 molecule. Functional assessment was performed using MM cell lines under standard and exhaustion-inducing conditions. Resistant model included in-house derived teclistamab-resistant MM cell lines and NFkB activated cells (Cas9 TRAF3 Knock-out) with acquired cross-resistance to variable anti-BCMA and anti-GPRC5D T cell engagers and CAR-T cells. Flow cytometry was performed using CytoFLEX and spectral Sony ID7000 systems to assess tumor clearance, T cells phenotype, and cells viability. **Results:** TRAIL armoring significantly enhanced BCMA CAR-T cell functionality across MM cell lines, under conditions of chronic antigenic stimulation and high disease burden (low E:T ratio). TRAIL-armored CAR-T cells effectively eradicated teclistamab-resistant and NFκB-activated MM cells, a capacity that was notably absent in unarmored CAR-T cells. However, under very high-density culture conditions, TRAIL expression induced mild fratricide (~10%) among CAR-T cells. To mitigate this effect, we engineered a TRAIL-CD28 chimera, fusing the extracellular and transmembrane TRAIL domains with CD28 intracellular signaling domain. This chimeric construct not only significantly mitigated fratricide, but also potently enhanced engineered T cells survival through CD28-mediated pro-survival signaling. TRAIL-CD28–armored CAR-T cells exhibited enhanced fitness profiles with preserved naïve- and central memory-like phenotypes and sustained BclxL expression—hallmarks of durable T cell memory function. Importantly, TRAIL-CD28 armoring of anti-BCMA CAR-T cells did not result in cytolysis of healthy donors PBMCs, consistent with their undetectable or low death receptors 4/5 expression. Ongoing animal studies with luciferase stably expressing MM cells are ongoing to evaluate the in vivo activity of these armored CAR-T cells. **Conclusions:** TRAIL-CD28 armoring of CAR T cells represents a promising strategy to enhance the efficacy of anti-BCMA CAR-T cells. These findings warrant further preclinical and clinical validation as a next-generation CAR-T for relapsed/refractory MM.

PA-086

Real-world Healthcare Resource Utilization (HCRU) Following Outpatient (OP) or Inpatient (IP) Administration of Ciltacabtagene Autoleucel (Cilta-cel)

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Introduction: OP administration of cilta-cel is feasible due to the predictable side effects of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). For relapsed multiple myeloma, OP administration has become more common and can reduce HCRU and expand treatment access. This study describes real-world HCRU following cilta-cel administration in IP and OP settings. **Methods:** We employed the Komodo Research Database (US claims database) to conduct descriptive analyses of HCRU among patients (pts) receiving cilta-cel after 4 or more prior lines of therapy stratified by IP or OP administration from 2/28/2022–6/30/2024. OP administration was defined as cilta-cel infusion occurring as an outpatient. Pts were followed to the earliest of 30 days post-infusion, loss of follow-up, or death. T-tests were used to perform unadjusted outcome comparisons between IP and OP administration cohorts. **Results:** Among 242 pts, 148 (61.2%) received cilta-cel in an IP setting and 94 (38.8%) in an OP setting. Baseline characteristics were comparable in IP and OP cohorts, with respect to median age (IP: 64 yrs, OP: 64 yrs), female sex (IP: 47.3%, OP: 42.6%), median Quan-Charlson Comorbidity Index (IP: 5, OP: 5), and median line of therapy of cilta-cel (IP: 6, OP: 5). For IP vs OP cilta-cel administration, all-grade CRS (IP: 58.8%, OP: 78.1%; $p < 0.05$) as well as fever (IP: 25.0%, OP: 78.1%; $p < 0.05$) were higher in the OP setting; however, grade ≥3 CRS was lower (IP: 1.4%, OP: 0.0%; $p = 0.16$). ICANS was comparable (IP: 13.5%, OP: 12.5%; $p = 0.84$), including grade ≥3 ICANS (IP: 2.0%, OP: 1.6%;

p = 0.81), as well as pancytopenia (IP: 64.2%, OP: 70.3%; p = 0.38). In the first 30 days post-infusion, use of tocilizumab (IP: 16.9%, OP: 11.7%) and dexamethasone (IP: 12.2%, OP: 13.8%) were similar. The 30-day mortality was similar between IP and OP cohorts (IP: 1.4% [n = 2], OP: 1.1% [n = 1]; p = 0.84). The mean number of hospitalization days over the 30 days post-infusion for IP vs OP cilta-cel administration was 14.9 [range: 1, 30] vs 7.7 [range: 1, 26] days (p < 0.001). At day 15 and day 20 post-infusion, the mean number of hospitalization days for IP vs OP administration was 13.0 vs 6.1 (p < 0.001) and 14.0 vs 6.5 (p < 0.001), respectively. Lastly, 31.9% (n = 30) of pts with OP administration did not require hospitalization within the first 30 days post-infusion. **Conclusions:** This real-world descriptive analysis demonstrates that OP administration of cilta-cel is feasible, with approximately one-third of pts not requiring hospitalization within the first 30 days post-infusion. The median number of hospitalization days was significantly lower in the OP setting at day 15, day 20, and day 30 post-infusion, showing significantly decreased HCRU. Overall, OP administration offers a pt-centric model, reduced HCRU with similar early safety outcomes, and could be widely adopted.

PA-087

Racial and Ethnic Differences in Outcomes of Multiple Myeloma Patients Treated with Teclistamab

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Introduction: Prior studies have identified racial and ethnic differences in clinical outcomes with CAR T-cell therapies in relapsed/refractory multiple myeloma (RRMM), but less work has focused on bispecific antibody therapy. We investigated racial and ethnic differences in safety and efficacy for patients with RRMM treated with standard of care teclistamab. **Methods:** Data for Non-Hispanic (NH) Black, NH White, and Hispanic patients treated with teclistamab from August 9, 2022, to January 1, 2024, were obtained from 16 institutions in the U.S. Multiple Myeloma Immunotherapy Consortium. Other racial and ethnic groups were not included due to small sample sizes which precluded meaningful statistical comparisons. Patient characteristics, safety, and therapy response were examined by race and ethnicity using chi-square, Fisher exact, and Kruskal-Wallis rank sum tests. Kaplan-Meier curves and log-rank tests were used to examine overall survival (OS) and progression-free survival (PFS) by race and ethnicity. **Results:** Of the 475 patients treated with teclistamab, NH Black and Hispanic patients comprised 20% (n = 95) and 8% (n = 39) of the cohort, respectively. Hispanic patients were younger than NH Black and White patients (median age 61 vs 65 vs 70 years; p < 0.001). NH Black patients had higher baseline absolute lymphocyte counts compared to Hispanic and NH White patients (1.0 vs 0.8 vs 0.6 k/uL; p < 0.001). No racial and ethnic differences in high-risk disease features and baseline cytopenias were observed. NH Black and Hispanic patients were more likely to have cytokine release syndrome (CRS) compared to NH White patients (64% vs 69% vs 49%; p = 0.005), with a higher rate of ≥ grade 3 CRS in Hispanic patients compared to NH White and NH Black patients (3% vs 1% vs 1%; p = 0.01). NH Black and Hispanic patients were more likely to have grade ≥ 3 neutropenia post-therapy (47% vs 65% vs 39%; p = 0.04) and severe infections requiring hospitalization or IV antibiotics (33% vs 36% vs 20%; p = 0.009) compared to NH White patients. NH Black patients were less likely to achieve a complete response at 3 months compared to NH White and Hispanic patients (7% vs 18% vs 15%; p = 0.04) but no racial and ethnic differences in best response were observed. Median follow-up was 7.6 months, and PFS and OS were similar across racial and ethnic groups. No other differences in baseline patient characteristics and outcomes were observed by race and ethnicity (p > 0.05). **Conclusions:** Among patients with RRMM treated with teclistamab, NH Black and Hispanic patients experienced a higher rate of safety events and NH Black patients had lower complete response rates at 3 months compared to NH White patients but no differences in best response or survival were observed. These findings highlight the need for additional investigation into contributors to racial and ethnic differences in toxicity and early treatment response.

PA-088

Analysis of Patients With Prior BCMA-Targeted Therapy and Those Achieving CR in REALiTAL: A Multi-Country Observational Study of Talquetamab in RRMM Outside of Clinical Trials

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Introduction: Talquetamab (Tal) is the first approved bispecific antibody targeting GPRC5D and CD3 for patients with triple-class-exposed RRMM. In MonumenTAL-1 (N = 375), Tal elicited deep, durable responses that persist with long-term follow-up (median 38.2 mo [QW], 30.3 mo [Q2W], and 30.3 mo [prior T-cell redirecting therapy (TCRT)]). Here, we report outcomes in patients receiving prior anti-BCMA TCRT and patients achieving complete response (CR) in REALiTAL. **Methods:** REALiTAL is a retrospective, international, non-interventional study that aims to describe the management and clinical outcomes of patients receiving Tal outside of clinical trials. Eligible patients provided informed consent and received the first dose of Tal on or before December 31, 2023. Data, including baseline characteristics, prior therapies, effectiveness, and safety information, were collected from medical records. Overall response rates (ORRs), time to first response (TTFR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were assessed. **Results:** Overall, 93 eligible patients (82 starting Q2W dosing) were included across 26 sites in 7 countries. Patients received a median of 5 prior lines of therapy. With a median follow-up of 15 (0.4–25.3) months, ORR was 66.7% (95% CI, 56.1–76.1), with 57% of patients achieving a very good partial response or better (≥VGPR). Median DOR, PFS, and OS were 12.3 mo (95% CI, 7.9–not estimable; NE), 8.2 mo (95% CI, 6.1–10.7), and 25.3 mo (95% CI, 17.3–NE), respectively. In those achieving CR (n = 17 [18.3%]), median DOR, PFS, and OS were NE (95% CI, 8.84–NE), NE (10.71–NE), and NE (NE–NE), respectively. Among patients with prior anti-BCMA TCRT (n = 33 [35.5%]), 12 received prior CAR-T and 23 received prior bispecific antibody (BsAb) therapy. For prior CAR-T and prior BsAb groups, ORRs were 66.7% (95% CI, 34.9–90.1) and 56.5% (95% CI, 34.5–76.8), with a median TTFR of 1.6 and 1 mo after a median duration of Tal treatment of 11.7 and 6.3 mo, respectively. For the prior CAR-T group, median DOR was NE (95% CI, 1.45–NE), PFS was 10.7 mo (95% CI, 2.23–NE), and OS was NE (95% CI, 4.47–NE). In the prior BsAb group, median DOR, PFS, and OS were 16.1 mo (95% CI, 5.95–NE), 7.4 mo (95% CI, 3.88–18.20), and NE (95% CI, 9.20–NE). Treatment-emergent adverse events occurred in 98.9% of patients and were mostly grade 1/2. Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome occurred in 55.9% (gr 3, 1.1%) and 2.2% (0 gr 3) of patients, respectively. Skin/nail and oral toxicities occurred in 67.7% (gr 3/4, 1.1%) and 66.7% (gr 3/4, 1.1%) of patients, respectively. Dysgeusia occurred in 56.9% of patients. **Conclusions:** REALiTAL showed similar efficacy and a manageable safety profile to that observed in MonumenTAL-1. Tal demonstrated durable responses, especially in patients achieving CR, including those who had prior anti-BCMA TCRT, highlighting Tal's potential as an effective real-world treatment for RRMM.

PA-089

Debulking Chemotherapy Abrogates the Risk of Non-Response in Multiple Myeloma Patients with High Tumor Burden Receiving Teclistamab

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Introduction: Teclistamab (tec) is highly effective for heavily pretreated multiple myeloma (MM) patients (pts), yet nearly 30–40% of pts fail to respond. Extramedullary disease, ISS stage, high marrow burden, and high soluble BCMA have been identified as markers of poor response in clinical trials. Here we explore whether debulking chemotherapy can successfully lower tumor burden and improve outcomes with tec. **Methods:** This was a retrospective study in relapsed refractory MM pts who received tec outside clinical trials from 11/2023–04/025. Debulking chemo, either D-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide)

or high-dose melphalan (HD-Mel), were administered to selected patients at the discretion of treating physician to reduce tumor burden prior to initiating tec. High myeloma disease burden (Hi-MM) was defined by presence of any of the following: extramedullary disease, ≥50% bone marrow plasmacytosis, secondary plasma cell leukemia, or need for transfusion support prior to initiating therapy, and was determined both pre-chemo (if applicable) and pre-tec. Primary outcome was overall response rate (ORR) to tec, with PFS and OS as secondary outcomes. **Results:** 35 pts were treated with tec; median age was 67 (range 48–90) years and 51% were male. Patients received a median of 5(range 3–11) prior lines of therapies, with 100% triple class refractory, 31.4% penta-drug refractory and 20% had prior anti-BCMA therapy exposure. 19 (54.3%) patients received debulking chemo: DPACE in 16, HD-Mel in 3. Hi-MM was present in 10/35 (28.6%) of patients prior to tec. ORR was significantly inferior in patients with Hi-MM prior to tec (2/10, 10%) compared to patients without Hi-MM (24/25, 96%, $p < 0.001$). Among pts who underwent chemo for Hi-MM, ORR to tec was 79% (15/19). All pts who responded to chemo and were no longer Hi-MM responded to tec (12/12, 100%), including all 4 pts who were primary refractory to a BCMA bispecific in the line prior to chemo. Patients with Hi-MM who did not receive chemo responded poorly to tec (2/6; 33.3%). Hi-MM was the only factor predicting response to tec (OR 0.01; 95% CI 0.01–0.09, $p < 0.001$) with no impact of any other pt or disease-related factor. At a median follow up of 6.9 months, pts with Hi-MM vs those without had inferior PFS (2.1 vs 10.6 months; $p < 0.001$) and OS (3.7 vs NR,$p < 0.001$). Pts with Hi-MM who underwent chemo prior to tec had similar PFS and OS to pts without Hi-MM. Hi-MM prior to tec was the only significant factor impacting survival outcomes (PFS:HR 16.83 (4.41, 64.18), $p < 0.001$); OS: HR 10.69 (2.52, 45.27), $p = 0.001$). **Conclusions:** High tumor burden was the major determining factor for response rates and survival outcomes after tec therapy, with response in 96% of pts without high burden. Pts with high burden who received debulking chemo had similar ORR, PFS, and OS to pts without high burden, with chemo abrogating the risk of non-response in pts with historically very poor responses.

PA-090

Deficiencies in Cellular Immunity Associated with Increased Risk of Infection with Bispecific Antibody Therapy in Multiple Myeloma

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Introduction: Multiple myeloma (MM), a disease of clonal plasma cells, leads to immune dysfunction, primarily thought to be humoral in nature. Bispecific antibodies (BiAb) have shown efficacy in engaging T cells to kill tumor cells, inducing deep and durable responses. Despite their efficacy, there is a significant infectious risk, with severe (grade 3 or higher) infections occurring in 7% to 45% of MM patients treated with BiAbs. While significant effort has been made to understand mechanisms of BiAb resistance, more information is needed to better identify patients at high risk of severe infection with BiAbs. We previously described a specific immunophenotype in MM patients with suboptimal responses to COVID vaccination. Based on our preliminary data, we hypothesize that a similar immunophenotype can help identify MM patients at greater risk for infection while on BiAb therapy. **Methods:** Peripheral blood mononuclear cells from 13 patients on BiAbs with variable infectious rates were characterized using a spectral flow cytometry antibody (Ab) panel to stain for myeloid and lymphoid cell subsets. **Results:** 11 of 13 (84.6%) patients achieved a stringent complete response (sCR) while on therapy. 12 of 13 (92.3%) patients experienced an infection of any grade, 5 of 13 (38%) experienced grade 3/4 infections and 1/13 (7.7%) experienced a grade 5 infection. When stratified into more infections (≥3 infections) or less infections (<3 infections), differences in immune cell subsets were identified between the groups. In the more infections group a decrease in B cells, subsets of Tfh cells, and mature cytolytic NK cells was seen. Similar percentages of dendritic cells and monocytes were seen between the groups. To further investigate the monocytes, we assessed expression of CD38, a surface glycoprotein on many leukocytes, as its expression indicates activation. We also assessed CD16 expression, an Fc receptor, as it is involved in Ab-dependent cell mediated cytotoxicity. We found in the less infections group that most monocytes were CD38+, but in the more infections group there was an additional distinct population of CD38- cells. Similarly, there was an additional population of CD16- cells in the more infections group that was not present in the less infections group. **Conclusions:** Treatment with BiAbs leads to deficiencies in humoral and cellular immunity. We demonstrate a distinct immunophenotype that is seen in patients who experience more infections, specifically impaired monocytes, B, Tfh, and NK cells. Independent validation of this immunophenotype in larger cohorts is ongoing to determine if it can be used to identify patients at higher infectious risk. Prompt identification of such patients may allow for early intervention, including IVIg, prophylactic antibiotics, or judicious changes in dosing frequency to allow for immune reconstitution. This will hopefully serve to mitigate the infectious toxicity of very effective BiAb treatments and rationally guide therapy selection in individual patients.

PA-091

Outcomes of Radiation Therapy Integrated with T-cell Engaging Bispecific Antibodies in Relapsed/Refractory Multiple Myeloma

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Introduction: Treatment options are limited for relapsed/refractory multiple myeloma (RRMM) patients (pts) who progress on T-cell engaging bispecific antibodies (bsAb) such as teclistamab (tec) and talquetamab (tal). Radiation therapy (RT) is commonly used for focally progressive or resistant RRMM, but its use with bsAb remains understudied. **Methods:** Retrospective single-center study of RRMM pts who received at least one full dose of tec or tal and received RT during their bsAb course. RT was categorized as adjuvant (ART: delivered within the first two bsAb cycles to target pre-existing or early lesions) or rescue (RRT: used for sites of progression after an initial response). BsAb treatment was continued in those receiving rescue radiation. **Results:** Our cohort of 41 pts had median age 67.9 years; 34 received tec + RT (22 ART, 16 RRT, 4 both), and 12 received tal + RT (7 ART, 7 RRT, 2 both); 17 received both tec and tal, only 5 received RT during both bsAb courses. Tal pts had more advanced disease (more prior lines (median 5.4 vs 4) and 66.7% prior exposure to anti-BCMA bsAb). Compared to those receiving RRT, pts in the ART group more frequently exhibited adverse disease features at baseline, including elevated ferritin, double-hit cytogenetics, and extramedullary disease (EMD). Median time to RT was 0.1 months (m) in the ART group and 6.9 m in the RRT group. Best overall response rate (encompassing effects of bsAb and RT) was 48.3% (14/29) in the ART and 73.9 (17/23) in the RRT group; ≥VGPR rate was 34.5% (10/29) in the ART group and 47.8% (11/23) in the RRT group. ART + bsAb had median progression-free survival (PFS) of 1.4 m, though 12-m PFS probability was 0.23 (95% CI 0.14–0.54). In the ART group, CRS G1/G2/G3 was seen in 5/3/1 pts and ICANS G1/G2/G3 in 2/3/1 pts. For RRT pts, estimated median PFS after rescue RT was 2.2 m (95% CI 0.92–3.75), and time to next treatment or death (TNTD) was 3.2 m (95% CI 1.5–5.8). In the RRT group, half (15/30) of the courses targeted all known sites of active disease at progression. Pts with rescue RT to all active sites had longer PFS (2.8 vs. 0.9 months, p = 0.0015) and TNTD (5.4 vs 1.2 months, p = 0.003) after RT compared to pts not treated at all active sites; for these pts, median post-RT PFS was 50% of the pre-RT PFS (range 10% to 250%), and probability of being alive and not requiring subsequent systemic therapy at six months was 0.38 (95% CI 0.16–0.87). RRT pts achieving long-term post-RT PFS (>12 months) were all on tec. No pts developed CRS or ICANS during RT in RRT group. **Conclusions:** RT can be safely used in patients treated with bsAb. ART was associated with short PFS and is likely a marker of aggressive disease, though a subset attained long-term PFS. RRT, particularly when all active disease sites were targeted, yielded additional PFS and time until next therapy or death that is clinically significant in this heavily pre-treated RRMM population.

PA-092

Clinicopathological Analysis of Parkinsonism-like Neurotoxicity after BCMA-Directed CAR-T Therapy: An Autopsy Case With Idecabtagene-Vicleucel

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Introduction: Chimeric antigen receptor T (CAR-T) cell therapy has emerged as a standard treatment for relapsed/refractory multiple myeloma. Although acute complications like cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are well recognized, delayed neurological effects such as movement and neurocognitive toxicities (MNTs) have gained attention. These may include Parkinsonism-like symptoms, particularly following BCMA-directed CAR-T therapies such as cilta-cel (Gust J. Blood. 2023). However, the pathophysiology of MNTs remains poorly understood, especially in idecabtagene vicleucel (ide-cel) therapy, where reported incidence is lower (Couturier A et al. HemaSphere. 2024). **Methods:** We report the clinical course and autopsy findings of a 58-year-old Japanese male with triple-class refractory IgG-κ multiple myeloma harboring t(4;14) and 1q gain. Following lymphodepletion, he received ide-cel therapy. We evaluated the patient's neurological symptoms, imaging, CSF analysis including CAR-T cell proportion and soluble BCMA (sBCMA) levels in serum and cerebrospinal fluid (CSF), and conducted postmortem brain histopathology and immunostaining. **Results:** The patient initially responded to ide-cel, achieving a metabolic complete response as assessed by FDG-PET/CT. On Day 25, Parkinsonism-like symptoms including bradykinesia, masked facies, and shuffling gait emerged without prior ICANS. CSF analysis on Day 40 revealed 61.5% CAR-T cells among just two lymphocytes/μL. A dopamine transporter scan showed mild asymmetrical reduction in uptake. Based on these findings, MNTs were diagnosed. Treatment with oral and intrathecal dexamethasone led to symptom improvement and decrease in CSF CAR-T proportion. Despite neurological recovery, the patient experienced systemic relapse of myeloma and fatal sepsis.

Autopsy showed widespread extramedullary tumor infiltration but no CNS lesions. The nerve cells in caudate nucleus were BCMA-positive on immunostaining, yet no neuronal loss or structural damage was evident. The sBCMA level in CSF increased from undetectable to 0.1025 ng/mL, while the post-mortem serum level was 5.31 ng/mL. **Conclusions:** MNTs following ide-cel may share mechanisms with cilta-cel (Van Oekelen O et al. Nature Medicine. 2021), potentially involving BCMA expression in basal ganglia. However, the therapeutic effect of steroidal drugs and pathological findings without neuronal damage were observed in our case, which suggests NMTs might be based on an immune-mediated rather than direct cytotoxic process. CSF CAR-T cell accumulation may reflect blood–brain barrier disruption. Early anti-inflammatory intervention could mitigate neurotoxicity. CNS involvement by myeloma cells should also be considered in MNTs, given the detection of sBCMA in the CSF.

PA-093

Outcomes of CAR-T Cell Therapy in Patients with AL Amyloidosis

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Introduction: The safety and efficacy of chimeric antigen receptor T-cell (CAR-T) therapy in patients with AL amyloidosis remain poorly characterized. Given the challenges posed by amyloid-related organ dysfunction, we evaluated the clinical outcomes of CAR-T therapy in this high-risk population. **Methods:** We retrospectively analyzed patients with biopsy-confirmed AL amyloidosis treated with CAR-T from March 2021 to April 2025. Clinical characteristics, treatment response, and safety outcomes were assessed. **Results:** Nine patients with systemic AL amyloidosis were included. Organ involvement included cardiac (8), renal (5), peripheral nerve (2), gastrointestinal (2), autonomic (1), and musculoskeletal (1). Five had single-organ, 4 had 2-organ, and 1 had 3-organ involvement. Five patients met CRAB criteria for concurrent multiple myeloma. Median age at infusion was 69 years (range 33–78). Six patients received ciltacabtagene autoleucel and 3 idecabtagene vicleucel. Patients had a median of 5 prior therapies (range 3–11), and 7 were triple-class refractory; none had prior T-cell redirecting therapies. At diagnosis, the Mayo 2004 with European modification stages were stage II (5), IIIa (3), and IIIb (1). The median duration of severe neutropenia (ANC<500/µl) within 30 days was 4 (range 0–9). Early immune effector cell-associated hematotoxicity (ICAHT) occurred in 7 patients (5 grade 1, 1 grade 2), and late ICAHT in 4 (2 grade 1, 1 grade 2, 1 grade 3). Rates were comparable to a reference cohort of 180 MM patients treated with CAR-T. Supportive measures included filgrastim (2) and romiplostim (1). Infections occurred in 3 patients, and HLH in 1 (with high marrow plasma cell burden). CRS occurred in 8 of 9 patients, with 2 grade 3 events, and was more frequent than in MM patients ($p < 0.01$). All cases resolved with supportive management. One patient with cardiac amyloidosis developed supraventricular tachycardia that was medically managed. No cases of ICANS, clinically significant worsening of AL-related organ function, delayed neurotoxicity, colitis, or secondary malignancies were observed. Eight patients were evaluable for hematologic response; all achieved complete response with a median time to best response of 31 days (range 26–138). Seven achieved minimal residual disease negativity at a median of 29 days (range 26–103). At a median follow-up of 19 months (range 4–20), none of the 3 ide-cel patients relapsed. Of three patients eligible for cardiac response assessment, one achieved partial, one very good partial, and one complete response, with a median time to best cardiac response of 9.2 months. None met criteria for renal response assessment. At a median follow-up of 18 months, no relapses or deaths were reported. **Conclusions:** CAR-T therapy in AL amyloidosis patients showed high response rates with manageable toxicities, despite prevalent cardiac involvement. These findings support the feasibility and therapeutic potential of CAR-T therapy in this understudied population.

PA-094

Early Mortality Associated with Real-World Bispecific Antibody Therapy for Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab (Tec) is the first approved BCMAxCD3 bispecific antibody (bsAb) for patients (pts) with relapsed/refractory multiple myeloma (RRMM) based on the MajesTEC-1 study. After a median follow-up of 14.1 months, 68 deaths (41.2%) were reported including 41 (24.8%) from progressive disease (PD) and 20 from infections (13 from COVID-19). Herein, we present an analysis of early mortality defined as death within 12 months of starting a bsAb for RRMM. **Methods:** This is an international multicenter retrospective study of pts with RRMM treated with bsAb on-label at 9 academic centers from 5 countries (US, UK, Greece, Spain, and Canada). Pts with RRMM treated with tec at the respective institutions between 5/24/22 to 1/4/24 were included in this analysis. Median follow-up was 14 months with data collected until 11/29/24. High-risk cytogenetic abnormality (HRCA) was defined as 1q+, t(4;14), t(14;16), t(14;20), and/or del(17p). Response was assessed using the IMWG criteria for response. Patient characteristics were summarized by frequency (percentage) or median (interquartile range [IQR] or range). Cox regressions were used to evaluate covariate effects on early mortality. **Results:** The 223 pts included in this analysis had the following characteristics: median age of 67 (range 33–91) with 24% ≥75 years; 45% female; 49% (86/176) with HRCAs; 29.4% (37/126) with extramedullary disease (EMD). Pts received a median of 6 (IQR, 4–8) prior lines of therapy with 52% (107/206) being penta-drug refractory and 94 (42%) pts with prior BCMA-directed therapy (DT; 29.8% antibody-drug conjugate [ADC] alone; 45.7% CART alone; 6.3% bsAb alone; 17.0% ADC and CART). ORR for 206 response-evaluable pts was 66% (25.2% ≥CR, 33.5% VGPR, 7.3% PR). Among the 223 pts, 80 (36%) died within 12 months of tec initiation including 61 who died ≤6 months. In this subgroup, median age was 66 (36–91), 58% were penta-refractory, 49% had prior BCMA-DT, 46% (19/41) had EMD, and 55% (35/63) had HRCAs. ORR for 70 response-evaluable pts was 31% (3 ≥CR and 10 VGPR); 31 pts had PD. Cause of death included 52 (65%) due to PD, 12 (15%) from infection, 2 from PD and infection, 10 (12.5%) due to other causes (notably, 3 from failure to thrive, 1 treatment-related, 1 cardiopulmonary failure, 1 intracranial hemorrhage, 1 liver failure, 1 sudden death), and 4 unknown. Regardless of the cause of death, 80% (63/79) of pts with early mortality had evidence of PD at the time of death. On multivariate analysis, early mortality was associated with lack of response to tec (HR 2.15, 95%CI, 1.11–4.18; P = 0.02) and presence of HRCA (HR 1.73, 95%CI, 1.03–2.88, P = 0.04). **Conclusions:** In this international real-world analysis of early mortality associated with bsAb therapy, the most common cause of death was progressive disease followed by infection. Risk factors for early mortality include lack of response and the presence of HRCAs. Additional data including pts treated with other bsAbs (talquetamab, elranatamab) will be presented at the meeting.

PA-095

Efficacy and Safety of CAR-T Therapy in CNS-MM

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Introduction: Multiple myeloma involving the central nervous system (CNS-MM) is rare, with an incidence of approximately 1%, and is associated with poor prognosis, exhibiting a median overall survival (OS) of less than 6 months. While CAR-T therapy has demonstrated remarkable efficacy in relapsed/refractory multiple myeloma (RRMM), its effectiveness and safety in CNS-MM remain an unmet clinical need. **Methods:** This retrospective study included 19 CNS-MM patients diagnosed between January 2016 and December 2024 across six centers. Diagnosis was based on the International Myeloma Working Group (IMWG) criteria and the 2018 definition by the Brazilian Dias group, incorporating pathological, cerebrospinal fluid (CSF) cytological, and imaging evidence. Treatment response was assessed using IMWG criteria, and overall survival (OS) and progression-free survival (PFS) were calculated via the Kaplan-Meier method. **Results:** A total of 19 CNS-MM patients were included in the study, comprising 5 with primary CNS-MM and 14 with secondary CNS-MM. The median interval from initial MM diagnosis to CNS involvement was 22.70 months. All patients received systemic therapy, with the entire cohort demonstrating a median OS of 4.33 months and median PFS of 3.33 months. Among these, 5 patients received additional CAR-T immunotherapy. The non-CAR-T group (n = 14) showed inferior outcomes (median OS: 2.53 months; median PFS: 2.37 months), whereas the CAR-T group, despite limited sample size, exhibited improved survival (median OS: 5.30 months; median PFS: 5.30 months). No severe toxicities (including CRS or ICANS) were observed in any patient. **Conclusions:** CAR-T therapy demonstrates modest efficacy and acceptable safety in CNS-MM, though further optimization of treatment strategies is warranted to enhance clinical outcomes.

PA-096

Abnormal Serum Immunofixation Patterns (ASIP) Are a Common Event Following BCMA CAR-T in Relapsed Refractory Multiple Myeloma and Are Often Preceded by Immunological Events

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Introduction: Abnormal serum immunofixation pattern (ASIP), defined as appearance of a monoclonal band with a different isotype than that of the multiple myeloma (MM), is seen in 10–50% of MM patients (pts) who undergo treatment and is associated with better outcomes. We describe the presence of ASIP in MM after BCMA CAR-T. **Methods:** Pts with relapsed MM who received BCMA CAR-T at two institutions were included. Clinical characteristics, serum protein electrophoresis/immunofixation (SPEP/sIFE), quantitative immunoglobulins, and immune events (vaccination/infection) were collected. Pts with ASIP after progression of disease (POD) were excluded. **Results:** 58 pts were included with 15 receiving idecabtagene autoleucel (26%) and 43 receiving ciltacabtagene autoleucel (74%). ASIP was seen in 18 pts (31%) during CAR-T follow-up while there was no POD, with 23 total ASIP events. The median time to ASIP was 10 months (range 7–18), and median duration was 1.64 months (0.9–4.5). 12 of 23 (52%) ASIP events were preceded within 60 days by an immunological event (9 infections (64%), 2 vaccinations (14%), 1 infection and vaccination (7%)). At 21 out of 23 ASIP events (91%), pts were hypogammaglobulinemic. There was a significantly higher median number of infections in ASIP pts versus non-ASIP pts (2 events (1, 3) versus 4 events (2, 6) p = 0.021), but no significant difference in proportion of pts with infections/vaccinations, or median number of vaccinations. In ASIP versus non-ASIP pts, IgA and IgM were lower than the lower limit of normal (LLN) a significantly higher proportion of the time (IgA low 94% versus 100% (p = 0.001), IgM low 69% versus 100% (p = 0.008)), and IgG was higher in ASIP pts. ASIP pts had generally lower rates of hypogammaglobulinemia. 6 pts (33%) had mass spectrometry (MS) performed at the time of ASIP, and all resulted with multiple small clones suggestive of oligoclonal pattern. All 18 ASIP pts (100%) achieved ≥ VGPR, while 29 of 40 (74%) non-ASIP pts achieved ≥ VGPR (p = 0.022), indicating deep response. The median PFS for ASIP pts was not reached (NR, 95% CI 32.2 - NR) and non-ASIP pts was 18.4 months (95% CI 13.0 - NR months) (p = 0.041). Landmark analyses were conducted at 7 months after CAR-T (25th percentile of time to ASIP) and 5 months, with no difference in PFS between groups. **Conclusions:** ASIP is a common phenomenon following BCMA CAR-T and was associated with hypogammaglobulinemia at the time of the ASIP episode, but overall ASIP pts had lower rates of hypogammaglobulinemia throughout their post-CAR-T course compared to non-ASIP pts. Infection or vaccination often preceded ASIP, suggesting ASIP may occur in pts with a relatively more preserved non-neoplastic plasma cell compartment in response to immunologic stimuli; MS results showing multiple clones provides further support. ASIP is significantly associated with deeper response, however landmark analysis accounting for selection bias shows that ASIP does not portend better PFS.

PA-097

Prophylactic Dexamethasone (dex) with Outpatient Step-Up Dosing (SUD) of Bispecific Antibodies (BsAb) in Multiple Myeloma (MM) v. Standard of Care (SOC) Inpatient Observation

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Introduction: Teclistamab (tec) and talquetamab (tal) are BsAb therapies approved for MM. Due to the risk of CRS and ICANS, the prescribing information recommends hospitalization for 48 hours after each SUD. This can be challenging for patients (pts), increasing healthcare resource utilization (HCRU) and cost. Herein, we compare the cost and feasibility of outpt SUD using prophylactic dex and remote monitoring via Hospital at Home (HaH) at Levine Cancer Institute (LCI) to standard 48 h inpt observation following each SUD at Wake Forest University. The aim was to reduce HCRU while maintaining safety. **Methods:** Pts at LCI received prophylactic dex 8 mg on the day after each SUD. On days between SUDs, pts were examined at home by Mobile Integrated Health worker who coordinated a virtual visit with a HaH internist and calculated their ICE score. Pts were provided a thermometer, blood pressure cuff, pulse oximeter, wearable monitor for heart and respiratory rate, and an electronic tablet to input vital signs every 4 hours. Pts had virtual access to HaH nursing staff 24/7. Grade 1 CRS was managed outpt with acetaminophen and additional doses of dex as needed, while persistent fever or higher grade CRS required evaluation at the hospital. Data related to safety outcomes, toxicity management, and HCRU were collected retrospectively for the 30-day period after starting a BsAb. Admission within 30 days was not counted towards HCRU if related to disease progression. **Results:** Outpatient SUD occurred for 32 LCI pts (16 tec, 16 tal) compared to 24 SOC pts (13 tec, 11 tal). The incidence of CRS was 59% for the LCI group (max grade [G] 1 41%, G2 19%) compared to 54% of the SOC group (G1 33%, G2 12.5%, G3 4%, G4 4%). Recurrent CRS with subsequent SUDs occurred in 32% of outpts and 46% of SOC pts. All observed ICANS was grade 1 and occurred in 6% of LCI pts v. 17% SOC. The mean dex dose per patient was 28.9 mg at LCI v. 3.3 mg for SOC. Tocilizumab use was significantly less for the LCI group with prophylactic dex (12.5% v. 42%; p = 0.03). The estimated total toci-related per patient cost was $868 in the LCI arm versus $2909 in the

SOC arm. Hospitalization within the first 30 days occurred in 43.8% of the LCI pts, with a mean of 1.1 inpt days per patient v. 7.8 days for SOC. The mean estimated cost per patient was $6,444 in the LCI cohort vs. $29,911 in the SOC cohort. Overall, this represents a relative cost savings of 0.78, indicating a 78% reduction in cost for outpatient SUD versus inpatient observation. **Conclusions:** Oupt BsAb step-up dosing can be given safely. It resulted in a reduction of 6.7 hospital days per patient and was associated with a 78% reduction in estimated cost per patient compared to inpatient observation. While prophylactic dex did not reduce CRS incidence, it resulted in no grade 3 or 4 CRS events and less tocilizumab administration which contributed substantially to overall cost savings.

PA-098

Excellent Outcomes with BCMA Directed T cell Redirecting Therapies in t(11,14) Relapsed/ Refractory Multiple Myeloma

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Introduction: The t(11,14) translocation is one of the most common primary cytogenetic abnormalities in multiple myeloma, that defines a biologically unique subset of multiple myeloma, characterized by overexpression of cyclin D1 and BCL-2, decreased expression of the adhesion molecule CD56, and increased frequency of light chain disease. While t(11,14) is considered a standard risk cytogenetic abnormality, the data on outcomes of t(11,14) patients is controversial, with evidence of suboptimal response to standard frontline inductions, and improved response with autologous transplant, particularly in Black patients. Outcomes are affected by coexisting cytogenetic abnormalities. Notably, plasma cell leukemia and AL amyloidosis are enriched with t(11,14). While T cells redirecting therapies (TCRT), including bispecific T cell engagers (BITEs) and CAR-T have revolutionized the outlook for patients with RRMM, little is known about specific effects of these therapies on t (11,14) myeloma. **Methods:** We retrospectively reviewed patients with RRMM treated with BCMA directed TCRT at our institution between 5/2021 and 2/2025 and analyzed outcomes of patients with or without t(11,14). Chi square and Fisher exact tests were used to compare outcomes between groups. MRD was evaluated by Clonoseq (NGS, 10^{-6}). **Results:** 18 pts with t(11,14) and 70 pts without t (11,14) were treated with TCRT (of them ide-cel, 38.9%/27.1%; cilta-cel, 27.8%/17.1%, teclistamab, 27.8%/42.9%, elranatamab 5.6%/12.9% respectively in patients with/without t(11,14)). Median age (68.7 vs 69.3) and prior hx of transplant (77.8% vs 70%) were similar in both groups. High risk cytogenetic abnormalities determined by mSMART4.0 were present in 33.3% patients with t(11,14) vs 58.6% without. With median follow-up of 14.9/13.2 m, numerically more patients achieved at least VGPR in the t(11,14) group (88.9% vs 75.7%, p 0.33). Among MRD evaluable patients, more patients in the t(11,14) group achieved MRD negativity at 10^{-6} by NGS (80% vs 51.1%, p 0.070). Significantly more patients in the t (11,14) group were progression free at 6 months (93.8% vs 63.8%, p 0.028). While in the non-t(11,14) group more patients had high risk disease, that may confound the results, when non-t(11,14) group was stratified by standard risk and high risk, rates of MRD and 6 months PFS were similar between the two groups and both inferior to the outcomes of the t(11,14) group. While CD56 expression was expectedly lower in the t(11,14) group (33.3% vs 68.6%), CD 56 expression did not correlate with the response to BCMA TCRT. **Conclusions:** In our institutional experience, patients with RRMM with t(11,14) had deeper and more durable responses with BCMA T cell redirecting therapies compared to patients without t(11,14). This finding may inform sequencing of therapies for t(11,14) myeloma and requires validation in larger studies.

PA-099

High ALC Peak Post Cilta-Cel Infusion Predicts Risk for Delayed Neurological Toxicities

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Introduction: Cilta-Cel is a very effective treatment option for patients with relapsed refractory multiple myeloma (RRMM), with updated CARTITUDE-1 analysis showing 5-year PFS of 33% in a highly refractory population. Delayed neurotoxicity is the most challenging toxicity of Cilta-Cel, potentially leading to debilitating complications. It is imperative to identify patients at risk and develop effective mitigation strategies. Recent retrospective studies found that patients with higher peak ALC post-infusion, that correlates with higher CAR-T expansion, were at increased risk for delayed toxicities. **Methods:** We analyzed toxicity outcomes of patients treated with Cilta-Cel at our institution between 11/2023 and 3/2025. Exact Fisher test and Student's t-test were used for statistical analysis. **Results:** Among 17 patients treated with Cilta-Cel, median peak ALC post infusion was 2.1 K/mm^3 (1–31.2). I6/17 (35.3%) patients had peak ALC >5 K/mm^3 (7–31.2), with median time to peak of 11 days post-infusion (10–12). Delayed neurological toxicities occurred in 6/ 17 (35.3%) patients, including 4 pts (23.5%) with grade 2 cranial nerve palsies (CNP), 2 pts (11.8%) with movement and neurocognitive toxicity (MNT), and 1 pt (5.9%) with grade 3 atypical Guilian Barre syndrome. The median day of CNP onset observed in 4 pts was 20 (range 18–36), and 2 of those pateints developed a second CNP event later in the course (d93, d120). All CNPs were treated with steroids and IVIG or steroids alone and improved. Both patients with MNT had extremely high ALC peaks of 31.2 K and 22.1 K. One

patient had prior CNP on day 18 (resolved) and subsequently developed MNT on day 66, that ultimately improved. Another patient developed concurrent progressive refractory MNT and severe immune mediated enterocolitis and passed on day 186 due to sepsis. The incidence of delayed toxicities was 5/6 (83.3%) among patients with ALC >5 K and 1/11 (9.1%) among patients with ALC<5 K (p = 0.005). Median peak ALC was 13.6 K (4.4–32.1) among patients with delayed toxicities and 2.2 K (1.1–13.1) without (p = 0.01). Of note, patients with delayed toxicities had higher incidence of CRS and hypofibrinogenemia during early post-infusion course compared to patients without (CRS: 100% vs 54.5%, median duration 3 days (1–5) vs 1.5 days (1–3), hypofibrinogenemia: 66.7% vs 0%). **Conclusions:** High ALC peak in the early post infusion course (median day 11) is a strong predictor of delayed neurotoxicities of Cilta-Cel, with a threshold of 5 K/mm^3 offering effective risk stratification. Risk mitigation strategies are needed for this patients' population.

PA-100

Efficacy of Subsequent T Cell Engagers following BCMA CAR-T Therapy in Patients with Relapsed/Refractory Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: B-cell maturation antigen (BCMA)-targeted therapies, including CAR-T, bispecific antibodies (BsAbs), and antibody-drug conjugates (ADCs), have significantly advanced the treatment of relapsed/refractory multiple myeloma (RRMM). However, disease progression after BCMA-therapies remains a critical challenge, and the response to subsequent salvage treatments in this setting is unclear. The purpose of this study is to evaluate the pooled objective response rates (ORR) of various BCMA and non-BCMA targeted therapies administered following prior BCMA CAR-T therapy. **Methods:** A systematic literature search was conducted to identify studies that investigated sequential therapies in RRMM patients using PubMed, ASH 2024, ASCO 2025, and EHA 2025 abstracts using the search terms (Multiple Myeloma) AND (Bispecific antibodies) OR (CAR-T cell therapy) OR (BCMA ADC) AND (Sequential therapies). Our search yielded 492 studies in PubMed, and 19 studies were included in the final analysis. Additionally, 5 abstracts from ASH and 7 abstracts from ASCO were included in the final analysis. We conducted a single-arm proportion meta-analysis for outcomes in various categories. A random-effects model was used for outcomes with high heterogeneity (defined by an I^2 statistic greater than 25% and a p-value in the Cochrane test greater than 0.1). Otherwise, a fixed effects model was used. Categorical outcomes were summarized by pooled proportion with 95% CI. $P < 0.05$ was considered statistically significant. All the analysis was carried out using R Studio desktop version 4.4.2. The primary outcome evaluated is ORR. **Results:** ORR was reported in 304 patients post-BCMA CART therapy. Subsequently, patients received one of 4 therapies: 1) Rechallenge with BCMA CAR-T (n = 35); 2) Non-BCMA CAR-T (n = 30); 3) BCMA BsAb (n = 97); 4) non-BCMA BsAb (n = 142). The pooled ORR is 0.64 (95% CI: 0.51–0.74). The ORR rates are 77%, 79%, 49%, and 69%, respectively, in four sub-groups. On further analysis, there was significantly higher ORR with non-BCMA targets as compared to BCMA targets (non-BCMA CAR-T plus BsAb vs BCMA CAR-T plus BsAb) [ORR = 0.73 (0.66–0.79) vs ORR = 0.58 (0.50–0.66), p = 0.006]. Similar trends of higher ORR were noticed with CAR-T compared to Bispecific antibodies, irrespective of the target [ORR = 0.85 (0.75–0.91) vs ORR = 0.57 (0.52 to 0.62), p < 0.001]. Additionally, we analyzed the cohort that received any prior BCMA followed by BCMA BsAbs, and the ORR was 51%. The funnel plot is symmetrical and shows no publication bias in all 4 subgroups (p = 0.56). Progression-free survival (PFS) was not consistently reported across the trials and hence not included. **Conclusions:** Following BCMA CART, non-BCMA targeted TCEs had superior ORR, and as a therapeutic modality, CART had better responses than BsAb. BCMA BsAb had lowest response rates and hence should be used only if other therapy modalities are unavailable. The durability of these responses needs to be determined in further studies.

PA-101

Long-Term Follow-Up from MajesTEC-1 China Cohort of Teclistamab in Patients with Relapsed/Refractory Multiple Myeloma: Efficacy Updates, Infection Profile and Immunoglobulin Usage

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Introduction: Teclistamab (tec) is the first approved BCMA × CD3 bispecific antibody in patients (pts) with triple-class

exposed relapsed/refractory multiple myeloma (RRMM) using weight-based dosing. In trials and real-world setting, tec has shown rapid, deep, and durable responses. We report longer-term follow-up (FU) results of Phase 2 MajesTEC-1 China cohort on efficacy, infection profile and immunoglobulin (Ig) usage. **Methods:** MajesTEC-1 China cohort enrolled 26 RRMM pts who had received ≥3 prior lines of therapy including a PI, IMiD and anti-CD38 mAb. After providing informed consent, pts received tec 1.5 mg/kg subcutaneous QW preceded by step-up dosing, pts could switch to less frequent dosing if achieved ≥CR for ≥6 mos. **Results:** As of Sep 27, 2024, mFU was 27.2 months (mos) (range: 0.8 to 33.4). Pts received a median of 10.1 mos of tec (range: 0.7 to 31.9). ORR, ≥VGPR, ≥CR and sCR were 76.9%, 76.9%, 57.7% and 50%, respectively. Among 13 pts (50%) who switched from QW to Q2W, median time to switch was 12.6 mos (range: 7.9 to 20.0) and 10/13 then moved to Q4W and remained in response. Overall median DOR was not reached (30-mos DOR: 60.0%); median PFS was 25.1 mos (30-mos PFS: 43.6%); and median OS was not reached (30-mos OS: 75.1%). Pts who achieved ≥CR had better DOR, PFS and OS: 30-mos rates were 80.0%, 80.0% and 93.3%, respectively. Treatment with tec was associated with a sustained improvement in all subscales of EORTC-QLQ C30, with median time to improvement ranging from 1.3 to 3.5 mos.In terms of infection profile, the incidence of new-onset grade ≥3 infections were more frequent within the first 6 mos of tec therapy and decreased over time: 53.8% (14/26) within first 6 mos, 47.4% (9/19) within >6 to 12 mos, 38.5% (5/13) within >12 to 18 mos, 18.2% (2/11) within >18 to 24 mos, and 14.3% (1/7) >24 mos. 24 pts (92.3%) had ≥1 postbaseline IgG level <400 mg/dL after tec therapy; median time to IgG <400 mg/dL was 1.4 mos (range: 1.1 to 4.8), and 22 pts (84.6%) received ≥1 dose of Ig replacement. Mean IgG level began to rise after 6 mos of tec therapy and remained consistently above 400 mg/dL after 8 mos. For neutropenia, grade ≥3 neutropenia was reported in 20 pts (76.9%). No pts discontinued tec due to neutropenia. No febrile neutropenia was reported. 23 pts (88.5%) received colony-stimulating factors, and the incidence of new-onset grade ≥3 neutropenia decreased over time.

Table

mFU	27.2 mos
ORR	76.9%
≥CR	57.7%
Median DOR	NR
· 30-mos DOR	60.0%
· 30-mos DOR in pts achieved ≥CR	80.0%
Median PFS	25.1 mos
· 30-mos PFS	43.6%
· 30-mos PFS in pts achieved ≥CR	80.0%
Median OS	NR
· 30-mos OS	75.1%
· 30-mos OS in pts achieved ≥CR	93.3%

Conclusions: With a mFU of 27.2 mos, tec consistently showed deep and durable responses. The overall safety profile remained consistent with a notable decrease in incidence of new onset high grade infections over time. These data are consistent with the MajesTEC-1 pivotal cohort and support tec as a promising treatment option for pts with triple-class exposed MM in China.

PA-102

Quality-Adjusted Survival Analysis of Cilta-Cel vs Standard of Care in Lenalidomide-Refractory Multiple Myeloma Patients who Received 1–3 Prior Lines of Therapy: CARTITUDE-4 Trial Population

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Introduction: In the CARTITUDE-4 trial (NCT04181827), a single ciltacabtagene autoleucel (cilta-cel) infusion significantly improved overall survival and prolonged progression-free survival vs standard of care (SOC) in patients (pts) with lenalidomide-refractory multiple myeloma (MM) with 1–3 prior lines of therapy. Quality-Adjusted Time Without Symptoms or Toxicity Analysis (Q-TWiST) is a validated clinical tool comprehensively integrating progression, survival, treatment toxicities, and pt quality of life (QoL) into a single metric to evaluate overall treatment effect. In this analysis, the Q-TWiST method was applied to evaluate the comprehensive benefit-risk profile of cilta-cel vs SOC using data from the CARTITUDE-4 trial. **Methods:** The analysis included the intent-to-treat population from CARTITUDE-4 (N = 419), with a maximum follow-up of 45 months. Consistent with Q-TWiST methodology, survival time was divided into 3 distinct health states: 1) time spent without disease progression (PD) and symptoms of toxicity (TWiST), 2) time with toxicity or side effects due to treatment prior to PD (TOX), and 3) time after PD (REL). Grade 3/4 AEs (both treatment-emergent and non−treatment-emergent) were used to determine TOX; Q-TWiST was computed as a weighted sum of mean time spent in TOX, TWiST, and REL states, where the weights are state-specific QoL utility scores. The base-case model used conventional utility values for each health state: TWiST (1.0), TOX (0.5), and REL (0.5). A 10−15% relative Q-TWiST gain was considered as a clinically important difference, based on established recommendations (Revicki et al. Qual Life Res. 2006). Sensitivity analyses were conducted to test the robustness of base-case results. **Results:** For the base-case, pts treated with cilta-cel showed a significantly longer time without grade 3/4

toxicity compared with pts receiving SOC, with a mean TWiST duration of 26.2 months vs 15.4 months, respectively. The mean TOX was 4.3 months vs 2.4 months, and mean REL was 6.4 months vs 14.3 months. Q-TWiST was significantly longer with cilta-cel by 7.7 months (95% CI, 4.8–10.5, P < 0.001), representing a relative gain of 32.1% compared with SOC. Sensitivity analyses results were consistent with the base-case. **Conclusions:** The relative Q-TWiST gain of cilta-cel vs SOC was a statistically significant and clinically meaningful gain in quality and quantity of survival, above the 10–15% threshold criteria generally considered as clinically important in literature, and to our knowledge, one of the highest relative gains to date. Our analysis further supports the favorable benefit-to-risk profile of cilta-cel compared with SOC in pts with lenalidomide-refractory MM as early as after first relapse.

PA-103

Value of the Treatment-free Period Following Ciltacabtagene Autoleucel Infusion in Patients with Relapsed/Refractory Multiple Myeloma: Preliminary Findings from a Qualitative Interview Study

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Introduction: Current treatment options for patients with relapsed/refractory multiple myeloma (RRMM) who have received ≥1 prior line of therapy can include a single ciltacabtagene autoleucel infusion (cilta-cel) without maintenance therapy, which can contribute to the potential benefit of a "treatment-free" period. This abstract presents preliminary findings from an ongoing qualitative interview study exploring patient perspectives and experiences of the treatment-free period following cilta-cel treatment for RRMM. **Methods:** US-based adult patients with RRMM who received cilta-cel ≥6 months before study enrollment and currently treatment free, recruited via the International Myeloma Foundation, participated in semi-structured, qualitative interviews that were audio-recorded and transcribed. Thematic analysis identified key themes associated with patients' interpretation of "treatment free" and their treatment-free experiences. **Results:** Interviews were completed with 15 patients (9 female/6 male; age range: 53–78; median time since cilta-cel: 13 months 4 days). Patient interpretations of being "treatment free" included freedom from treatment side effects, absence of symptoms, increased freedom of time, and a return to 'normal' life. The treatment-free period for most patients was a positive experience with substantial benefits for their HRQOL; "well, I definitely feel better, and I think I'm better off." Patients reported that they were more able to engage in normal, everyday activities, and notable improvements in their psychological/emotional well-being; 8 patients reported that they no longer ascribed to viewing themselves as a 'patient' due to the reduction in medical appointments/absence of continuous treatments; "I don't really see myself as a patient anymore." Patients highlighted the meaningfulness of increased involvement in family life and strengthening of familial bonds because they were treatment free. Challenges associated with the treatment-free period focused on the fear of potential relapse (n = 8) and the resumption of treatment; for many patients, being off continuous therapy represented an important achievement. The most important changes experienced during the treatment-free period included: improved well-being/HRQOL/increased energy (n = 10), increased free time (n = 8), feeling cancer/disease free (n = 7), and freedom from medication/treatment (n = 7). For most patients (n = 9), the biggest impact of being treatment free was improved psychological wellbeing; "It gave me back enjoyment of life". **Conclusions:** These initial interviews provide valuable insights on the patient-perceived value of the treatment-free period following cilta-cel treatment for patients with RRMM. Notably, improvements in patients' overall HRQOL and the impact of freedom from disease and treatment improved patients' perceptions of themselves and their lives. The changes experienced by patients emphasize the positive impact of living without continuous treatment.

PA-104

Splenomegaly is Associated with High-Tumor Burden, Prolonged Cytopenia and Adverse Outcome after BCMA-directed CAR T-Cell Therapy

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Introduction: Chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) have emerged as a transformative treatment modality for patients with relapsed or refractory multiple myeloma (RRMM). Despite impressive initial responses, the majority of patients ultimately relapse, and treatment is frequently complicated by substantial toxicities, particularly

hematologic adverse events. Splenic enlargement has previously been associated with disease burden in RRMM. In this study, we investigated the prognostic significance of spleen volume in the context of BCMA-directed CAR T-cell therapy. **Methods:** We retrospectively analyzed clinical and imaging data from 73 patients with RRMM who received either idecabtagene vicleucel or ciltacabtagene autoleucel at the University Hospital Leipzig. Spleen volume was assessed using CT–based volumetric analysis performed prior to lymphodepletion and 30 days post-CAR T-cell infusion. Spleen size measurements were correlated with established surrogates of tumor burden, including metabolic tumor volume (mTV) derived from PET/CT and serum levels of soluble BCMA (sBCMA). Additionally, we evaluated the association between spleen volume and prolonged hematologic toxicity, progression-free survival (PFS), and overall survival (OS). **Results:** Baseline clinical and demographic characteristics were similar between patients with and without splenomegaly, which was defined using a volumetric cutoff of >340 cm^3. Spleen volume was associated with post-treatment hematologic toxicity. Specifically, patients who developed severe thrombocytopenia following CAR T-cell infusion had significantly larger spleen volumes than those without (304.9 vs. 207.9 cm^3; $p < 0.01$). Likewise, patients experiencing prolonged thrombocytopenia exhibited greater spleen volumes compared to those with more transient cytopenias (302.0 vs. 206.8 cm^3; $p < 0.01$). Assessment of tumor burden revealed elevated mTV on PET/CT imaging (602.0 vs. 86.9 mL; $p < 0.05$), as well as higher circulating levels of sBCMA (54.0 vs. 4.5 ng/mL; $p < 0.05$), indicating an association between spleen size and systemic disease burden. Furthermore, splenomegaly was significantly associated with inferior PFS (HR: 8.9, 95% CI: 2.29–35.1; $p < 0.01$) and OS (HR: 8.3, 95% CI: 1.4–49.7; $p < 0.05$), outperforming established prognostic indicators such as sBCMA levels, the EASIX score, and the CAR-Hematotox score. **Conclusions:** Spleen volume represents a robust and easily measurable prognostic biomarker in patients undergoing BCMA-directed CAR T-cell therapy. These findings underscore the potential utility of incorporating spleen size into routine clinical assessment protocols. Moreover, they highlight the rationale for exploring therapeutic strategies aimed at reducing splenic volume as a means to mitigate toxicity and improve patient outcomes.

PA-105

CART–ASCT–CART2 Sandwich Regimen as Frontline Therapy: A Phase II Trial in Patients with Primary Plasma Cell Leukemia

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Introduction: Primary plasma cell leukemia (pPCL) is the most aggressive form of plasma cell neoplasm, associated with poor prognosis and lacking effective treatment options. Previous studies have demonstrated that pPCL patients may benefit from BCMA CAR T-cell therapy, and promising results have also been reported with the combination of ASCT with CAR T-cell therapy in HRNDMM. Based on these findings, we initiated an ongoing phase II trial (NCT05870917) to evaluate the sequential CART–ASCT–CART2 (CAC) sandwich regimen as frontline therapy for newly diagnosed, transplant-eligible (TE) pPCL patients. This approach aims to deepen remission with pre-transplant CAR T therapy and eradicate MRD through post-ASCT consolidation. Notably, this is the first study to combine ASCT with CAR T therapy in pPCL. **Methods:** This is a single-arm, open-label, phase II investigator-initiated trial enrolling transplant-eligible NDpPCL patients. All patients first receive PI +IMID-based induction therapy, followed by a single infusion of anti-BCMA CAR T-cells after 3-day lymphodepletion with fludarabine and cyclophosphamide. One month post-CAR T infusion, patients undergo three cycles of consolidation therapy followed by ASCT. On day +3 (±1) post-ASCT, a second CAR T infusion (CART2) is administered. Maintenance therapy continues until progression. Autologous stem cells are infused on day 0, and the target CAR T-cell dose for each infusion ranged from 2×10^6/kg to 4×10^6/kg. **Results:** As of April 20, 2025, with the median follow-up time was 12.5 months (range 6.2–25.7), a total of 20 patients have been enrolled. The median age of these patients is 53 years (range 31–66). 11 patients completed CAC therapy and are currently in the maintenance phase and 7 patients are in the consolidation phase after the first CART. The current median follow-up from the first CAR T-cell infusion is 6.7 months (range 0.2–13.0). Following the first CAR T-cell infusion, 80% of patients achieved CR or better, and 90% achieved MRD negativity. Among 11 patients who completed CAC regimen, all achieved sCR, with only one case of MRD re-positivity occurring 3 months after the initial CAR T-cell infusion. No cases of relapse, disease progression, or death have been observed among these patients to date. The median time of neutrophil and platelet recovery were 15 days (range 11–23) and 12 days (range 9–17) after ASCT, respectively. Excluding two patients who died of adenovirus infection following the first CAR T-cell infusion, no severe CRS (>grade 2) were reported among the remaining patients. And no cases of ICANS were observed in any of the enrolled patients. The CART2 was also well tolerated, with no ICANS reported. **Conclusions:** The CART–ASCT–CART2 sandwich regimen demonstrated a favorable safety profile and encouraging efficacy in newly diagnosed, transplant-eligible patients with primary plasma cell leukemia (pPCL).These encouraging results warrant confirmation in a larger cohort to assess durability and long-term outcomes.

PA-106

BCMA CAR T-Cell Therapy in Newly Diagnosed Transplant-ineligible Multiple Myeloma: An Open Label, Single-arm, Phase 2 Study (CAREMM-001)

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Introduction: BCMA-directed CAR-T cell therapies have demonstrated deep and durable responses in relapsed/refractory multiple myeloma (RRMM), including in elder and frail patients. However, prospective data in transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM) patients are lacking. Here, we report the efficacy and safety data of BCMA CAR-T therapy in frontline setting for transplant-ineligible NDMM patients in CAREMM-001 study (NCT05860036). **Methods:** This single-arm, phase 2 trial enrolled NDMM patients deemed ineligible for ASCT due to age, frailty, comorbidities, or repeated failure of stem cell mobilization. After 3–4 cycles of VRd-based induction treatment, patients received lymphodepletion and a single infusion of academic BCMA CAR-T cells (3×10^6 cells/kg), followed by consolidation and lenalidomide maintenance. Primary endpoints were safety and MRD negativity following infusion. Secondary endpoints included complete response rate, PFS, OS, and duration of remission. **Results:** Between April 2023 and December 2024, forty patients were enrolled, with a median age of 68 years (range, 46–75). High-risk characteristics were prevalent: 45% were ISS III, and 38.5% met criteria for ultra-high-risk, defined by extramedullary disease, circulating plasma cells ≥2%, or double-hit cytogenetics. All patients underwent apheresis within induction period, but four patients withdrew due to severe infection (n = 2) and renal dysfunction (n = 2). Finally, 36 patients received standard lymphodepleting and infusion. At a median follow-up of 12.8 months, all infused patients achieved MRD negativity at day 28 post-infusion and sustained through last follow-up. The overall response rate (ORR) was 100%, with 88.9% achieving sCR. Among 23 patients with enough follow-up, all demonstrated sustained MRD negativity for ≥12 months. No relapses have occurred to date; median PFS, OS, and DOR were not reached. The most common AEs were hematological that were thought to be associated with the lymphodepletion, with grade ≥3 neutropenia (88.9%) and lymphopenia (100%). Early ICAHT occurred in 52.8%, with only 2 grade 3; late ICAHT occurred in 37.5% of patients, and only one grade 3. Hypogammaglobulinemia occurred in 44.4% of patients, most recovered with reduced supportive IVIG frequency. Infections occurred in 31.2% (≥3 grade in 18.8%), most commonly respiratory. CRS occurred in 52.8% (all grade 1–2), with a median onset of 2 days and duration of 3 days. Two patients had grade 1 ICANs. All patients exhibited robust peripheral expansion. Median Cmax was 56,742 copies/μg gDNA (range, 6,627–235,215), median time to reach peak expansion was 11 days, and AUC0–28 was 605,180 (range, 57,001–2,828,539). **Conclusions:** Frontline BCMA CAR-T therapy induced deep and durable responses with a favorable safety profile in TIE NDMM patients, including those with ultra-high-risk features. These results support its potential as a transformative first-line option for transplant-ineligible myeloma.

PA-107

Impact of Frailty Tools on Outcomes in Myeloma: MRP and Simplified Index Predict Survival but Differ in Infection Risk Stratification

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Introduction: Approximately two-thirds of newly diagnosed multiple myeloma patients exhibit varying degrees of frailty, with at least 40% experiencing severe frailty. As age increases, frailty often intensifies, leading to more complications, deteriorating renal function, and worsening physical condition, making some patients ineligible for anti-myeloma treatment. Frailty significantly impacts the overall survival (OS) of multiple myeloma patients, making its assessment crucial in treatment planning. In 2019, the UK Myeloma Alliance developed the Myeloma Risk Profile (MRP) score. In 2020, Facon et al. introduced a Simplified Frailty Index (FI) that streamlines assessment indicators and time, effectively stratifying patient frailty. This study aims to compare the application of MRP and Simplified FI in Chinese multiple myeloma patients to identify a more suitable frailty assessment method for clinical practice. **Methods:** This study is a retrospective single-center study that enrolled a total of 205 newly diagnosed multiple myeloma (NDMM) patients, with collection and analysis of patients' clinical data.Patients were divided into frail and non-frail groups based on MRP and Simplified FI assessments. Kaplan-Meier analysis was used to compare the cumulative incidence of early grade ≥3 infections, overall survival (OS), and progression-free survival (PFS). ROC curves, AUC values, and Youden's index compared the predictive values for OS, PFS, and early grade ≥3 infections. **Results:** The incidence of early grade ≥3 infections was significantly higher in the frail groups (52.54%vs.36.30%and 51.85%vs.33.87%, both $P < 0.05$). The frail groups had significantly shorter OS (28 vs. 55 months and 34 vs. 58 months) and PFS (15 vs. 33 months and 16 vs. 34 months; $P < 0.001$) with increased mortality

risk (HR: 1.849 and 1.810). One-year mortality was significantly higher in frail patients (P < 0.005). Patients in the common frail group had the worst early grade ≥3 infection rates, OS, and PFS, but no significant difference compared to individual frailty groups (P > 0.05). Delong analysis showed no significant difference in predictive performance between the two frailty assessment tools for OS and PFS (P < 0.05). MRP was ineffective in predicting early grade ≥3 infections (P = 0.237), while FI was effective (P = 0.012). **Conclusions:** Both MRP and FI are effective frailty assessment tools in elderly MM patients. They significantly correlate with OS, PFS, and the risk of early grade ≥3 infections. Future studies should expand the sample size and incorporate more research on frailty-guided treatment approaches.Corresponding author:Weiwei Tian.

PA-108

A Comparison of Chemo-free Strategy with Plerixafor Plus G-CSF Versus High-Dose Cyclophosphamide Plus G-CSF as First-line PBSC Mobilization in Multiple Myeloma Patients: A Chinese Explorative Study

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Introduction: Plerixafor plus G-CSF (PLE+G-CSF) has demonstrated superior mobilization efficacy compared to cyclophosphamide plus G-CSF (CY+G-CSF) in multiple myeloma (MM) patients. However, the use of two or more vials of plerixafor to achieve sufficient stem cell mobilization may be financially prohibitive for some patients. This study aims to explore a more efficient and cost-effective mobilization scheme by using only one vial of plerixafor throughout the entire mobilization process. **Methods:** A retrospective analysis was conducted on 220 MM patients who underwent hematopoietic stem cell mobilization using either PLE+G-CSF (n = 98) or CY+G-CSF (n = 122) prior to ASCT at our center. In our protocol, a single preparation of plerixafor was used, with the first injection delivering a sufficient dose and the remainder administered during the second injection for steady-state mobilization. The mobilization efficiency, adverse events, average total cost of mobilization, and hematopoietic reconstruction post transplantation were analyzed and compared between the two groups. **Results:** The plerixafor mobilization strategy significantly improved the success rate of mobilization (85.7% vs. 74.6%, P = 0.042) and reduced the time of apheresis (1 (1, 2) d vs. 2 (1, 3) d, P < 0.001) compared to the CY group. Additionally, PLE mobilization decreased the need for salvage mobilization and antibiotic use. There was no significant difference in the time to hematopoietic reconstruction between the two groups. Multivariate logistic regression identified three favorable predictors for successful stem cell collection: baseline absolute platelet count ≥204 × 109/L (OR 1.01, 95% CI: 1–1.02, P = 0.013), day −1 peripheral blood CD34+ cell count ≥11/μL (OR 1.07, 95% CI: 1.03–1.12, P < 0.001), and the use of PLE+G-CSF mobilization (OR 7.61, 95% CI: 1.57–58.32, P = 0.025). **Conclusions:** This study demonstrates that the PLE+G-CSF strategy, even when utilizing only one vial of plerixafor, achieves a higher mobilization success rate, requires fewer apheresis time, and results in fewer adverse events compared to the CY+G-CSF strategy. Furthermore, this approach partially alleviates the financial burden on patients. Factors associated with successful stem cell collection include absolute platelet count ≥204 × 109/L at baseline, day −1 PBCD34 ≥11/μL, and PLE+G-CSF mobilization.

PA-109

Changes in Patient-reported Distress and Symptom Burden During Talquetamab Therapy in Multiple Myeloma: A Descriptive Analysis

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Introduction: Talquetamab (TAL) is a first-in-class bispecific T-cell engager targeting GPRC5D and CD3, approved for relapsed/refractory multiple myeloma. While it has promising efficacy, its novel mechanism is associated with a distinct toxicity profile. The impact of TAL on patient-reported distress and symptom burden has not been previously described. This study evaluates real-world changes in distress and symptoms during TAL therapy. **Methods:** We analyzed 47 MM patients treated with TAL at a single institution. Distress was assessed using the NCCN Distress Thermometer and problem checklist, capturing practical, social, spiritual, emotional, and physical concerns. This is administered routinely to clinic patients. 32 patients who completed at least one assessment before and after initiating TAL therapy are included in the analysis below. **Results:** The median age was 64.2 years with 62.5% males. The majority were non-Hispanic (NH) White (88.2.%), followed by NH Black (5.9%), and other racial/ethnic groups (5.9%). High-risk cytogenetics were present in 46.9% of patients, and 51.8% had ISS stage II/III disease. The median number of prior lines was six. Patients remained on TAL for a median of 3.7 months and experienced a median weight loss of 13.2 pounds. Distress increased in 53.0% of patients (17/32) compared to 47% (15/32) with stable or improved scores. The overall median distress increased from 1.0 at baseline to 2.0 on treatment. Among those with worsening distress, scores rose from 1.0 to 4.0; in contrast, the improved group saw scores decline from 1.0 to 0.0. Practical,

social, and spiritual concerns remained largely unchanged. Emotional symptoms, such as worry and nervousness, generally improved, with nervousness decreasing from 15.6% pre-TAL to 3.1% during therapy. In contrast, physical symptom burden increased in both groups. Fatigue rose from 34.4% to 50.0%, eating-related concerns emerged in 28.1% (previously 0%), dry/itchy skin increased from 15.6% to 46.9%, mouth sores from 3.1% to 15.6%, and breathing difficulties from 6.3% to 12.5%. These effects were more pronounced among patients with increased distress: fatigue rose from 41.2% to 76.5%, dry/itchy skin from 11.8% to 64.7%, and eating concerns from 0.0% to 41.2%. **Conclusions:** TAL is associated with an increase in symptom burden, particularly fatigue, dermatologic effects, and eating-related concerns. While over half of patients experienced worsening distress, nearly half had stable or improved scores, with many noting reductions in emotional symptoms such as nervousness and worry. These findings highlight the complexity of the treatment experience, where disease control may coexist with declining physical well-being but preserved or even improved emotional adjustment. Routine distress screening and proactive supportive care are paramount to identifying patients at risk for symptom deterioration during TAL therapy.

PA-110

Denosumab-Related Osteonecrosis of the Jaw in Patients with Multiple Myeloma: A Chinese Single-Center Retrospective Cohort Study

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Introduction: Denosumab, an antiresorptive agent that inhibits osteoclast activity, was approved for osteoporosis treatment (60 mg/6 months) in 2010 and for bone metastases or multiple myeloma (MM) (120 mg/4 weeks) in 2011 to delay or reduce skeletal-related events. A critical adverse effect during long-term use is medication-related osteonecrosis of the jaw (MRONJ), with an incidence of approximately 4%, making it the most common adverse event leading to treatment discontinuation. MRONJ causes severe pain, bone exposure, and infection, significantly impairing quality of life. However, its insidious early symptoms often lead to delayed diagnosis. Denosumab was only approved in China in November 2020, and clinical data remain scarce. This study aimed to characterize denosumab-associated MRONJ in Chinese MM patients and optimize treatment strategies. **Methods:** Twelve MRONJ cases diagnosed among 287 MM patients receiving denosumab at our center from January 2021 to December 2024 were retrospectively analyzed. Clinical manifestations, imaging findings, risk factors, and treatment outcomes were compared with 275 non-MRONJ controls. **Results:** Incidence: MRONJ occurred in 4.2% (12/287), with a median denosumab treatment duration of 26.5 months (range: 12–32). Clinical Presentation: 83.3% (10/12) presented with atypical dental pain or gingival swelling, and 41.7% (5/12) experienced tooth loss. Imaging: Trabecular bone abnormalities were observed in 58.3% (7/12), while sequestrum formation occurred in only 16.7% (2/12). Local Triggers: 4 cases (33.3%) had predisposing factors (e.g., tooth extraction). Risk Factors: MRONJ patients had longer denosumab exposure (26.5 vs. 15 months, $P = 0.003$) and lower vitamin D3 levels (14.88 vs. 17.78 ng/mL, $P = 0.001$) compared to controls. No significant differences were observed in gender, age, or anemia severity ($P > 0.05$). Treatment Outcomes: 91.7% (11/12) were diagnosed at early stages (I–II). After specialized treatment, 83.3% (10/12) regained oral function. **Conclusions:** MRONJ primarily occurs in MM patients after ≥2 years of denosumab therapy. Insidious clinical manifestations and vitamin D3 deficiency are potential risk factors. Early multidisciplinary intervention improves prognosis.

PA-111

Assessing Positive Behavioral Change in Myeloma Care: An MMRF Longitudinal Study

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Introduction: Multiple myeloma (MM) is an uncommon and complex blood cancer. While treatment advances are promising, the rapid pace of drug development makes it difficult for patients and community providers to stay updated on evolving standards of care. Staying informed is critical: when patients understand their disease, they are better equipped to self-advocate and pursue optimal outcomes. **Methods:** A longitudinal survey was developed to measure behavioral changes after attending a patient education program (online or hybrid). It focused on improving understanding of treatment options, awareness of symptoms and side effects, and consideration of clinical trials and care planning. **Results:** In 2024, 5,500 patients and caregivers participated in MMRF's educational programs, featuring myeloma specialists and covering topics from diagnosis to relapse. The survey was sent to participants every 3 months post-program. Of 4,581 surveys delivered, the response rate was 14% (n = 647) including 576 patients, 52 caregivers, and 19 identifying as "other." Among patients, 87% (n = 506) reported at least one positive behavioral change related to their myeloma care. The following reflects the percentage of all patients reporting changes, categories may include overlap: Active Communication: 63% (n = 365) reported being better able to discuss current and emerging treatment options with their doctor, leading to more informed conversations about therapies appropriate to their disease stage. **Lab Diagnosis and Interpretation:** 50% (n = 288) were better equipped to interpret test results and engage with their doctor about these findings. MMRF Resources: 39% (n = 223) accessed MMRF tools that helped them make informed decisions about treatment. Treatment Goals & Personal Needs: 26% (n = 153) proactively communicated with their care team regarding individual treatment goals. 12% of patients (n = 70) reported barriers to change, most

commonly citing limited access to a myeloma specialist or academic medical center, and lack of knowledge about disease/treatment options. **Conclusions:** To address these barriers, the MMRF will implement two analyses. A geospatial analysis will uncover regional patterns among patients with limited access to myeloma specialists or academic centers. By leveraging our CRM, which tracks patient registration, we can identify trends and explore how to expand services – such as utilizing our Patient Navigation Center (PNC) or digital education to bridge geographic gaps in access. Second, to understand knowledge barriers, we will segment respondents who reported low knowledge or awareness about treatment options and analyze their engagement. This Includes program attendance, interactions with the PNC, and email communications.Insights from both efforts will inform tailored programming for under-engaged audiences. Ultimately, this work strengthens education efforts that meet patients where they are – equipping them with the knowledge and confidence to advocate for themselves throughout their myeloma journey.

PA-112

Navigating Myeloma: Behavioral and Emotional Outcomes from a Patient-Centered Navigation Resource

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Introduction: Multiple myeloma is an uncommon and complicated blood cancer. Advances in research over the last 20 years have created numerous treatment options. However, this abundance can make it difficult for patients to stay updated with the latest therapies, especially in community settings. It is essential for patients to be aware of these developments and actively participate in their care to optimize outcomes. Our mission is to accelerate a cure for each and every patient, and one of our three strategic pillars is to empower the entire myeloma community to improve care and outcomes for all patients. **Methods:** The Patient Navigation Center (PNC) at the Multiple Myeloma Research Foundation (MMRF) is a free resource for multiple myeloma patients and caregivers. Staffed by three experienced oncology professionals, the PNC offers personalized information, emotional support, and guidance on clinical trials, empowering patients to make informed decisions. Patients can reach the PNC by phone, email, or web form, and each interaction is tracked as a case in our CRM platform. PNC nurses work with patients until their needs are addressed, and insights are shared with the education team. Monthly reviews help identify trends, ensuring key themes are integrated into education programs. **Results:** To assess impact, two surveys are conducted: one post-interaction with the PNC and a longitudinal survey 90 days after initial contact. In 2024, over 2,000 patients and caregivers contacted the PNC. In 2024, 867 patients received the longitudinal survey, yielding a 19% response rate (n = 167). Among respondents, 90% reported positive steps after speaking with the PNC – key actions included communicating treatment goals with their care team (62%), discussing test results (55%), seeking a second opinion (32%), and discussing with their doctor the prospect of considering a clinical trial (19%). Optional likert scale questions assessed emotional impact. Of those who responded (n = 132), 62% felt more empowered, 53% reported greater confidence in discussing treatment options, and 53% experienced relief after interacting with the PNC. Additionally, 84% agreed or strongly agreed that speaking with a patient navigator helped reduce anxiety or distress about their diagnosis, and 81% felt they better understood their condition. **Conclusions:** Our data reveals communication with Patient Navigators positively impacts patients and caregivers navigating multiple myeloma. However, 7% of respondents did not take positive steps. Future efforts will focus on conducting a gap analysis to explore barriers and the patterns influencing behavior changes. Key factors will include disease stage, frequency of communication with the PNC, and geographic location. By investigating these variables, we aim to develop more targeted strategies to address unmet needs and improve outcomes for multiple myeloma patients.

PA-113

Time Constraints and Treatment Decisions: How Time Allowed for Decision Making Affects Patient Experience in Relapsed Refractory Multiple Myeloma

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Introduction: Relapsed-refractory multiple myeloma (RRMM) management requires balancing the complexity of treatment options against the urgency of relapse. This study examines how the time allowed for treatment decisions affects patient satisfaction, comfort, and understanding, highlighting the need for proactive treatment planning. **Methods:** This retrospective, cross-sectional survey included RRMM patients from Feb. 14, 2023, to Jan. 1, 2024, via HealthTree Cure Hub. The 30-question survey covered 11 decision-making domains during treatment changes, categorizing decision-making time as ≤1 week or >1 week for initial and recent treatment choices. Participants rated factors using 5-point Likert scales: influence (0–4), satisfaction, comfort, perception of care quality, and treatment utilization (1–5). **Results:** Out of 784 participants, 296 relapsed patients reported decision-making times: 169 (57%) had ≤1 week, and 127 (43%) had >1 week. Participants averaged 66 ± 9

years old; 52% female, 91% White, 5% Black, 6% Hispanic/Latino, and 46% held graduate degrees. The cohort given <1 week expressed less satisfaction with their level of involvement in the treatment decision-making process (4.0 ± 0.9 v. 4.2 ± 0.8, $p < 0.05$) and were less comfortable with their final treatment decision (4.2 ± 0.8 v. 4.4 ± 0.7, $p < 0.05$). However, when a change in therapy was decided, time did not have an effect on the number of patients who suggested a different treatment or modification (>1 week: 42% vs. ≤1 week: 44%). In addition, the cohort rated their high-risk status as more influential for their treatment decision (2.2 ± 1.7 vs. 1.7 ± 1.8, $p < 0.05$) and were more likely to have the doctor make the final treatment decision (54%, n = 68 vs. 30%, n = 50, $p < 0.001$). The cohort given >1 week rated side effect severity as more influential at the first treatment change (>1 week: 3.5 ± 1.3 vs. ≤1 week: 3.1 ± 1.2, $p < 0.05$), a higher understanding of: FDA-approved therapies (3.9 ± 1.0 v. 3.6 ± 1.1, $p < 0.05$), efficacy of treatments (3.8 ± 0.9 v. 3.5 ± 1.0, $p < 0.05$), and efficacy-side effects balance (3.8 ± 0.9 v. 3.6 ± 1.1, $p < 0.05$). They also rated their own research on myeloma more favorably (3.9 ± 1 v. 3.5 ± 1.1, $p < 0.05$). Both groups utilized educational resources at similar rates, but those with >1 week reported a higher use of webinars (3.2 ± 1.3 v. 2.9 ± 1.3, $p < 0.05$). There was no difference in satisfaction with the level of education and familiarity with treatment options. **Conclusions:** Most patients have less than a week to make a treatment decision, which often leads them to defer to their doctor and feel influenced by their high-risk status. Patients given >1 week reported greater satisfaction, comfort, and understanding of therapies. This highlights the need for proactive treatment strategies, supporting the idea that "there is no just-in-time education or trust," emphasizing the importance of being prepared for a myeloma relapse.

PA-114

Role of the Combination of 3 T Whole-Body MRI and 18F-FDG PET/CT in the Management of Multiple Myeloma and Smoldering Myeloma: The New era of Imaging

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Introduction: FDG-PET/TC and MRI are both imaging diagnostic tools adopted in diagnosis and/or response assessment in multiple myeloma (MM) which can be useful in smoldering, newly diagnosed as well in relapsed myeloma. **Methods:** From January 2021 to April 2025, we enrolled into a prospective trial 159 consecutive patients (63 Male; mean age, 67 years ± 10 [SD]) divided into 3 groups; 51 had a newly diagnosed MM according to the IMWG (group 1); 23 were in follow-up after autologous stem cell transplantation with clinical or laboratory data suspicious for relapse or progression (group 2) and 38 were affected by relapsed/refractory MM during treatment (group 3). In addition we enrolled 47 patients newly diagnosed high risk SMM, according to IMWG (19 Male, mean age 59 years+-10 [SD]). **Results:** On a per-patient basis, 144/159 (90%) had concordant PET/CT and WB-MRI scans, while 16/159 (10%) had discordant scans in terms of positivity/negativity. Among concordant studies, 54/159 (34%) were negative with both imaging methods while 103/159 (65%) were positive at both (including FLs and/or BMI). Among discordant studies, 14/16 had a positive WB-MRI scan and a negative PET-CT scan (6 cases with BMI or micronodular involvement alone), whereas 2/16 had a positive PET-CT and a negative WB-MRI. PET/CT detected FLs pattern in 103/159 patients, WB-MRI alone identified FLs pattern in 11 patients. The combination of the two methods led to a change of management in 99/159 (62%), highlighted in the case of suspected post-transplant relapse. Furthermore, WB-MRI led to a change of management for incidental findings in additional 9 patients (8 suspected malignancies and 1 spinal cord compression). Interim analysis in HR- SMM showed discordance between the results of the two imaging modalities in 32/159 (21%). WB-MRI detected BMI pattern without any overt focal lesion in 14 patients (only 1 correlated with PET/CT) and FLs pattern in 9 patients (4 confirmed also in PET/CT), while PET/CT detected an additional FLs pattern in 1 patient, without bone lytic lesion evidence at the CT images. **Conclusions:** Our preliminary data underlines the fundamental role of functional imaging in the evaluation of FLs and BMI in MM with a superior detection rate of WB-MRI related to the ability to identify diffuse and micronodular pattern. A potential complementary role of the two methods in clinical management could be suggested in suspicion of relapsed or progressing MM. Furthermore our prospective trial supports the utmost role of WB-MRI (performed according to MY-RADS) in the assessment of high risk Smoldering Myeloma.

PA-115

An Orthopaedic-Guided Exercise Intervention for Newly Diagnosed Multiple Myeloma Patients is Feasible, Safe and Improves Patient-Reported Outcomes (GMMG-HD8-INDEX Trial)

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Introduction: Due to painful osteolytic bone lesions, physical exercise is often avoided in newly diagnosed multiple myeloma (NDMM) patients. Modern quadruplet-therapies have significantly improved treatment-tolerability and -effectivity, which raises the question whether long-term immobilization and functional decline are still inevitable. Aim of this study was to evaluate safety, feasibility and effectivity of an early exercise intervention. **Methods:** Fifty transplant-eligible NDMM patients were included. All patients received an orthopaedic consultation. Bone instability was not defined as an exclusion criteria and patients were randomized 2:1 to an intervention group (IG) or standard of care (SOC). The IG received an exercise plan for whole body resistance training. Patients were monitored weekly via an online training-app and orthopaedic follow-up examination was conducted in every treatment cycle. Patient-reported outcomes (PRO) and functional performance (FP) were evaluated at baseline (T0), after induction therapy (T1) and after autologous stem cell transplantation(T2). **Results:** The recruitment rate was 100%, with exercise feasibility achieved in 71% and exercise protocol adherence exceeding 90% among all patients. Individual adaptation of exercise plans was necessary for 65% of patients at T0, and training intensity could be increased in 59% during treatment. Bone stability was evaluated using the Spinal Instability Neoplastic Score (SINS1 58%, SINS2 40%, SINS3 2%). In 16% of patients, weight-bearing activities were restricted or excluded due to severe instability of the lower extremities/pelvis. New vertebral fractures were detected at T2 in 21% of patients in SOC and 18% in the IG—rates consistent with expectations. One fracture of an unstable subtrochanteric femoral osteolysis occurred (unrelated to the exercise intervention), which was treated surgically and training could be resumed 10 days post-surgery. FP was limited in 40% of patients at T0 due to pain or bone instability. PROs varied widely. However, fear of movement or injury (TSK-11) and fear of falling (FES-I) showed significant improvement in the IG between T0 and both T1 and T2 ($p < 0.05$). Pain levels (VAS) also significantly decreased in the IG from T0 to T2 ($p < 0.05$). Moreover, regular use of pain medication decreased notably in the IG (from 55.5% at T0 to 12% at T2), while it increased in the SOC group (from 30% to 44%). **Conclusions:** The demand for an orthopaedic consultation and subsequent exercise recommendations in NDMM patients is high, as reflected by the recruitment, feasibility and adherence rates of this exercise trial. We were able to demonstrate that an early orthopaedic-guided exercise intervention is feasible and safe, also for patients with unstable bone lesions. However, exercise protocols need to be adapted individually and regular orthopaedic follow-up visits are imperative. Our results show that painful symptoms and fear of movement and falling can be effectively addressed by an exercise intervention.

PA-116

Progression Patterns by Positron Emission Tomography (PET) for Relapsed/Refractory Multiple Myeloma (RRMM) after CAR T cell Therapy: Potential role for Radiotherapy (RT)?

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Introduction: Chimeric antigen receptor (CAR) T-cell therapy has shown remarkable efficacy in MM. However, many patients (pts) have incomplete and non-durable responses. We characterized post-CAR T progression for RRMM, using PET to identify high risk lesions that may benefit from bridging RT prior to CAR T. **Methods:** We analyzed 71 MM pts treated btw 2017–2022 with BCMA-directed CAR T (38 experimental, 33 commercial products). A total of 529 FDG-avid lesions on pre-CAR T PET (pre-apheresis if bridging therapy, pre-lymphodepleting chemotherapy if no bridging), and 321 lesions on post-CAR T PET at first failure were categorized, with failure defined as radiologic and/or serologic progression according to Lugano and International Myeloma Working Group criteria, respectively. At the pt level, we classified disease as osseous (O), extramedullary (EM)/paramedullary (PM), or mixed O and EM/PM. Individual lesions were classified as O, EM, or PM. Lesions were also classified as progressive, stable, or new at pre-CAR T PET according to SUV change from preceding PET. Failure of a lesion present on pre-CAR T PET was defined as progression involving the same anatomic structure and within 3 cm from initial lesion. Pearson's X2 test was used to compare pre- and post-CART PET. Kaplan-Meier curves for progression-free survival (PFS) were constructed. **Results:** Pre-CAR T PET was performed at median 1.4 months (range, 0.2–8.5) prior to CAR T, with 27 (39%) pts receiving systemic bridging, 10 (14%) RT +/- systemic, and 32 (46%) none. Median number of PET avid sites pre-CAR T was 6 (0–9) per pt. Of the 71 pts, 34 (53%) had mixed O and EM/PM, 24 (37%) O only, and 6 (10%) EM/PM only; 7 (10%) had no lesions. Of the 529 lesions on pre-CAR T PET, 351 (66%) were O, 131 (25%) EM, and 47 (9%) PM. A total of 61 (86%) pts progressed post-CAR T (median time to progression of 6 months (interquartile range: 2–11)), 28 (46%) of whom had first failure in new and pre-existing sites, 17 (20%) in new sites only, 6 (10%) in pre-existing sites only, and 10 (16%) serologically only. At the lesion level, 101/321 (31%) failures occurred in lesions on pre-CAR T PET. At failure, EM (44% vs 25%) and PM (12% vs 9%) lesions made up a higher percentage of all lesions compared to pre-CAR T ($p < 0.001$). Of the initial 529 lesions, failure occurred in 44/131 (34%) EM, 16/47 (34%) PM, and 41/351 (12%) O sites ($p < 0.001$). Lesions progressing at time of pre-CAR T PET failed more frequently (41/143, 29%) than those that were stable (20/130, 15%) or new (24/175, 14%) ($p = 0.002$). PFS was worse in pts with EM disease ($p < 0.001$) and >3 lesions ($p = 0.037$) pre-CART. **Conclusions:** EM and PM sites

progressed locally at higher rates than O sites, as did progressive lesions pre-CAR T. PFS was worse in EM/PM sites, suggesting higher risk lesion characteristics for which targeted RT cytoreduction may be beneficial. Further analysis could inform integrating selective site RT pre-CAR T as a bridging intervention.

PA-117

Optimisation of Patient-Reported Outcome Measurement (PROMs) for Patients with Haematological Cancer Receiving CAR-T and Bispecific Antibodies: Multi-Stakeholder Perspectives

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Introduction: Chimeric antigen receptor T-cell therapy (CAR-T) and T-cell engaging bispecific antibodies (BsAbs) are promising treatments for myeloma, leukaemia and lymphoma. However, they are associated with unique toxicities and high symptom burden. Standardised validated quality of life (QoL)/PROM tools are needed that capture the unique treatment related toxicity on QoL. The aim of this project was to explore and understand current experiences and challenges in PROM/QoL for BsAbs and CAR-T treatments in haematology and what can be done to further improve our understanding of patients' experiences. **Methods:** We conducted 2 online workshops and interviews with patients, carers, patient organisations, expert physicians, researchers, industry, regulatory and payer representatives. Thematic analysis was conducted to identify key themes. **Results:** Thirty stakeholders participated in the 2 workshops, and we conducted 15 virtual interviews. Insights included that PROM selection for CAR-T and BsABs therapies is challenging, and no single PROM captures the domains most important to patients. Older general established QoL tools dominate despite their limitations. Capturing real-world patients' specific treatment-related experiences and the broader impacts on emotional, social and mental health is missing. **Conclusions:** New sensitive PROMs tailored to CAR-T and BsAbs are required but harmonisation of QoL measures and follow-up timepoints is needed to optimise current PROM use in clinical trials and routine care in the interim. Continuing to capture patient-centred data on quality of life is invaluable to help build the evidence base whilst new tools are in development.

PA-118

Assessing the Correlation Between Canadian Multiple Myeloma Patients' and Caregivers' Perceived Quality of Life and Assessments of Validated Quality of Life Instruments

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Introduction: Multiple myeloma (MM) patients experience a higher symptom burden and lower quality of life (QoL) than those with other hematologic cancers. The disease also affects families of patients, with caregivers often receiving little guidance or psychological support. While validated patient- and caregiver-reported outcome (PRO and CRO) questionnaires are widely used to assess the QoL of MM patients and caregivers, they were developed before recent therapeutic advances that have altered the disease course. As a result, these tools may no longer fully reflect MM patient and caregiver experiences. **Methods:** A cross-sectional, observational study was conducted across all Canadian provinces in MM patients and caregivers of MM patients to assess the correlation between QoL scores and individuals' perception of QoL. Adult participants were identified through Myeloma Canada's database and data were collected using the PROxy Network web-based platform. All data were self-reported by patients or caregivers and included demographic and disease-related characteristics. Patients completed the EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L, ESAS-R, and a numeric rating scale (NRS) assessing their perceived QoL. Caregivers completed the CarGOQoL and a NRS reflecting their perceived QoL. Both also provided free-text comments specifying how MM has impacted their QoL. Spearman's correlation coefficient was used to examine the strength of the association between the global scores from the questionnaires and the participants' perceived QoL. **Results:** A total of 305 patients (49.8% male; mean age: 65.6 years, Standard Deviation [SD] = 9.0) and 104 caregivers (74.0% female; mean age: 61.6 years, SD = 12.4) participated in the study between October 2024 and February 2025. At the time of the survey, 27.2% of patients and 32.7% of caregivers reported that the patient had experienced a relapse of MM. Correlation analysis revealed a moderate association between patients' self-perceived QoL and each global score from validated PRO questionnaires, with correlation coefficients (r) ranging from 0.59 to 0.65. Notably, even the MM-specific EORTC QLQ-MY20 demonstrated only a moderate correlation with patients' perceived QoL, ranking among the lowest ($r = 0.59$; 95% confidence interval [CI]: 0.51–0.66; $p < 0.001$). The caregiver-reported QoL, as measured by the CarGOQoL, showed a moderate correlation with caregivers' self-perceived QoL ($r = 0.54$; 95% CI: 0.38–0.67; $p < 0.001$). **Conclusions:** The moderate correlations demonstrate that the content of QoL questionnaires for MM patients and their caregivers needs to be adapted to better reflect the evolving

challenges they face. Advances in treatment have brought changes in disease trajectory such as longer survival, evolving side effect profiles, and long-term health issues that are not adequately assessed in current PRO and CRO instruments. Analysis of the comment box section provided insights aligned with the results of the correlation analysis.

PA-119

When ICAN(S) Becomes ICAN'T: Clinician and Staff Perspectives on In-Hospital Neurotoxicity Grading

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Introduction: Guidelines from the American Society for Transplantation and Cellular Therapy (ASTCT) propose use of the Immune Effector Cell-Associated Encephalopathy (ICE) score as a means by which to grade Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). However, ICE scoring may not appropriately capture ICANS among patients with limited English proficiency or diverse educational or cultural backgrounds. With the development of protocols for early ICANS treatment and the advent of CAR-T repurposing for solid tumors, creation of an accessible neurotoxicity grading framework (and an accurate clinical correlate) for all patients is paramount. **Methods:** Using a quantitative and qualitative descriptive study design, we surveyed staff members at a United States safety-net hospital experienced in grading the ICE score. We then performed an iterative thematic analysis of data embedded within free-text responses and used a modified version of the theoretical framework of acceptability to guide evaluation of a future adapted ICE score. **Results:** Of the 36 survey respondents, most (27/36, 75%) agreed that lack of language concordance could lead to inaccurate ICE scores. While translation services were thought to be used appropriately (33/36, 92%), logistical barriers including availability of interpreter services (in-person, phone, iPad) were thought to impact quality of care for non-native English-speaking patients (32/36, 89%). Additional barriers to accurate ICE scoring included patient literacy, numeracy (e.g., cultural differences in measuring time), education level, or disability status (e.g., hearing or vision loss, memory or cognitive impairment). Nearly all participants (32/36, 89%) believed that a modification of the ICE score could improve quality of care, especially for non-native English speakers. Based on the perceived effectiveness of the current ICE scoring metric, staff members proposed suggestions for improvement, including baseline neurological testing and alternative scoring systems to facilitate accessibility. **Conclusions:** This needs assessment demonstrated stakeholder perspectives on the standard ICE score; associated challenges among patients with limited English proficiency and illiteracy; and the utility of an alternative language-concordant and culturally humble grading system for neurotoxicity among non-native English speakers. Based on our needs assessment, we have collaborated with a multidisciplinary team of oncologists and neurologists to design a prototype for a preliminary modification of the ICE score, which we intend to validate in future work.

PA-120

Prognostic of Baseline 18F-FDG PET/CT in Transplant-Eligible Patients with Newly Diagnosed Multiple Myeloma

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Introduction: Bone disease is a hallmark of multiple myeloma (MM), and whole-body imaging plays a key role in staging and prognostication. Among available modalities, 18F-FDG PET/CT uniquely combines anatomical and metabolic information. While previous studies have highlighted the prognostic relevance of parameters such as the number of focal lesions and the maximum standardized uptake value (SUVmax), real-world data remain scarce. **Methods:** We conducted a retrospective study including consecutive transplant-eligible patients with newly diagnosed MM (NDMM) who underwent baseline 18F-FDG PET/CT and received bortezomib-based induction therapy (± anti-CD38 monoclonal antibodies), followed by autologous stem cell transplantation (ASCT) and maintenance, according to an intention-to-treat approach. The prognostic value of the number of focal lesions (FL) (as both continuous and categorical variable) and SUVmax at baseline were assessed. Optimal thresholds for predicting 3-year progression-free survival (PFS3) were defined using receiver operating characteristic (ROC) curve analysis. Associations between PET/CT parameters and PFS3 were explored using logistic regression, adjusted for known prognostic factors. **Results:** A total of 124 patients were included (median age: 58 years; range: 39–73), with a median follow-up of 39 months (IQR 20–75). The median PFS was 74 months (95%CI 36.6–62.3), while median overall survival was not reached. ROC analysis identified ≥4 focal lesions as the optimal cutoff to predict PFS3 (AUC 0.59; sensitivity 55.6%, specificity 58.8%); SUVmax ≥9.2 showed limited prognostic utility (AUC 0.50). In univariate analysis, the presence of ≥4 lesions showed a trend toward inferior PFS3 ($p = 0.18$). However, in multivariate analysis, neither ≥4 lesions ($p = 0.47$) nor SUVmax ≥9.2 ($p = 0.61$) were independently associated with PFS3. In contrast, minimal residual disease (MRD) positivity ($p = 0.009$) and failure to achieve complete response (CR) or stringent CR (sCR) ($p = 0.058$) were associated with poorer outcomes. Notably, quadruplet induction therapy was significantly associated with a reduced risk of progression at 3 years ($p = 0.011$). **Conclusions:** In newly diagnosed, transplant-eligible MM patients, baseline PET/CT findings—particularly the number of focal lesions—may provide valuable prognostic insight. Although not independently predictive in multivariate analysis, ≥4 lesions were associated with a trend toward earlier progression. Our findings emphasize the prognostic impact of deep responses (MRD negativity and CR/sCR)

and the potential benefit of quadruplet induction therapy in mitigating high-risk disease features such as extensive bone involvement. Further large-scale studies are warranted to refine the role of PET/CT in prognostic models for MM.

PA-121

Patient-Reported Quality of Life with Linvoseltamab in Triple-Class Exposed Patients with Relapsed/Refractory Multiple Myeloma: 2-year Results from the LINKER-MM1 Phase 1/2 Clinical Trial

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Introduction: In LINKER-MM1, most patients (pts) with relapsed/refractory multiple myeloma treated with linvoseltamab reported overall improvement or stability in quality of life (QoL), physical functioning (PF), pain, and fatigue over 84 weeks. Here, we present results over 104 weeks. **Methods:** We evaluated 117 pts in LINKER-MM1 who were assigned to receive the 200 mg dose of linvoseltamab. The EORTC QLQ-C30 (global health status [GHS]/QoL, PF, pain, and fatigue) and EQ-5D-3L were conducted at baseline (BL), Week (W) 4, and every 4 weeks thereafter. Least squares (LS) mean change from BL and 95% confidence interval (CI) were estimated at each time point and overall using a mixed effects model for repeated measures; 10- (QLQ-C30) and 12-point (EQ-5D-3L visual analog scale [VAS]) changes were considered clinically meaningful. As there was no adjustment for multiplicity, statistical significance is nominal. Kaplan–Meier curves assessed time to definitive deterioration (TTDD) defined from first dose to first meaningful worsening seen at all later time points or if there were no subsequent assessments. **Results:** Questionnaire completion rates were >80% through W80 and decreased to 52% at W104. LS mean changes showed durable improvement over the treatment duration in key QLQ-C30 scales, including GHS/QoL, with clinically meaningful improvements at W44 (10.0), W92 (12.2), W96 (10.0), W100 (11.9), and W104 (10.1), and EQ-5D-3L VAS, with clinically meaningful improvements at W72 (12.2) and W92 (13.8); pain improvement was meaningful at most time points (W20, −15.6; W24, −13.1; W28, −11.0; W40, −10.1; W52, −13.8; W56, −10.5; W64, −10.0; W68, −12.8; W72, −11.2; W76, −13.4; W88, −14.4; W96, −10.2; W100, −12.7; W104, −11.8). Improvements in PF were seen through W20, and were generally maintained thereafter. Fatigue generally improved from W4 onwards, with clinically meaningful improvements at W68 (−10.1), W72 (−12.0), W76 (−11.6), W100 (−14.0), and W104 (−10.8). LS mean changes from BL reached nominal statistical significance (ie, 95% CI of change did not cross 0) for most weeks after W12 for GHS/QoL, W20 for PF, W16 for fatigue, W8 for pain, and W20 for EQ-5D-3L VAS. Overall LS mean (95% CI) improvement was clinically meaningful for pain (−10.2 [−13.8, −6.6]), and of nominal statistical significance for GHS/QoL (7.0 [5.4, 8.6]), PF (4.5 [2.5, 6.6]), fatigue (−7.4 [−10.0, −4.9]) and EQ-5D-3L VAS (8.0 [5.0, 11.0]). Median TTDD was not reached (>104 weeks). **Conclusions:** Improvements in pt-reported QoL, PF, pain, and fatigue were robust over 2 years of linvoseltamab treatment, complementing clinical benefits and supporting a favorable benefit–risk profile.

PA-122

Inadequate Racial Reporting among References Forming the Basis of NCCN Guidelines for Multiple Myeloma and Systemic Light Chain Amyloidosis

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Introduction: Black individuals make up 13.6% of the U.S. population and account for approximately 20% of new multiple myeloma (MM) diagnoses. The incidence of MM in black individuals is twofold higher compared to white individuals however, the incidence and percentage of blacks with systemic light chain amyloidosis (SLCA) has yet to be defined. The National Comprehensive Cancer Network (NCCN) guidelines are widely used to inform the evaluation, diagnosis and treatment of these conditions. Prior analyses of the International Working Group (IMWG) guidelines have shown poor black representation in supporting studies. We conducted a literature review of the racial demographics of the clinical studies referenced in the 2024 NCCN guidelines for MM and SLCA. **Methods:** 342 references cited in NCCN-MM and SLCA Guidelines Version 4.2024 (283 MM-related, 59 SLCA-related) were analyzed. Five reviewers independently screened and included only original, English-language clinical studies specific to MM or SLCA. Exclusions included review articles, non-clinical studies, commentaries, abstracts, case reports,

animal studies, and duplicate data that was previously referenced. Inter-reviewer concordance was near 100%; discrepancies were resolved by consensus, and racial data were analyzed. **Results:** SLCA: Of 59 SLCA references, 42 clinical studies (4994 patients) met criteria for inclusion in this analysis (20 retrospective studies, 14 therapeutic trials, and 8 prospective observational studies). Only 2 studies (4.8%) reported racial demographics—with ~90% White participants and unclear remaining demographics. The remaining 39 studies (92.9%) did not report information on race or ethnicity. MM: Of 283 MM references reviewed, 187 met the inclusion criteria in this analysis. 133 references had no racial data published and only 38 publications specified the number of Black participants. In the 38 analyzable studies, only 7.6% of participants were Black. Racial reporting has increased over time. From 2000–2004, 1/9 studies reported race data (11.1%), compared to 4/30 studies (13.3%) between 2005–2009, 10/44 studies (22.7%) between 2010–2014, 22/55 (40.0%) between 2015–2019, and 17/44 (38.6%) between 2020–2024. **Conclusions:** Black individuals are underrepresented in the clinical evidence base used to construct NCCN guidelines for MM and SLCA. Within the NCCN guidelines for SLCA, there was no published data on the inclusion of Blacks. While racial reporting in MM studies has improved over time, the proportion of Black participants remains far below the true incidence of the disease. To improve equity and relevance, we encourage the NCCN to champion the mandatory reporting of racial demographics in cited studies and to promote more representative patient enrollment that aligns with disease prevalence across racial groups.

PA-123

Optimizing Skeletal Health: A Retrospective Analysis of Bone-Modifying Agent Prescription Patterns and Incidence of Skeletal-Related Events in Multiple Myeloma

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Introduction: Skeletal-related events (SREs) in multiple myeloma (MM) contribute to significant morbidity. Bone-modifying agents (BMAs) are a fundamental component of bone disease treatment in MM. The impact of BMA prescribing patterns on SREs remains an area of ongoing investigation. The primary aims of this study are to investigate adherence to the International Myeloma Working Group (IMWG) guidelines for BMA use, assess delays or omissions in BMA initiation and examine the incidence of SREs following BMA treatment. **Methods:** We conducted a retrospective study that included all newly-diagnosed and relapsed/refractory MM patients seen at a single academic cancer center between 04/28/2018 to 01/06/2025. Patients with diagnosis other than MM, less than 1 year of follow-up after diagnosis, and no MM treatment were excluded. Time from diagnosis to BMA initiation and reason for delay were evaluated, as well as rationale for switching between different BMAs. BMA administration was evaluated for compliance with the 2021 IMWG guideline. Total numbers of SREs were calculated and stratified by duration of BMA use, and new SREs after BMA use were assessed. **Results:** 127 patients were included in our final analysis. Median age was 67 years and 50.8% were female. 58 (45.6%) developed SREs during the study period, and the majority of these patients (45 patient, 36.2%) only had one SRE event. 44 patients (32.8%) had SRE at baseline (within 60 days of diagnosis). 99 patients (77.9%) were prescribed BMA after diagnosis of MM (73.4% zolendronate and 18.2% denosumab). Among these, 53 patients (53.6%) received BMA within 3 months. 38 (29.9%) had delays in BMA initiation, most commonly due to delayed dental clearance (14, 34.1%), physician decision (5, 12.2%), and patient refusal in (5, 12.2%). A total of 12 patients switched BMA type, with suboptimal eGFR (5 patients, 41.7%) being the top reason. 51 patients (48.1%) received dental screening before BMA initiation. 22 (16.4%) patients developed SREs after BMA treatment, with most events (8 cases, 36%) between 2 and 5 years after the first dose of BMA. 24 (17.9%) patients suffered relapse, among which 18 (75%) received BMA. Number of SREs followed a similar distribution for BMA duration ≥5 years versus <5 years. Overall, 67 (52.7%) patients had BMA prescriptions that deviated from the IMWG guideline, most commonly due to delayed (25 patients, 45.4%) or omitted (22 patients, 40%) administration. **Conclusions:** Less than 50% of BMA prescribing practices were consistent with the guideline. The most common reason for non-compliance was delay or omission in BMA administration rather than BMA frequency or duration. Postponed dental clearance is the most common reason for delay in BMA initiation. More than one-third of patients developed SREs following BMA treatment, particularly between two to five years after the first dose, which is comparable to previous studies. Future studies may look into initiatives to improve guideline adherence.

PA-124

Evaluating the Most Influential Factors in Decision-Making in Women and Men with Relapsed Multiple Myeloma

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Introduction: Gender's influence on treatment decision-making in Refractory/Relapsed Multiple Myeloma (RRMM) presents complex healthcare challenges. This study analyzes gender-based factors affecting RRMM treatment choices. **Methods:** A survey was administered via HealthTree Cure Hub (PMID: 35271305) from February 14 to November 8, 2023. The 30-question survey assessed 11 decision-making domains at treatment changes, categorizing influential factors as treatment-related, patient-related, or myeloma-related. Participants rated influence using a 5-point scale (1 = not influential, to 5 = extremely influential). Patients with ≥1 relapse (RRMM) were stratified by gender (women [F], men [M]). **Results:** Of 688 survey respondents, 289 were RRMM patients (mean age: 66 ± 9 years); 55% were female, 91% identified as White, 5% as Black, 6% as Hispanic or Latino/a, and 48% had a professional school education. Across all surveyed factors, women rated them as equally or more influential than men, with similar top-rated factors within each domain. Among treatment-related factors, both men and women ranked the top four most influential as treatment efficacy (F: 4.3 ± 1.0, M: 4.1 ± 1.1, $p < 0.05$), meeting treatment criteria (F: 3.5 ± 1.4, M: 3.3 ± 1.3, $p < 0.05$), treatment availability (F: 3.4 ± 1.5, M: 3.1 ± 1.5, $p < 0.05$), and potential severity of side effects (F: 3.4 ± 1.3, M: 3.2 ± 1.1, $p < 0.05$). Regarding patient-related factors, both groups ranked the top most influential as the impact on quality of life (F: 3.6 ± 1.3, M: 3.2 ± 1.3, $p < 0.05$) and the ability to care for themselves (F: 3.2 ± 1.4, M: 2.9 ± 1.4, $p < 0.05$). In terms of myeloma-related factors, they ranked the top most influential as relapse aggressiveness (F: 3.3 ± 1.8, M: 2.8 ± 1.8, $p < 0.05$), duration of previous treatment response (F: 2.7 ± 1.7, M: 2.5 ± 1.6, $p < 0.05$), and level of organ involvement (F: 2.6 ± 2.0, M: 2.3 ± 1.9, $p < 0.05$). **Conclusions:** The survey results indicate that both men and women consider similar factors as the most influential in their treatment decision-making process following a multiple myeloma relapse. The treatment-related factors include treatment efficacy, meeting treatment criteria, treatment availability, and the potential severity of side effects. For patient-related factors, both genders emphasized the impact on quality of life and the ability to care for themselves as crucial. In the myeloma disease-related factors, they highlighted the aggressiveness of the relapsing myeloma, the duration of previous treatment response, and the level of organ involvement as critical. Statistically significant differences were observed between men and women in their ratings of all these factors, with women consistently rating them slightly higher.

PA-125

Physical Activity Patterns, Barriers, and Motivators in Multiple Myeloma and Precursor Disease Patients: A Cross-Sectional Survey

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Introduction: While exercise improves physical and emotional outcomes in patients with multiple myeloma (MM), little is known about actual activity levels and perceived barriers in this population and those with precursor conditions such as smoldering MM (SMM) or monoclonal gammopathy of undetermined significance (MGUS). Identifying these gaps is crucial for tailoring supportive interventions and improving patient-reported outcomes in MM care. **Methods:** We conducted a cross-sectional, IRB-approved survey of adult patients (≥18 years) with self-reported MM or precursor disease diagnoses, using the International Physical Activity Questionnaire (IPAQ) and custom barrier/motivator Likert items. Patients were categorized by total weekly metabolic equivalent (MET)-minutes, low (<600 MET-minutes/week), moderate (600–2,999 MET-minutes/week) and high (≥3,000 MET-minutes/week). Barriers and motivators were assessed using 5-point Likert scales. Quantitative differences across groups were tested using chi-square or nonparametric comparisons. **Results:** Of 883 respondents, 432 (49%) reported high activity levels, 273 (31%) moderate, and 178 (20%) low. 490 respondents self-reported their diagnosis, MM 434 (89%), SMM 41 (8%), and MGUS 15 (3%). Among MM patients (n = 434), only 52 (12%) met or exceeded recommended physical activity levels (≥600 MET-min/week), compared to 25/56 (45%) of SMM and MGUS patients combined ($p < 0.001$). The median MET-min/week for vigorous activity in the high group was 1,920 (Q1–Q3: 720–3,600), moderate activity 1,290 (480–2,520), and walking 1,386 (594–2,772). Mean sitting time was 5.7 ± 3.6 hr/day across all respondents, with MM patients sitting longer than precursor counterparts ($p < 0.05$). The most endorsed barriers to exercise among all patients included lack of energy (n = 412, 58%), lack of motivation (n = 347, 49%), and illness-related limitations (n = 328, 46%). Among MM patients, 273 (63%) reported fatigue as a key barrier compared to 35 (46%) of precursor patients ($p = 0.01$). Only 9 (1%) reported that their physician advised against exercise. Top motivators included improving physical health (n = 386, 58%) and mental health (n = 319, 48%). Among highly active respondents (n = 432), 237 (73%) strongly agreed that they exercised for physical health benefits, compared to 26 (22%) of those in the low activity group (n = 178). **Conclusions:** This large cohort analysis reveals that most MM patients do not meet recommended physical activity levels, primarily due to fatigue and lack of motivation. In contrast, patients with precursor conditions reported higher activity levels and fewer limitations. These findings emphasize the need for MM-specific supportive interventions, including fatigue-adapted regimens and counseling, to address both perceived and actual limitations. Our data support integrating physical activity promotion into MM care pathways and provide a foundation for future interventional studies.

PA-126

Post-Traumatic Growth, Flourishing, and Spiritual Practice Among Adults with Blood Cancer: A Patient-Reported Wellbeing Cross-Sectional Study

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Introduction: A diagnosis of blood cancer can affect emotional, social, and spiritual wellbeing alongside physical health. Some patients describe post-traumatic growth (PTG), meaning personal development such as greater appreciation for life or stronger relationships after serious illness. Others report flourishing, a broad sense of wellbeing across life satisfaction, purpose, emotional stability, and connectedness. This study evaluated PTG, flourishing, and spiritual or religious practices among adults with blood cancer using validated patient-reported measures. **Methods:** Adults (≥18 years) with self-reported blood cancer or precursor conditions enrolled in the HealthTree Cure Hub registry completed a cross-sectional survey. Instruments included the 10-item Post-Traumatic Growth Inventory–Short Form (PTGI-SF), 10-item Flourishing Index, and items on belief in a higher power and frequency of private spiritual or religious practices. Descriptive and exploratory statistical analyses were conducted. **Results:** Among 624 respondents (mean age 67.3 ± 9.2 years; 59% female), 469 (75.2%) completed the survey. 87% reported being diagnosed with Multiple Myeloma, 6% CLL, 4% MDS, and 3% other blood cancers. PTG indicators were common: 79% reported increased appreciation for life, 76% noted shifts in priorities, and 64% reported stronger relationships and improved coping. The average Flourishing Index score was 72.3 ± 12.3 (out of 100). Highest domain scores included: purpose (7.6 ± 1.7), mental health (7.4 ± 1.8), satisfaction (7.2 ± 1.9), happiness (7.1 ± 2.0); physical health was lower (6.3 ± 2.2). Most (n = 421; 83%) stated their life feels worthwhile. Belief in a god or a higher power was reported by 79% (n = 376); 63% (n = 305) engaged in private religious/spiritual practice at least monthly. Among those who believed in God (n = 383), 65% described the relationship as warm and supportive. Women scored higher on total flourishing (73.1 ± 12.1) than men (70.4 ± 12.6), a significant difference ($p = 0.03$). No differences were found across age quartiles ($p = 0.27$). **Conclusions:** In this large national registry sample, a substantial proportion of adults with blood cancer reported indicators of psychological growth and meaningful engagement with life, despite serious illness related distress. These results reinforce that wellbeing and distress can coexist, and that many patients experience purpose, emotional strength, and connection. Spiritual belief and practice emerged as relevant supports, and meaningful dimensions of patient experience. Incorporating structured psychosocial and spiritual assessments into care may better support the emotional and existential needs of patients throughout their cancer journey. Further research should examine how these self-reported outcomes relate to clinical stage, treatment decisions, and survivorship.

PA-127

Survey-Based Research into Patient-Physician Communication and Treatment Decision-Making Preferences in Newly Diagnosed Multiple Myeloma

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Introduction: We aimed to clarify the realities of patient-physician communication and investigate changes in patients' expectations, emotions, knowledge, and decision-making preferences during treatment for newly diagnosed multiple myeloma (NDMM). **Methods:** An observational survey was conducted between September and November 2024 in Japan. Patients with NDMM who had not received hematopoietic stem cell transplantation completed a 34-item survey covering communication status, treatment expectations, values, emotions, disease knowledge, and decision-making preferences. Hematologists completed an 18-item survey on their perspectives about communication and treatment decisions. Responses were analyzed in two phases: at start of treatment and at disease stabilization. **Results:** A total of 220 patients (median age: 73.5 years) and 120 hematologists were included. Most patients had been diagnosed with multiple myeloma for ≥3 years. Common induction regimens reported by patients were Bd (bortezomib, dexamethasone) (19.1%), DLd (daratumumab, lenalidomide, dexamethasone) (11.8%), and Ld (lenalidomide, dexamethasone) (11.4%). Both at the start of treatment and at disease stabilization, the proportion of patients being presented or receiving explanations about treatment options was 45.9% and 50.3%, respectively, and those asked about their preference was 23.6% and 25.2%, respectively. Conversely, these proportions were notably higher for physicians at the start of treatment and at disease stabilization: 82.5% and 65.0% presented or explained about treatment options, and 67.5% and 50.8% asked for patients' preferences, respectively. Overall, the number of negative emotions (e.g. "worried" and "confused") significantly decreased at disease stabilization ($p < 0.001$), whereas the number of positive emotions (e.g. "optimistic/hopeful," "confident," and "excited)," which were initially low, significantly increased ($p < 0.001$). Patients' knowledge about the disease and treatment options significantly increased from the start of treatment to disease stabilization ($p < 0.001$), with "some" or "detailed knowledge" rising from 15.0% to 75.0% for the disease

and from 15.0% to 62.7% for treatment options. Patients' expectations for most treatment attributes, such as "improved quality of life," "longer survival," and "long time to recurrence," increased from the start of treatment to disease stabilization. Nearly half of patients (44.5%) preferred a shared role in decision-making; however, in actual practice, the proportion of patients who had a shared role was 21.8%. **Conclusions:** A disparity was observed in perceptions of communication between patients and physicians, and patients' expectations, emotions, and knowledge changed from the start of treatment to disease stabilization. Physicians should recognize these changes in patients and communicate more effectively about treatment options and plans at each treatment phase, including when the disease is stabilized.

PA-128

Measles Antibody IgG Levels in Treatment Exposed Patients with Multiple Myeloma

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Introduction: As of May 2025, the United States has reported over 1,046 confirmed measles cases across 31 states, surpassing the 285 cases reported in 2024. Ninety-seven percent of cases are in unvaccinated individuals. Eleven percent of cases required hospitalization, and three cases resulted in death (Centers for Disease Control and Prevention, 2025). The measles, mumps, and rubella (MMR) vaccine is contraindicated in patients with multiple myeloma (MM) within two years post autologous stem cell transplant (ASCT) due to immunosuppression caused by myeloablative chemotherapy. Two years post ASCT, many patients cannot receive the MMR vaccine because of ongoing immunosuppressive therapy for which live vaccines remain contraindicated. In addition, the impact of immunotherapies on measles immunity has not been reported. We sought to better understand immunity to measles in patients with MM to assess risk as measles rates rise. **Methods:** Data was collected via chart extraction using the electronic medical record from February to May 2025. The sample included patients with MM treated at the Wilmot Cancer Institute who expressed concern about contracting measles. Data was collected about diagnosis, time since diagnosis, duration on MM therapy, current treatment regimen, time on current treatment regimen, ASCT history, chimeric antigen receptor t-cell therapy history, intravenous immunoglobulin (IVIG) infusion history, measles antibody IgG level, and post ASCT MMR vaccine history. Patients with MM or Smoldering MM were included. Our review was limited by not knowing original vaccination status and antibody levels. **Results:** Twenty-one patients requested measles IgG antibody levels. Of this sample, ten patients had negative or equivocal results, indicating inadequate antibodies toward the measles virus. Of those with negative results, the time since diagnosis ranged from 13 to 117 months and 70% had ASCT. In addition, 90% of these patients remain on treatment and 80% are not eligible to receive MMR vaccine due to treatment related immunosuppression. Fifty-five percent of patients on daratumumab had negative results and 44% of patients who had ASCT had negative results. Among patients who have received IVIG, 75% had positive levels. Of the two patients that did receive post-transplant MMR vaccination, one had a positive result. The patient with a negative result received a second ASCT after MMR vaccination. We will continue to check for late breaking data through 8/31/25 and fully characterize patients with and without immunity. **Conclusions:** Patients with MM are at an increased risk of contracting measles due to immunosuppression and research is needed to determine which patients are at highest risk. Updated clinical guidelines are needed for re-vaccinating patients post-ASCT while on active therapy. Research toward other means of protection for patients, such as the use of IVIG, may help safeguard this at-risk population.

PA-129

Co-Designing an Implementation Strategy for a Nurse and Pharmacist-Led Intervention Addressing the Long-term Needs of Patients Living with Multiple Myeloma (MM)

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Introduction: People living long-term with myeloma are at an increased risk of cardiovascular disease, secondary primary malignancies, infections, and age-related health issues. The aim of this study is to apply implementation science methods to co-design and develop a strategy for embedding a nurse and pharmacist-led intervention into routine follow-up care for people living with MM in preparation for a pilot feasibility study. **Methods:** A qualitative study was conducted to inform the development of an implementation strategy for a nurse and pharmacist-led intervention addressing the long-term needs of people living with MM. The first phase involved co-designing the intervention with key stakeholders. Three focus groups were conducted with 14 multidisciplinary participants, including clinicians and service administrators from the multiple myeloma (MM) service. Data were analysed using a deductive approach, guided by the Action, Actor, Context, Target, and Time (AACTT) framework. This framework was used to map existing care pathways and specify preferred implementation strategies, including 'who' should perform specific actions, 'what' they should do, 'when' and 'where' it should occur, and 'to whom' it should be directed. **Results:** Participants identified changes required to embed the intervention into routine follow-up care. The haematologist was identified as a key stakeholder

of the MM team to introduce the intervention to the patient. Patients who were greater than 3 months into maintenance treatment and with stable disease were identified as eligible for the intervention. A referral was generated by the haematologist to the MM specialist nurse who triaged the referral and requested the administration team to book consecutive pharmacist and nurse clinic appointments. Patient reported outcome measurements (PROMs) including MYPOS, Brief Fatigue Inventory and COST FACIT 2, were sent to the patient by the MM specialist nurse 1–2 weeks prior to the clinic appointment. The pharmacist-led review involved a comprehensive medication review including assessing supportive care prescribing, drug interactions, patient adherence and symptom management, as well as supporting medication management and education. The nurse-led review undertook a comprehensive health assessment informed by the PROMs and with a distinct survivorship focus including adherence to vaccination, recommended cancer prevention screening, modifiable cardiovascular risk factors and promoting healthy lifestyle behaviours. A care plan was developed with a set of recommendations which was sent to the patient, their GP, the haematologist and other health care providers involved in patient's care. **Conclusions:** This implementation strategy provides a systematically structured approach to delivering an intervention that is aligned with what is acceptable and feasible for clinicians in the MM team; and offers an assessment of the long-term needs of patients living with MM.

PA-130

Melphalan Induced Intestinal Mucositis in Autologous Hematopoietic Stem Cell Transplant: Rapid Response to Short Course of Oral Budesonide

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Introduction: Approximately, 40% of patients receiving high dose melphalan (HDM) develop grade III or IV diarrhea (CTCAE 5.0) that promptly improves upon neutrophilic engraftment. Persistence of grade III-IV diarrhea beyond 24 hours post engraftment results in significant morbidity and prolongs hospitalization. **Methods:** Histopathologic finding of colonic crypt inflammation in a patient with persistent diarrhea (first on table 1), led to use of short course of oral budesonide (BUD) resulting in rapid and sustained resolution of diarrhea. We here, document 20 such cases and discuss its role in reducing morbidity and duration of hospitalization. Persistent grade III–IV diarrhea 24 hours after neutrophil engraftment defined persistent diarrhea from melphalan. Infectious workup including stool examination for salmonella, shigella, rotavirus, cryptosporidium, clostridium difficile were performed. **Results:** The median age of 20 patients was 66 (range, 44–74) years, (Females = 10, Males = 10). A total of 10 patients with multiple myeloma (MM) received melphalan 200 mg/m^2. A total of 4 MM patients 140 mg/m^2 (Age = 3, renal failure = 1) as did 6 patients with lymphoma/leukemia (table 1). Median time to neutrophilic engraftment following autologous stem cell transplant (ASCT) was day +12 (range, 9–13) days. Colonoscopy in one patient (first patient in table 1) confirmed patchy crypt apoptosis and crypt abscess formation. Standard supportive care including antidiarrheals offered no improvement. Oral budesonide (BUD) at 3–9 mg daily was introduced at median of 2 (range, −4 to11) days after engraftment in 14 patients. Based on the established safety of post engraftment BUD, a total of 6 patients received BUD pre-engraftment. Median time for diarrhea improvement was 1-day (range, 1–7) days. The median duration of BUD administration was 2 (range, 1–13) days. Median time to discharge from BUD initiation was 2 days (range 1–7). One patient was excluded from analysis as his stool tested positive for rotavirus; he too promptly responded to BUD. The median cumulative dose of BUD was 18 mg (range, 9–60). **Conclusions:** We believe that reduction in gut inflammation by BUD improves melphalan induced intestinal mucositis. Neither pre-engraftment nor post-engraftment BUD produced any untoward effects from short courses of BUD. Oral BUD results in rapid resolution of lower GI toxicity of HDM, facilitates discharge and lowers cost of hospitalization.

PA-131

Gender Disparities in Sexual Health Communication Among Patients with Multiple Myeloma: a HealthTree Patient Based Survey Study

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Introduction: Sexual health is a critical yet frequently overlooked component of comprehensive care for individuals with multiple myeloma (MM). Only a single study (Henkelman et al, J Psychosoc Oncol Res Pract 2023) has investigated sexual health in a small cohort of 25 women and 40 men with MM; in this survey-based study, patients reported that their symptoms were underaddressed by providers. We sought to examine these findings in a larger cohort with a focus on gender-specific and age-specific differences in sexual health and communication with providers. **Methods:** This was a cross-sectional survey of patients with MM using the HealthTree Cure Hub platform. Statistical analyses, including chi-squared tests and regression models, were used to identify trends between groups. **Results:** Responses from 345 MM patients (164 women, 181 men)

were analyzed. The median age was 66 years, with female respondents younger (62 vs. 68, $p < 0.001$) and diagnosed at an earlier age (57 vs. 61 years) than male respondents. Survey completion rates were 72% versus 83% for women and men, respectively. Moderate to major impacts on sexual health related to MM or its treatment were reported by 72% of women and 71% of men. Top concerns among women were decreased libido (64%), vaginal dryness (55%), and arousal (46%). For men, top concerns were erectile dysfunction (58%), decreased libido (54%), and arousal (43%). Among women aged <55, 52% reported a major impact versus 33% aged ≥65 ($p = 0.017$); among men aged 55–64, 63% reported a major impact versus 37% aged ≥65 ($p = 0.014$). Among patients aged <55 at submission, 3% of women and 25% of men reported fertility concerns at diagnosis. Men were more comfortable than women discussing sexual health with their MM care team (75% vs. 45%, $p < 0.001$) and were more likely to initiate the conversation (36% vs. 24%, $p = 0.043$). Among symptomatic respondents, only 16% of women received vaginal hormone therapy, whereas 68% of men received treatment for erectile dysfunction. **Conclusions:** Sexual health is affected by MM or its treatment in both male and female patients, but the pattern of negative impact is much more prominent in patients aged <65. We found substantial gender disparities in communication regarding sexual health. Despite similar prevalences of vaginal dryness in women and erectile dysfunction in men, women were much less likely to receive treatment. Despite data that vaginal hormonal therapy does not increase the risk of venous thromboembolism (Svendsen, Basic Clin Pharmacol Toxicol 2021), vaginal hormonal therapy is being utilized in only a minority of female patients despite its potential role in managing sexual health concerns. While limited by survey response bias, our study highlights the need for prospective gender and age-specific guidance around sexual health in MM.

PA-132

Current Survival and Causes of Mortality of Myeloma Patients in Real Word Setting

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Introduction: Therapy of multiple myeloma (MM) is constantly improving, and the overall survival (OS) rate is now over 5 years with many patients (pts) living 10 years or more. The rate of comorbidities at time of MM diagnosis is estimated to be 54%; with longer survival rates this finding impacts the long-term clinical management of these pts. In our study we aimed to evaluate the OS of MM pts and identify causes of death in a real-world setting. **Methods:** This retrospective chart review included patients diagnosed with MM between 2000–2023 treated at our regional cancer center, serving a population over 500,000, both urban and rural. Pts with solitary plasmacytoma or amyloid, who has not progressed to symptomatic myeloma, and those who received <1 cycle of therapy were excluded. Treatment was provided via standard provincial public funding programs. Causes of death were assessed by electronic medical records. If a pt had progressive myeloma at the time of death, the cause of death was considered related to myeloma, irrespective of reported cause. OS was calculated by Kaplan-Meier curves from time of anti-myeloma therapy initiation until the last assessment (cut off May 05, 2025) or death. **Results:** 429 pts were evaluated. Median age was 68 [range 41 to 96] years, male/female ratio 1.4 : 1. 13.5% of MGUS/smoldering myeloma or isolated plasmacytoma pts progressed to symptomatic myeloma. IgG myeloma was the most common subtype (47.3%), followed by non-IgG (20%) and free light chain (20.9%) isotypes. 68.54% of pts had standard-risk FISH/cytogenetics while 18.4% had known high-risk (del17p and/or t[4;14]) features. 254 patients died. While MM was most common cause of death (33.6%), most pts died from non-MM related causes, including failure to thrive (22.05%), infections (17.71%), secondary malignancies (8.66%), cardiac issues (7.48%), bleeding (5.12%), and non-infectious respiratory causes (4.33%). Disease status at the last assessment included: CR/VGPR in 57.58%, PR/stable disease in 19.11% and myeloma progression in 23.31% of the pts. Median OS for all pts was 76 months [2–282]. Patients with standard-risk FISH/cytogenetics had median OS of 88 months [2–282], compared to 60 months [2–211] in the high-risk group. A subgroup of pts with 13q- only (assessed by metaphase karyotyping), had an OS of 79 months [3–163]. **Conclusions:** In the community setting pts with MM, even with high-risk disease, typically survive more than 5 years. The majority (over 66%) die from non-MM-related causes. This observation emphasizes the importance of recognizing comorbidities and utilizing multidisciplinary care for pts with this malignancy.

PA-133

Update of the EORTC Quality of Life Multiple Myeloma Module (EORTC QLQ-MY20). Results from the Phase I-II EORTC Prospective Study

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Introduction: The European Organization for the Research and Treatment of Cancer Myeloma module (EORTC QLQ-MY20), used alongside the EORTC QLQ-C30 core questionnaire, was published in 1999 to assess health-related quality of life in patients with multiple myeloma (MM). Since its development, major advances in the MM treatment at diagnosis and following multiple subsequent relapses, have improved the survival rates. To ensure the EORTC QLQ-MY20 remains relevant and captures the disease and treatment experience, and to address limitations of the original module, a Phase I-II prospective study was conducted. Structured interviews with MM patients and MM expert healthcare professionals were conducted to inform module modification. **Methods:** The module update was conducted in accordance with the EORTC Quality of Life Group module development guidelines. Following the conduct of two literature reviews, collating a list of concepts, and identifying methodological problems with the original module, and a review of side effects of MM treatments, qualitative interviews took place with n = 93 patients and n = 20 healthcare professionals across Europe (7 countries) and the Middle East (1 country), to assess the relevance/importance of the concepts and to elicit any further concepts for consideration. Concepts rated as sufficiently relevant/important according to a priori criteria were used to create a conceptual framework. **Results:** 20 issues met the criteria for importance and relevance from the patient and healthcare professional interviews and were deemed to be specific to MM and/or MM treatment; 11 items were from the original QLQ-MY20 and 9 were new concepts. 9 items from the original module were removed as they were not deemed sufficiently relevant/important and/or were not specific to MM. Items were refined based on discussions with collaborators and EORTC feedback, resulting in 24 items (QLQ-MY24); a conceptual framework was developed to illustrate the groups of items hypothesized to measure similar concept/symptom domains. These groups of items included: pain, neuropathy, infection, oedema, tiredness, weight loss, ocular, oral, restlessness/agitation, and hair loss. **Conclusions:** This prospective study has identified items relevant and important to MM patients' QOL in the era of new therapeutic approaches. Next steps in phase III, will include debriefing interviews with patients with MM to identify and rectify potential problems in administration and to identify missing/redundant concepts. Preliminary evaluation of psychometric properties and international validation field testing of the new proposed updated QOL module is then expected.

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Factors Influencing the Outcome of Salvage Second Autologous Stem Cell Transplant in Relapsed Multiple Myeloma

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Introduction: Salvage second autologous stem cell transplantation (ASCT2) is a therapeutic option for relapsed multiple myeloma (MM) following a prolonged response to initial autologous stem cell transplantation (ASCT1). However, its clinical relevance remains debated in the era of novel therapies, including anti-CD38 agents and immunotherapies. **Methods:** This retrospective study analyzed MM patients who underwent ASCT2 after relapse post-ASCT1 at our center from January 2007 to March 2025. Median progression-free survival (PFS), overall survival (OS), and PFS2 (time from ASCT2 to progression) were estimated using the Kaplan-Meier method. Patients were stratified into two groups based on PFS2 (≥6 months vs. <6 months) to compare clinical characteristics. **Results:** Among 26 enrolled patients, the median follow-up was 78.5 months (IQR 64–115). The overall median PFS and OS were 30 (IQR 10–65) and 48 (IQR 27–67) months, respectively. Using a PFS2 cutoff of 6 months, 20 patients were classified into the PFS2≥6-month group and 6 patients into the PFS2 <6-month group. Compared to the PFS2 ≥6-month group, the PFS2 <6-month group exhibited younger median age at diagnosis and ASCT1, higher serum calcium at relapse, higher prevalence of extramedullary disease (EMD) at diagnosis and relapse, and increased incidence of infections within 100 days post-transplant ($p < 0.05$). No significant differences were observed in sex, M-protein type, hemoglobin levels, creatinine levels, albumin levels, β2-microglobulin levels, plasma cell percent of bone marrow, induction efficacy post-ASCT2, maintenance therapy, use of novel agents after first relapse, conditioning regimens, hematopoietic recovery time post-ASCT2, or intertransplant interval. Multivariate analysis confirmed younger age at diagnosis, elevated serum calcium at relapse, EMD at diagnosis and relapse, and post-transplant infections as independent risk factors for PFS2 ($p < 0.05$). **Conclusions:** In MM patients undergoing ASCT2, younger age, hypercalcemia at relapse, and extramedullary infiltration correlate with inferior PFS2.

PA-135

Evaluating the Efficacy and Tolerability of PJP prophylaxis with TMP-SMX in Autologous Stem Cell Transplants for Lymphoma or Myeloma: A Retrospective Cohort Study

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Introduction: Patients undergoing allogeneic (HSCT) and autologous stem cell transplantation (ASCT) are at increased risk of Pneumocystis jirovecii pneumonia (PJP). Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended as PJP prophylaxis for patients undergoing HSCT; its routine use in ASCT is debated. The aim of this study is to evaluate the efficacy and safety of TMP-SMX prophylaxis post-ASCT, facilitated by local practice changes when routine prophylaxis was implemented in October 2020. **Methods:** This retrospective study included consecutive adults undergoing ASCT for myeloma or lymphoma. Outcomes were compared between two cohorts: patients prescribed PJP prophylaxis with TMP-SMX for 3 months, and those who were not prescribed prophylaxis. The primary outcomes were rate of PJP infection and all-cause mortality at 3 months post-ASCT. Secondary outcomes included rates of PJP-related mortality, transfusion, rehospitalization, adverse effects and adherence. Laboratory values were collected prior to starting prophylaxis, at 1- and 3-months post-ASCT. Statistical analyses were performed using proportion or Fisher's exact tests for categorical variables, and t-tests, Wilcoxon-Mann-Whitney, Negative Binomial Regression or ANOVA for continuous variables with RStudio (v1.4.1717). **Results:** A total of 199 patients were included, with 86 in the TMP-SMX prophylaxis cohort (median age 64, range 22–75), and 113 in the no prophylaxis cohort (median age 63, range 34–75). Rate of adherence to TMP-SMX prophylaxis was 87%. Reasons for discontinuation included neutropenia (3), pancytopenia (1), gastrointestinal effects (3), rash (1), dyspnea (1), and missed prescriptions (2). No cases of PJP occurred in the no prophylaxis cohort. There was 1 case of presumed PJP infection in the prophylaxis cohort in a patient who stopped prophylaxis due to intolerance. There was no significant difference in all-cause mortality between cohorts in the first 3 months post-ASCT. There were no PJP-related deaths. There were 24 infections in prophylaxis cohort and 36 infections in no prophylaxis cohort ($P = 0.88$). Rate of rehospitalization was 10% higher in the prophylaxis cohort ($P = 0.048$), with no differences in length of hospitalization per patient ($P = 0.28$) or rate of ICU admission ($P = 0.66$). There were no significant differences in hemoglobin, platelet, and neutrophil levels between cohorts ($P > 0.20$). Similarly, no significant differences were observed in red blood cell and platelet transfusions during the first month between the cohorts ($P = 0.06$, 0.74 respectively). There was 1 case of acute kidney injury in the prophylaxis cohort and 2 cases in the no prophylaxis cohort. **Conclusions:** TMP-SMX can be considered in post-ASCT where it is well tolerated with minimal adverse events and high rates of adherence. Further study with a larger prospective population is needed to capture sufficient cases of PJP and determine the impact of TMP-SMX prophylaxis on reducing PJP-related morbidity and mortality.

PA-136

An Effective Lenalidomide Desensitization for Delayed Hypersensitivity-Induced Rash in Patients with Multiple Myeloma

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Introduction: Lenalidomide is a standard of care in newly diagnosed multiple myeloma (MM). Some MM patients might develop delayed hypersensitivity to lenalidomide, which can lead to treatment discontinuation. Desensitization to lenalidomide can help these patients to complete treatment courses. Here, we aimed to review lenalidomide-treated MM patients who developed delayed hypersensitivity-induced rash were treated with desensitization. **Methods:** We have developed and are using a desensitization protocol for patients who developed delayed hypersensitivity after using lenalidomide since 2022. A retrospective analysis of medical files of MM patients, who were desensitized by this protocol. Patients were treated between March 2022 and December 2024. A desensitization protocol was performed on patients with lenalidomide-induced delayed hypersensitivity accompanied by skin rash and itching of grade 2 or higher. Desensitization was designed as a 21-day protocol to reach the dose of 25 mg. The starting dose was 0.1 mg in a dilution of 0.4/100 of the target 25 mg, escalating gradually. Once the target dose was tolerated, the modified tailored protocol was maintained in the following cycles. **Results:** During the study period, a total of 114 patients were newly diagnosed with multiple myeloma. All of them received chemotherapy including lenalidomide as first-line treatment. Delayed hypersensitivity to lenalidomide like urticaria, eczematous rash, or maculopapular erupotions occurred in 33 patients who received lenalidomide-based chemotherapy as first-line treatment. Among the 33 patients, lenalidomide desensitization was performed on 14 patients with severe symptoms. The median age of these patients was 65 years (range, 52–82 years). Of these, 8 received RVD regimen and 6 received Rd regimen. The median dose of lenalidomide administered to them was 22 mg/day, and the median time to onset was 14 days (range, 7–35 days). Of the 14 patients, 12 (85.7%) succeeded in completing the protocol and thus were able to continue lenalidomide treatment cycles. The 12 patients tolerated their target dose. Because itching was a common adverse effect of lenalidomide, antihistamines were used to control itching for all enrolled patients, and for patients with skin eruption of grade 2 or 3, low-dose steroids were used concurrently. None of the patients that were treated with desensitization had severe immune-mediated or non-dermatologic adverse reactions. Of the two patients in whom lenalidomide desensitization failed, one developed grade IV skin eruption and received high-dose steroid therapy, and the other patients continued to have itching, leading to discontinuation of lenalidomide in both patients. **Conclusions:** Desensitization to lenalidomide is safe and effective. Desensitization of lenalidomide-induced delayed

hypersensitivity can reduce lenalidomide discontinuation and allow for more effective treatment of multiple myeloma.

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Predicting Early Mortality Risk in Newly Diagnosed Multiple Myeloma Patients

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Introduction: The overall survival of patients with multiple myeloma (MM) has markedly improved over the last three decades with the widespread adoption of novel agents. However, a subset of newly diagnosed MM patients continues to experience early mortality. This study aims to identify risk factors associated with early mortality in patients with MM. **Methods:** We included consecutive patients with newly diagnosed MM at Taipei Veterans General Hospital in Taiwan between November 1, 2002 and April 30, 2025. Patients lacking histopathologic confirmation were excluded. Early mortality was defined as death occurring within 60 days of initial diagnosis. Risk factors for mortality were assessed using a Cox proportional hazards model. The variables with a p-value < 0.1 in the univariate analysis were included in the multivariate model. **Results:** During the 22-year study period, a total of 754 patients with newly diagnosed MM were enrolled. The median age of the patients was 68 years (range 23–97 years) and 59.4% were male. Early mortality occurred in 79 patients (10.5%). In the multivariate analysis, body mass index (BMI) < 18.5 kg/m^2 (adjusted hazard ratios [HR] 3.29; 95% confidence interval [CI] 1.86–5.81), male sex (adjusted HR 2.58, 95% CI 1.42–4.70), Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (adjusted HR 6.72, 95% CI 3.23–13.97), platelet count < 100,000/μl (adjusted HR 2.07, 95% CI 1.20–3.58), and elevated lactate dehydrogenase (LDH) levels (adjusted HR 1.74, 95% CI 1.02–2.98) were identified as independent predictors of early mortality. **Conclusions:** The early mortality rate remains high (10.5%) in patients with MM. Low BMI, male sex, ECOG performance status ≥ 2, thrombocytopenia, and elevated LDH levels are associated with an increased risk of early mortality. Identification of high-risk patients warrants targeted efforts to develop strategies for prevention, early detection, and effective management to mitigate risk.

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Health-Related Quality of Life in a "Real-World" Cohort of Chilean Patients with Multiple Myeloma

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Introduction: The advances in new therapeutic options in multiple myeloma (MM) have improved survival rates. However, due to the disease itself or its treatment, patients experience deterioration in other physical, social, and emotional aspects, which is why quality of life Health-related quality of life (HRQoL) is an important variable to understand. There is no data on HRQoL in a Chilean cohort. The main aim was to evaluate HRQoL in a consecutive cohort of patients with multiple myeloma (MM) from 2023 to 2024, at different stages of the disease. **Methods:** Observational cross-sectional study. The surveyed patients were divided into newly diagnosed patients (NDMM), refractory or relapsed patients (RRMM), and triple-class exposed or triple-class refractory patients (TCE/TCR), defined as patients who had used at least one IMID, one proteasome inhibitor, and one anti-CD38 monoclonal antibody. Additionally, sociodemographic and clinical data were collected. The EORTC QLQ-C30 questionnaire (for cancer in general), and the MY20, (specific for MM), both validated in Chile, were used. Results were analyzed according to the guidelines of the corresponding EORTC manual. The study was approved by the corresponding ethics committee. **Results:** A total of 186 patients were evaluated. 51.2% were male, with an median age of 68 years. The global HRQoL in the cohort was 56.3 (SD 23.2), with 59.0 (SD 24.4) for NDMM, 52.9 (SD 22.7) for RRMM, and 68.9 (SD 14.4) for TCE/TCR ($p = 0.023$), where the latter group was significantly younger, with ages of 67.8 vs 73.3 vs 55.7 years respectively ($p < 0.001$). In terms of analysis by other subgroups, women had worse perceptions on the physical functioning scale ($p = 0.014$), fatigue ($p = 0.005$), nausea and vomiting ($p = 0.011$), dyspnea ($p = 0.007$), loss of appetite ($p = 0.008$), constipation ($p = 0.014$), adverse effects ($p < 0.001$), and body image ($p = 0.002$). Patients with PS ≥2 had worse perception on the global HRQoL scale ($p = 0.001$), in physical functioning ($p = 0.002$), role ($p = 0.016$), emotional ($p = 0.050$), and cognitive ($p = 0.001$) scales, as well as on the pain ($p = 0.020$), insomnia ($p = 0.045$), and adverse effects scales ($p < 0.001$). By age groups (< 60, between 60 and 75, and > 75 years), worse perception of social functioning ($p = 0.047$), insomnia ($p = 0.014$), and financial difficulties ($p = 0.001$) were observed in those under 60 years old. There were no differences in HRQoL by treatment line, BMI, or education level. **Conclusions:** Global HRQoL was low in these patients, similar to other studies. The best perception was reported by TCE/TCR patients, which may be due to them being younger patients. Women, patients with ECOG PS ≥2, and those < 60 years old have significantly worse perception of

their HRQoL in several aspects. This study sheds light on which groups should be intervened in certain areas of their HRQoL during the course of their illness.

PA-139

Romosozumab for Patients with Multiple Myeloma with Skeletal Events on Zoledronic Acid

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Introduction: Myeloma bone disease (MBD) is found in 80% of patients with newly diagnosed multiple myeloma (MM) and is associated with substantial morbidity and mortality. Bisphosphonates and denosumab, which inhibit bone resorption, are standard of care for treatment and prevention of myeloma bone disease. However these treatments do not replace lost bone or repair bone lesions and 45% of patients will experience a skeletal related event (SRE) despite these therapies. Sclerostin is a protein produced by osteocytes embedded in bone and inhibits bone formation. Anti-sclerostin antibodies alone, and in combination with bisphosphonates, have been demonstrated to improve bone mineral density and fracture resistance in MM mouse models. Furthermore, romosuzumab, an anti-sclerostin antibody, has been demonstrated in Phase III trials to decrease fracture rates in post-menopausal women with osteoporosis. We aim to evaluate the safety and efficacy of romosuzumab in patients with MM who have had a SRE despite bisphosphonate therapy. **Methods:** This is a single arm, pilot study of romosuzumab 210 mg subcutaneously monthly for 12 months in twelve patients who have had a SRE despite bisphosphonate therapy. The primary objective is to determine safety of romosozumab and its impact on bone turnover markers (P1NP and beta-CTx). Secondary objectives are to assess effect of romosuzumab on bone mineral density (BMD) at 6 and 12 months, SRE and myeloma progression free survival (PFS). Patients will have bone marrow biopsies at baseline, cycle 3 and cycle 12 to explore changes in the bone marrow microenvironment and describe interactions between the bone microenvironment and tumour cells. **Results:** At the time of abstract submission, 8 patients have been recruited to this study with a median age of 71. The median line of myeloma therapy at time of consent was 2 (range 1–8). At screening, median T score was 0.6 at the lumbar spine and −1 for mean total hip. Number of lytic lesions on CT skeletal survey was none (n = 1), 1 (n = 1), 1–3 (n = 1) or >3 (n = 5). Two patients experienced local injection site reactions but there have been no other treatment emergent adverse events. Assessment of bone turnover markers demonstrate an increase in the bone-formation marker P1NP with the greatest increase seen four weeks after dose 1 (median % change 185%, range −54% to 350%). and a sustained decrease in the bone-resorption marker beta-CTX. BMD measured at total hip and lumbar spine increased at six (n = 1, 8%) and 12 months (n = 1, 19%) of treatment relative to baseline. There have been no new SREs in participants. **Conclusions:** In this interim analysis romosozumab has demonstrated an increase in bone formation in patients with multiple myeloma previously treated with bisphosphonates. There have been no safety concerns. Further recruitment and analysis will add to this dataset prior to presentation at IMS.

PA-140

Imaging Quality and Detection Ability of Whole-body Low-dose CT for Bone and Extraosseous Lesions in Multiple Myeloma

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Introduction: Since bone disease is the most frequent disease-related condition of multiple myeloma (MM), cross-sectional imaging modalities play an important role in detection of bone disease in MM. While whole-body low-dose CT (WBLDCT) is recommended to assess bone disease by the latest diagnostic criteria of IMWG, there is little information on imaging quality assessment and protocol of WBLDCT for MM bone disease. We herein aimed to evaluate the imaging quality and detection ability of WBLDCT compared with whole-body standard-dose CT (WBSDCT) in MM patients for bone and extraosseous lesions. **Methods:** We retrospectively analyzed MM patients with bone disease who underwent WBCT from January 2020 to May 2025 in Tokushima University. All MM patients underwent both WBLDCT and WBSDCT within one year after diagnosis with 320-rows scanner CT machine (Canon Medical Systems, Otawara, Japan). We calculated the contrast-to-noise ratios (CNRs) of the gluteus medius muscle and lumbar spine (L4) to air in WBLDCT and WBSDCT. Statistical analyses were performed using the Mann- Whitney U test to compare the mean of data between the groups, and Spearman's rank correlation test to assess relationships between quantitative values. **Results:** Thirty MM patients with a median age of 70.5 (range 53–85) were evaluated. R2-ISS was diagnosed with Low, Low-Intermediate, Intermediate-High, and High in 5, 10, 10, and 5 patients, respectively. Radiation exposure dose was significantly lower in WBLDCT than WBSDCT (3.54 ± 1.94 vs 11.54 ± 5.25 mGy, respectively; $p < 0.0001$). Body mass index (BMI) was 24.26 ± 3.91 kg/m^2; radiation exposure dose was proportionally increased with BMI in both WBLDCT and WBSDCT. CT values were 47.66 ± 9.20 vs 45.64 ± 10.88 HU in

muscle (p = 0.610) and 87.96 ± 30.51 vs 92.00 ± 35.67 HU in bone (p = 0.728) by WBLDCT and WBSDCT, respectively. CNRs of muscle and bone were comparable between WBLDCT and WBSDCT (89.89 ± 24.14 vs 103.22 ± 34.38 in muscle [p = 0.072]; 42.77 ± 18.82 vs 43.88 ± 18.04 in bone [p = 0.773], respectively). However, CNRs of muscle in obese MM patients (BMI > 25, n = 11) were significantly lower in WBLDCT than WBSDCT (90.25 ± 18.33 vs 116.95 ± 38.72 in muscle [p = 0.003]). **Conclusions:** Besides generally accepted advantages of lower radiation exposure and ease of use, these results suggest that WBLDCT may provide therapeutically important information on not only bone disease but also lesions outside of bone, including extramedullary disease and other comorbidities in non-obese MM patients. A multi-center prospective study can be warranted to further optimize CNRs in WBLDCT as a whole-body screening modality by low-dose techniques, including tuning radiation doses, especially in MM patients with obesity.

PA-141

The Optimising Outcomes in Myeloma Patients with Frailty (OOMPF) Study

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy, with highest prevalence in elderly people, which is rising due to the globally aging population. Despite rapidly expanding treatment options, their suitability can be variable for older MM patients due to complications such as frailty, often connected with the older age of diagnosis. A variety of frailty assessments exist within MM, but none are routinely used in clinical practice and there is no globally accepted definition of frailty. This likely means that there are challenges for haematology clinicians in assessing frailty, but previous studies do not appear to have explored this. The OOMPF Study aims to explore haematology clinicians' perspectives on frailty and assessing it in people with MM on active treatment. **Methods:** Following institutional ethics approval, semi-structured intervws were undertaken with a purposive sample of UK based haematologists, advanced nurse practitioners, clinical nurse specialists and specialist pharmacists. Participants were recruited through national and local professional networks. The interview topic guide was designed based on the study aims and objectives, literature review, and expert opinion. Topics included the perceived purpose of assessing frailty in MM, perspectives on assessing frailty in routine clinical practice and implementing a standardised approach to MM frailty assessment. Patient and Public Involvement and Engagement was sought through The MyelomaUK Patient and Carers Research Panel, and stakeholder consultation. Interviews were conducted on Microsoft Teams, recorded for verbatim transcription, and analysed using the framework analysis technique. **Results:** Twenty-four interviews were conducted. Participants were spilt across medical (29%), nursing (33%) and pharmacy (38%). Participants reported that frailty assessment in MM tended to be either a subjective visual observation to provide a basis for making treatment decisions or, less commonly, a standardised holistic assessment process. Issues related to assessing frailty in MM patients were reported to include: no consensus on the definition of frailty; how it should best be assessed or whose role it should be to assess it. Participants identified various challenges in implementing a standardised frailty assessment for MM patients routinely, which were grouped as being logistical, behavioural, or attitudinal in nature. **Conclusions:** This is the first study to our knowledge exploring haematology clinicians' perspectives on frailty assessment for people with MM and the findings indicate that challenges particularly exist in how to define frailty and the best means of assessing it. Limitations included the potential for selection bias, and a high participation rate from England. Nevertheless, the findings suggest a need for development of an agreed definition of frailty in MM and an acceptable means of assessing it for use in routine practice.

PA-142

Assessment of Extraosseous Multiple Myeloma Using Whole-Body Imaging Techniques: PET/CT, MRI, and MIBI

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Introduction: The presence of extraosseous manifestations (EM) in multiple myeloma (MM), including both paramedullary and extramedullary involvement, is a significant negative prognostic factor. However, the detection of EM is limited by the variability and sensitivity of imaging techniques. Conventional X-ray imaging has very low sensitivity; therefore, more advanced whole-body imaging modalities are recommended. Our aim was to compare the efficacy of three whole-body imaging techniques - PET/CT, whole-body magnetic resonance imaging (MRI), and 99mTc-MIBI scintigraphy - in detecting EM in MM patients. **Methods:** We analyzed a cohort of 80 MM patients who underwent all three imaging modalities. We evaluated the presence and number of EM lesions and assessed concordance between the methods. Outcomes were compared based on lesion detection (presence vs. absence) and the total number of lesions. Statistical analysis was performed using IBM SPSS Statistics (version 23), employing the Chi-squared test, Wilcoxon test, and Fisher's exact test with Bonferroni correction. A p-value < 0.05 was considered statistically significant. **Results:** The proportion of detected extraosseous manifestations (EM) varied by imaging modality. MRI detected no EM lesions in 92.5% of patients, one lesion in 6.3%, and three or more in 1.3%. PET/CT was more sensitive: 78.8% had no EM, 13.8% had one, 3.8% had two, and

3.8% had three or more lesions. MIBI scintigraphy had the lowest detection: 97.5% showed no lesions, 1.3% one lesion, and 1.3% three or more. Comparing MRI and PET/CT, both detected EM in 8.8% and no lesions in 77.5% of patients, with an overall concordance of 86.3% and discordance in 13.7%. PET/CT revealed significantly more EM than MRI ($p = 0.001$). MRI vs. MIBI showed EM detection in 2.5% and no lesions in 91.3%, with 93.8% concordance and 6.3% discordance. The difference was not statistically significant ($p = 0.063$), though MRI had slightly better sensitivity. PET/CT vs. MIBI: both detected EM in 2.5% and no lesions in 77.5%, with 80.0% concordance and 20.0% discordance. PET/CT showed a significantly higher EM detection rate ($p < 0.0001$). Wilcoxon test showed significant differences in lesion numbers between PET/CT and MRI ($p = 0.003$), and PET/CT and MIBI ($p = 0.0004$); the MRI vs. MIBI difference was not significant ($p = 0.076$). **Conclusions:** Whole-body imaging plays a crucial role in the diagnosis and prognostication of multiple myeloma. While all three imaging techniques showed high concordance, PET/CT demonstrated significantly higher sensitivity in detecting extraosseous lesions and should be considered the preferred method when available. Supported by MH CZ – DRO (FNOl, 00098892) and IGA_LF_2025_005.

PA-143

mQOL, a Text-based Remote Therapeutic Monitoring (RTM) Platform for Symptom (Sx) and Quality of Life (QoL) Tracking in Multiple Myeloma (MM): Interim Results from a Prospective Observational Study

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Introduction: Introduction: Real-time Sx and QoL data are critical in managing multiple myeloma (MM) patients. mQOL is an easy HIPAA-compliant text-based platform allowing patients to proactively provide their Sx and QoL data, which is communicated continuously to their healthcare provider (HCP). This may facilitate earlier recognition of status changes and enable more timely clinical interventions. **Methods:** We conducted a single-center study using the mQOL RTM platform. Fifty MM patients in three cohorts were enrolled- newly diagnosed (ND), relapsed/refractory (RR), and on maintenance (MAINT) therapy. Nine Sx questions texted to patients as follows according to their cohort: < !NDMM: daily for 30 days <> QW until done < RRMM: daily for 30 days <> QW until done < ! MAINT: QW throughout. Additionally, 10 QoL questions selected from the EORTC-QLQ-30 instrument were texted QOW to all patients. We used EORTC scoring (1-Not at all; 4-Very much) to assess severity for all questions. Potential actionable events were defined as an increase of > 2 and any value of 4. Participants completed Sx and QoL check-ins by text for 90 days, with completion rates, response burden, and data utility analyzed. **Results:** Results: Patients were enrolled between Mar 27 and May 12, 2025 (median age 68 years [range, 47–91]; RRMM 38%, MAINT 59%, NDMM 3%) A total of 6090 questions were asked. Patients in the NDMM and RRMM cohorts averaged 31 questions/ patient/week. Those in the MAINT cohort averaged 14 questions/patient/week. Sx and QoL check-in completion rates were both > 97%. Average QoL scores were low with mean ratings for tiredness (1.64), pain (1.68), and psychosocial burden (1.74). Sx tracking revealed bone pain (1.55) and neuropathy (1.70) were the most frequent complaints. The median time on study was 5 weeks during which 108 potentially actionable events were identified. Time burden to complete mQOL assessments was minimal, averaging < 3 minutes, and this frequent assessment of Sx's and QoL via the platform allowed additional clinical insights into the effects of treatment and myeloma on patients. **Conclusions:** Conclusion: The mQOL platform demonstrated excellent feasibility, high patient adherence, and the potential for enhancing patient outcomes. Notably, the high number of potential actionable events flagged identifies clinically significant problems that can be immediately addressed by clinicians. mQOL offers the opportunity to gain a better understanding of the effect of treatments and the disease on myeloma patients in a more accurate manner. These data support validation of mQOL as a real-time, patient-centered RTM tool to optimize Sx management and QoL outcomes for MM patients. Expansion into a large, multi-center study assessing different treatments and actionable interventions is being planned.

PA-144

Whole Body Magnetic Resonance Imaging (WBMRI) for Response Evaluation in Patients with Multiple Myeloma

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Introduction: Whole-body magnetic resonance imaging (WBMRI) is a sensitive technique for diagnosing myeloma bone disease and it has been incorporated as an integral part in the imaging

workup for patients with suspected newly diagnosed multiple myeloma (NDMM). **Methods:** This ongoing, prospective, cohort study involved consecutive individuals with NDMM who underwent WBMRI at diagnosis, two months post-diagnosis, and one year thereafter. All included patients gave written informed permission, and the research received approval from the institutional review board. **Results:** A total of 93 individuals with NDMM were included, with a median age of 69 years (range 31–89). At baseline, 56 patients (60.2%) exhibited a focal MRI pattern, 18 patients (19.3%) displayed a normal pattern, 11 patients (11.8%) presented a diffuse pattern, and 8 patients (8.7%) demonstrated a mixed pattern. Paramedullary disease (PMD) was seen in 17 individuals (18.3%), whereas fractures were noted in 23 patients (24.7%). Two months post-treatment commencement, 86 patients (92.5%) achieved at least partial remission (PR). Imaging responses were as follows: 7 (7.3%) complete response (CR), 41 (44.1%) near complete response (nCR), 16 (17.2%) partial response (PR), 8 (8.6%) stable disease (SD), and 18 (19.4%) maintained a normal pattern at baseline. Fourteen out of seventeen patients with PMD had a response, yielding a rate of 82.4%. The baseline imaging pattern was substantially correlated with the imaging response at the second WBMRI with a favorable effect among patients presenting with focal pattern (Fisher's, $p < 0.001$), but not with the serum response ($p = 0.369$). In a median follow-up period of 6.2 months (range 0.9–22.4), 4 patients (4.3%) had disease progression and 4 (4.3%) succumbed to disease. A single disease progression event was detected during the second WBMRI, prior to the haematological or clinical progression. At the one-year evaluation, 34 patients had a third whole-body MRI. Of them, 16 (47.1%) achieved complete response (CR), 11 (32.4%) attained near complete response (nCR), and 2 (5.9%) exhibited partial response (PR). Thirteen patients (14.0%) were identified with new fractures during the second WBMRI assessment. Those cases were not classified as progressing myeloma, since there were no new osteolyses or plasmacytomas, and the patients exhibited haematologic response. The skeletal-related events were attributed to the baseline load of myeloma bone disease, which diminished swiftly with therapy. The existence of fractures detected by WBMRI at baseline was statistically substantially correlated with new fracture occurrences at the second WBMRI ($p = 0.015$). **Conclusions:** In conclusion, sequential WBMRI may enhance serum disease response evaluation in individuals with NDMM and requires additional prospective validation.

PA-145

Treatment-Free Hospitalization-Free Time With CAR T-Cell Therapy Versus Standard Regimens and Quality of Life Implications in Patients With Relapsed/Refractory MM: Findings From the KarMMa-3 Trial

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Introduction: An increasing number of treatments have become available for relapsed/refractory multiple myeloma (RRMM). They are generally treat-to-progression treatments, require continuous dosing and can result in cumulative toxicities. In contrast, CAR T-cell therapies represent a one-time infusion and offer the potential for a treatment-free interval despite potential early onset toxicities. This study utilized data from the KarMMa-3 trial to investigate treatment-free hospitalization-free time and compared quality of life (QoL)-adjusted event-free survival (EFS) in patients with RRMM treated with idecabtagene vicleucel (ide-cel) versus standard regimens, accounting for hospitalizations due to infusion, serious adverse events, and other factors. **Methods:** EFS, defined as the time from randomization to progressive disease, next anti-myeloma treatment, or death, was partitioned into 4 health states based on study treatment and hospitalization status. Patients could contribute multiple episodes in each health state. Time spent in each health state was calculated using restricted mean survival time (RMST). The mean QoL in each health state was assessed using the EQ-5D index, wherein 1 represents full health and 0 represents a state perceived as no better than death. QoL-adjusted EFS, defined as the sum of RMST in each state weighted by the mean EQ-5D index in that state, was reported. **Results:** 348 efficacy-evaluable patients were included in the analysis (ide-cel, n = 225; standard regimen, n = 123). The mean EFS (95% CI) was 18 mo (16, 20) in the ide-cel and 9 mo (7, 11) in the standard regimen arms. Patients treated with ide-cel spent most of their EFS time in a treatment-free hospitalization-free state, with an average (95% CI) of 16 mo (14–18) compared with 0.16 mo (0.07–0.28) for those on standard regimens. Patients on standard regimens spent much of their EFS time on study treatment while being hospitalization-free, with a mean of 9 mo (7–10) versus 1.84 mo (1.76–1.94) for ide-cel patients. Within the treatment-free hospitalization-free state, ide-cel patients reported a mean EQ-5D index (SD) of 0.80 (0.14) compared with 0.66 (0.05) for standard regimen patients. In the state where patients were under treatment and hospitalization-free, the mean EQ-5D index (SD) was 0.75 (0.20) for ide-cel and 0.75 (0.17) for standard regimen patients. Overall, the QoL-adjusted EFS (95% CI) was 14 mo (13–16) in the ide-cel arm compared with 7 mo (5–8) in the standard regimen arm ($P < 0.0001$). **Conclusions:** Patients receiving ide-cel experienced significantly longer QoL-adjusted EFS, driven by a prolonged treatment-free and hospitalization-free state, as well as improved QoL in this state, during which their QoL matched that of the general population of the same age. These results provide further understanding of both survival and QoL benefits of a one-time infusion of ide-cel versus the treat-to-progression standard regimen.

PA-146

The Role of Caregivers in Multiple Myeloma Care: A Social Work Perspective at the Ampath Multiple Myeloma Program (Ammp)

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Introduction: Multiple myeloma (MM) is a chronic, complex cancer requiring long-term management, significantly affecting both patients and their caregivers. At the AMPATH (Academic Model Providing Access to Healthcare) Multiple Myeloma Program, caregivers support patients throughout their treatment journey, often facing emotional, physical, and financial burdens. Social workers play a key role in equipping caregivers to cope effectively while preserving their well-being. This paper explores the role of caregivers in MM care at AMMP and highlights the interventions of a social worker in addressing caregiver challenges. Focus areas include emotional support, financial navigation, and access to care resources. **Methods:** Based on the experience of a social worker at AMPATH, this report reflects support provided to caregivers through one annual group session and monthly individual counseling (totaling 12–15 hours/year). Approximately 70 caregivers attend the group session. Data is gathered via informal feedback and self-reports on caregiver stress and satisfaction. The social worker also refers caregivers to financial aid and community resources. **Results:** Support group sessions reach 65–70 caregivers, with 70% reporting reduced stress and improved coping. Over the past year, at least 15 caregivers received financial referrals. Counseling led to a 60% improvement in stress management and increased caregiver empowerment. Participants also reported greater satisfaction and lower burnout levels. **Conclusions:** Caregivers are central to the success of MM treatment. Social work interventions—though limited in scope—are vital in supporting caregivers emotionally and practically. The integration of caregiver-focused support within AMPATH enhances the overall treatment experience, promotes caregiver resilience, and contributes to better outcomes for both patients and families.

PA-147

Nutritional Status of Adults with Multiple Myeloma and its Association with Disease Progression and Survival

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Introduction: Nutritional status and malnutrition have been repeatedly reported as significant predictors of disease progression and survival in many cancer patients, especially those with solid tumors. Although there is evidence that poor nutritional status can be also present in patients with hematological malignancies, including multiple myeloma (MM), its prevalence and impact on disease outcomes have not been widely explored in adequate samples. **Methods:** A large cohort of 915 newly diagnosed patients with MM, commenced to start systemic therapy, were included in this study. All patients underwent basic clinical and anthropometric evaluation, while a wide panel of blood biomarkers was measured from venous blood samples. Patients' nutritional status was estimated using the Nutritional Risk Index (NRI), calculated by the formula 1.519* [albumin (g/L)] + 41.7*(current weight/ ideal body weight). The optimum cut-off point of NRI for disease progression and survival was estimated with maximally ranked statistics in this sample. Survival analysis was then used to estimate the prognostic value of NRI. **Results:** Among the 915 patients of this cohort, 359 (39.2%) experienced disease progression on first line treatment and 213 (23.3%) died after a median follow-up of 6.1 years. The optimal cutoff, by maximally ranked statistics, for PFS and OS, were: 107.3 and 102.8, respectively. A total of 359 (39.2%) patients had NRI > 107.3 and 213 (23.3%) NRI > 102.8. Univariate survival analysis revealed that high NRI was significantly associated with a 28% lower risk of disease progression (HR: 0.72, 95% CI: 0.59–0.89, $p = 0.002$) and 44% lower risk of death (HR: 0.56, 95%CI: 0.43–0.74, $p < 0.001$). The association of NRI with both disease progression (HR: 0.71, 95%CI: 0.57–0.88, $p = 0.002$) and death (HR: 0.62, 95%CI: 0.47–0.82, $p < 0.001$), was still significant after adjusting for the effect of common confounders including age, sex, R-ISS, ECOG performance status, and HDM-ASCT. **Conclusions:** The results of this study indicate that malnutrition may be present in patients with MM, and that poor nutritional status before systemic therapy initiation is independently associated with both disease progression and survival. Screening for malnutrition in every patient before therapy would help identify patients at risk and plan early dietary support in parallel to their anti-myeloma treatment.

PA-148

Infectious Complications in Patients with Multiple Myeloma: A Scoping Review

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Introduction: Multiple Myeloma (MM) patients face heightened infection risks due to disease-related immunosuppression and therapies. Emerging data suggest that novel immunotherapies (bispecific antibodies, CAR-T) may further alter infection profile in patients, but evidence remains fragmented. This scoping review aims to map existing literature on characteristics and outcomes of infections in MM patients and highlight key gaps. **Methods:** We searched PubMed/MEDLINE and Google Scholar using broad search terms combining "multiple myeloma" and "infection." Studies published between 2000 and 2025 were considered, with the final search conducted on 6th May 2025. Eligible studies included those that reported both the site of infection and the identified pathogen in patients with multiple myeloma. Case reports, reviews, editorials, and conference abstracts without full data were excluded. A total of 21 studies met the inclusion criteria. Data was collected and organized in Microsoft Excel, and synthesized descriptively through tabulation and frequency analysis to highlight common patterns and trends across studies. **Results:** A total of 7,442 MM patients with infections were identified. Median age ranged from 56–72 years (17 studies); other three studies reported mean values and one reported average value. 13 studies reported ISS staging, with 4,624 patients (63.9%) in stages I–II and 2,613 patients (36.1%) in stage III. Among 20 studies, 4,501 (42.8%) were female and 5,995 (57.2%) male. IgG subtype was most common (95.1%), followed by IgA (2.7%) and light chain (1.9%). Infections were highest post-stem cell transplant (80.9%), followed by bispecific antibodies (5.2%) and IMiDs (3.7%). Of 9,403 reported infection sites, respiratory (43.6%) was most common, followed by bloodstream (23.7%) and skin/soft tissue (10.7%). Bacteria predominated, followed by viruses and fungi. Frequently reported pathogens included E. coli, Staphylococcus, Streptococcus, VZV, SARS-CoV-2, influenza, and Candida species. Despite the infection burden, only 1,281 (17.21%) patients were reported to have received prophylaxis, suggesting limited use or under reporting. 745 (58.2%) hospitalizations were reported across 13 studies, 125 (15.8%) ICU admissions in 8 studies, and 1,481 (11.6%) infection-related deaths in 18 studies. It is important to note that one large study contributed disproportionately to some parameters, skewing aggregate figures and limiting cross-study generalizability, high incidence of viral infections can be influenced due to COVID-19 infections. **Conclusions:** There is a lack of standardized criteria for infection reporting, especially in emerging therapies such as CAR-T and bispecific antibodies. These findings highlight the need for prospective studies to better define infection risk by treatment, establish prophylaxis guidelines, assess outcomes in underrepresented subgroups and need of standardized reporting of infections.

PA-149

Daratumumab versus Lenalidomide Maintenance Therapy in Newly Diagnosed Multiple Myeloma – Quality of Life and Efficacy Results from a Randomized Investigator-initiated Trial

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Introduction: Lenalidomide (len) has been standard maintenance therapy in multiple myeloma (MM). Daratumumab (dara) maintenance when compared to observation has shown improved PFS. This is the first and only randomized trial (NCT04497961; n = 89) that evaluated single agent dara vs len maintenance. The study is closed to accrual and final results for primary endpoint of difference in EORTC-QLQ-C30 global health status (GHS) and secondary endpoints of efficacy and toxicity will be presented. **Methods:** Pts with MM who achieve a ≥VGPR after induction were eligible. Randomization was stratified by age and ASCT status 1:1. Pts had annual bone marrow and imaging. QLQ-C30 responses were compared used a mixed effects linear regression model with random intercept. Response (median follow up 16.8 months (m) until efficacy data cutoff 10/2024) including MRD negativity by flow cytometry (>10–5) was assessed per IMWG 2016 criteria, Kaplan–Meier approach was used to estimate PFS, and toxicities were graded per CTCAE v5.0. **Results:** Median age was 64, 57% male; 72% White, 25.8% had high risk cytogenetics (t(4;14), t(14;16), t(14;20), del17p, gain/amp 1q or del1p), 64% received dara during induction, 79% received ASCT. The mean baseline GHS for the overall study was 72 (95%CI 69, 75). There was a significant increase in GHS per cycle (mean 0.18; 95%CI 0.1, 0.26) on maintenance. There was no difference in the primary endpoint of GHS between two arms ($p = 0.5$). The total QLQ score did not change with time on maintenance ($p = 0.5$) and there was no difference between the arms ($p = 0.8$). Improvement in social functioning ($p \leq 0.001$) and insomnia ($p \leq 0.001$) and worsening nausea/vomiting ($p \leq 0.001$), diarrhea ($p \leq 0.001$), appetite loss ($p = 0.03$) and dyspnea ($p = 0.04$) were noted with time on maintenance overall. When compared to dara, there was improvement in emotional functioning ($p = 0.01$), constipation ($p = 0.02$) and worsening in diarrhea ($p \leq 0.001$) and dyspnea ($p = 0.04$) in the len arm. Best responses in len arm were 50% sCR, 11.9% CR, 35.7% VGPR and 2.4% POD and in dara arm 72.1% sCR, 11.6% CR and 16.3% VGPR. Therefore, ≥CR rates

were 61.9% and 83.7% respectively. MRD negativity rates at screening and post baseline assessment were 47.6% and 53.3% in len arm and 50% and 64.5% in dara arm. PFS rates at 12 m and 24 m were 91% and 75.8% in len arm and 97.5% and 84.7% in dara arm. There were 13 serious adverse events in len arm and 22 in dara arm of which 42% and 32% were infections. Of 17 pts that came off study, 10 were due to POD (6 len arm; 4 dara arm). **Conclusions:** GHS improved with time on maintenance although was not different between arms. While best response, PFS and MRD negativity were numerically higher in dara arm, the study was not powered for efficacy comparison. These data add to ongoing maintenance trials utilizing anti-CD38 monoclonal antibodies. Given encouraging tolerability and efficacy, dara may be considered an effective maintenance option, especially in pts with len intolerance.

PA-150

Obesity as a Prognostic Factor in Newly Diagnosed Multiple Myeloma in a Mexican Population

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Introduction: In Mexico, obesity is a major public health problem with a rising prevalence, estimated to affect 36.1% of the population as of 2018.1,2 In the context of plasma cell dyscrasias, obesity has been associated with an increased risk of developing monoclonal gammopathy of undetermined significance (MGUS)3 and multiple myeloma (MM).4 However, the impact of obesity on overall survival (OS) in MM remains controversial.5,6. **Methods:** We conducted a retrospective, observational study at a single tertiary care cancer center in Mexico City. The study population consisted of patients with newly diagnosed MM (NDMM) according to the 2014 International Myeloma Workshop criteria, from April 2014 to December 2023. Clinical data were obtained from medical records, and the criteria to diagnosis and classification utilized was The Lancet Diabetes & Endocrinology Commission that included body mass index (BMI) and organ, tissue or body system.7 The overall survival (OS) was calculated with Kaplan-Meier method. **Results:** A total of 343 patients with NDMM were included. The median age at diagnosis was 57 years (SD ± 11.5); 60% were male. The distribution by International Staging System (ISS) stage was: S-I (3.1%), S-II (31.2%), and S-III (29.7%). By breaking down the damage caused by obesity 66.2% have cardiovascular disease, 38.7% osteoarthritis, 27.5% type 2 diabetes, 13.7% non-alcoholic fatty liver disease and 5% dyslipidemia. The mean weight was 68.8 kg (SD ± 17) and the mean BMI was 26.5 kg/m^2 (SD ± 5.5). BMI categories were: malnutrition (2.3%), normal weight (33.5%), overweight (39.4%), and obese (23.3%). The median OS was 26 months. No statistically significant difference in OS was observed across subgroups (p = 0.124). **Conclusions:** The prevalence of obesity in our cohort was 23.3%, comparable to the 29% reported by Shah et al. in a larger cohort of 1,120 patients. In our study, obesity did not significantly impact overall survival. To our knowledge, this is the first report evaluating the relationship between obesity utilized the new criteria and survival in Mexican patients with NDMM.

PA-151

Identification of Extracardiac Organ Involvement in Systemic Light Chain Amyloidosis using 18F-Florbetaben Positron Emission Tomography

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Introduction: 18F-florbetaben is an emerging radiotracer with high affinity for the β-pleated amyloid fibrils. Preliminary investigations utilizing 18F-florbetaben positron emission tomography/computed tomography (PET/CT) in patients with systemic amyloidosis have demonstrated its efficacy in detecting cardiac amyloid deposition, with clear differentiation from non-amyloid controls. Given its specificity for amyloid structures, 18F-florbetaben also holds promise for the non-invasive assessment of extracardiac organ involvement in systemic amyloidosis, potentially broadening its clinical utility beyond cardiac imaging. **Methods:** Patients with a confirmed diagnosis of systemic light-chain (AL) amyloidosis, either newly diagnosed or previously treated, were prospectively enrolled in this study. All participants underwent baseline imaging with 18F-florbetaben PET/CT, followed by a repeat scan at 6-months. Imaging acquisition was performed from immediately post-intravenous administration of the radiotracer to 40 minutes. Qualitative assessment of 18F-florbetaben uptake and retention was conducted across the myocardium and visceral organs within the thoracic and upper abdominal fields of view. Tracer distribution patterns were evaluated to identify potential amyloid involvement beyond the cardiac structures, with particular attention to extracardiac organ uptake suggestive of systemic disease burden. **Results:** A total of 17 participants underwent baseline 18F-florbetaben PET/CT. Of these, 7 patients completed a follow-up scan at the 6-month timepoint. There were 9 deaths during the study duration, all due to progressive AL amyloidosis; with 4 of these occurring prior to the planned second imaging timepoint. The median overall survival for the cohort was 8.48 years. Pulmonary uptake was observed in 4 patients, characterized predominantly by a diffuse distribution pattern. Skeletal uptake was noted in 6 patients, while splenic uptake was identified in 2 cases. Hepatic uptake was prominent in all participants, with no discernible difference in uptake intensity between patients with known hepatic involvement and those without, thus limiting its ability to identify liver involvement in these patients. Noticeable bowel uptake was observed in a single patient. Due to the limited field

of view in the cardiac imaging protocol, the kidneys were not adequately visualised and thus renal uptake could not be assessed. **Conclusions:** In addition to the previously demonstrated utility of evaluating cardiac amyloid burden, 18F-florbetaben PET/CT shows promising potential for detecting extracardiac involvement in organs such as the lungs and spleen, which are not routinely able to be assessed by conventional imaging or biopsy due to the lack of specific, non-invasive diagnostic modalities. The identification of amyloid deposition in these sites suggests that 18F-florbetaben PET/CT may serve as a valuable adjunctive tool in the comprehensive assessment of systemic disease burden.

PA-152

PRO-Guided Treatment Readiness for Daratumumab in Myeloma: Feasibility and Accuracy

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Introduction: For patients with multiple myeloma receiving daratumumab, standard pre-treatment evaluations typically rely on in-person clinical assessments. However, as outpatient cancer care increasingly explores digital and patient-centered solutions, the use of Patient Reported Outcome (PRO) data to assess treatment readiness has gained interest. This study aimed to investigate whether PRO data can reliably replace routine clinical evaluations prior to daratumumab administration, and to assess the overall feasibility of implementing such a strategy in daily practice. **Methods:** We developed an electronic questionnaire addressing common side effects to daratumumab and an algorithm stratifying patients according to their responses. Applying a mixed-method study design, we tested its usability, defined in this study as reliability, learnability, and user satisfaction. Quantitative data were descriptively analyzed, and positive predictive value and negative predictive value were calculated using the standard clinical evaluation – conducted independently and without knowledge of the algorithm's output – as the reference standard. Qualitative data were obtained from individual, semi-structured interviews with patients (n = 19) and a focus group interview with healthcare professionals (n = 4); data were analyzed using a hermeneutic approach. **Results:** With a positive predictive value of 100%, we found the questionnaire able to identify patients physically fit for treatment without need for further consultation. Of 179 completed questionnaires, the algorithm recommended treatment in 142 cases, thus demonstrating the potential of PRO data to replace standard clinical evaluations in 79% of cases. However, with a patient response rate of 77%, we also found that some patients were unable to report side effects digitally using a smartphone themselves. With respect to gender and age we found no statistical difference between patients being able or unable to complete the questionnaires. Qualitative findings were confirmative suggesting that patients had very different perceptions of registering their side effects themselves. **Conclusions:** Self-reporting of side effects prior to treatment is advantageous and flexible for the majority of patients. For patients able to complete the questionnaires, it is reliable and capable of replacing the usual clinical evaluation in determining treatment readiness. It thus holds potential to release resources at the hospital. However, further studies are needed to better understand which patients benefit from this approach and which require additional support. Identifying key factors influencing usability, such as digital literacy, cognitive function, and patient preferences, will be essential for optimizing implementation in a clinical setting.

PA-153

Operationalising Patient Selection for Outpatient Transplant in Multiple Myeloma: Subjective Versus Objective Measures

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Introduction: Rigorous patient selection is key to a successful outpatient (OP) autologous stem cell transplant (ASCT) program for myeloma (MM). However, there is heterogeneity in the selection process between institutions. At our experienced centre, OP selection of fitter ASCT patients is largely done by subjective eyeball test, with no specific criteria to mandate inpatient (IP) ASCT. We aimed to determine whether the selection process could be objectively operationalised using simple clinical tools. **Methods:** In a prospective study at our centre, MM patients already selected for transplant (IP or OP) undergo a battery of subjective and objective frailty assessments prior to ASCT: 1) objective measures of fitness [hand grip strength, 6-min walk test, Timed Up and Go, 2) subjective measures of function (Rockwood Frailty, Karnofsky Performance [KPS], ECOG), 3) comorbidity index (HCT-CI), 4) integrative scores (R-MCI, IMWG-GA) and 5) organ function (eGFR, serum albumin, BNP, PFT, ECHO). Post-ASCT, acute grade 3–4 organ toxicities and mortality to Day 100, ICU use and length of stay (LOS) are collected. Apart from tests of organ function, none of the above are used officially for OP ASCT selection. We then looked to see if the subjectively selected OP cohort could objectively be described using frailty tests (one or more in combination). Chi2 or Fisher's exact test for IP vs OP comparisons were used, as appropriate. **Results:** Of 398 consecutive ASCT patients, 151 (37.9%) were selected for OP at MD discretion.

When comparing OP to IP, there were no differences in demographics (age, gender, BMI), severe toxicities, ICU admissions or mortality within 100 days. As expected in this selected ASCT population, no patients had ECOG ≥4 or KPS ≤40. Only 26 (6.5%) received dose-reduced melphalan. When comparing objective frailty measures between IP and OP, the handgrip test was the most reliable fitness test (11% unable to perform walk-based tests) with weak handgrip in 15.2% OP vs 28.1% IP ($p < 0.01$). Not surprisingly, the OP group were less likely to have poor KPS ≤70 ($p < 0.01$), had fewer comorbidities as per HCT-CI ≥4 ($p < 0.01$), had higher serum albumin ($p = 0.03$) and less renal impairment eGFR < 60 ml/min ($p < 0.01$). Using these 5 selected objective tests, we identified that patients deficient in ≥2 measures had increased risk of ≥2 severe transplant-related toxicities ($p = 0.03$), correlating with IP status, as selected by subjective eyeball method ($p < 0.01$). **Conclusions:** When experienced transplant MDs subjectively select for OP vs IP ASCT, outcomes (toxicities, ICU use, 100-day mortality) are similar despite the IP cohort having worse frailty/fitness measures. This is presumably due in part to enhanced inpatient care and monitoring. Using a combination of 5 simple clinical tools, we can operationalise the OP selection for ASCT more objectively and reproducibly. This is useful for less experienced centres expanding into OP ASCT and could be validated for OP selection of complex immunotherapies such as CAR-T.

PA-154

Health-Related Quality of Life in Indian Patients with Multiple Myeloma: A Pan-India Digital Survey-Based Assessment

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Introduction: Multiple myeloma (MM) significantly affects patients' health-related quality of life (HR-QoL) due to the combined burden of disease symptoms and treatment-related toxicities. While novel therapies introduced over the past decade have improved survival, their real-world impact on quality of life, particularly in resource-limited settings, remains unclear. Evaluating HR-QoL in this context can provide valuable insights into the overall effectiveness of treatment and highlight existing gaps in current care practices. In this study, we sought to evaluate the HR-QoL of MM patients across India through a digital, patient-led survey approach. **Methods:** We conducted a cross-sectional, questionnaire-based study among patients with MM who were members of a nationwide WhatsApp group of MM survivors and caregivers. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and disease-specific QLQ-MY20 validated questionnaires were circulated through this digital platform using SurveyMonkey. Data were analysed using JMP software. The QLQ-C30 evaluated global health status, five functional domains (physical, role, emotional, cognitive, social), three symptom scales (fatigue, pain, nausea/vomiting), and six single-item symptoms (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The QLQ-MY20 assessed disease symptoms, treatment side effects, future perspective, and body image. Scores ranged from 0 to 100, with higher scores indicating better functioning or lower symptom burden. **Results:** This digitally conducted survey demonstrated high functioning across all QLQ-C30 domains. Participants reported good global health (mean: 75.26) and preserved functioning in physical (78.38), emotional (79.47), cognitive (79.12), social (74.38), and role (82.28) areas. However, fatigue (32.63) and financial difficulties (40.00) emerged as key concerns, with pain (21.20), insomnia (23.85), and constipation (28.77) also affecting quality of life. Nausea, diarrhoea, and dyspnoea were reported less frequently. The QLQ-MY20 module indicated a mild symptom burden (disease symptoms: 19.75; treatment side effects: 18.25), while scores for future perspective (77.75) and body image (70.40) reflected a generally positive outlook. **Conclusions:** This study, conducted via a pan-India WhatsApp group of MM patients, highlights encouraging levels of functioning and overall quality of life in a digitally connected subset of patients. Despite the positive trends, fatigue and financial stress remain prominent issues warranting targeted intervention. The findings underscore the potential of digital platforms for patient engagement and research but also suggest the need for broader outreach to include under-represented and less digitally literate populations for a more comprehensive understanding of HR-QoL in MM in India.

PA-155

Diagnostic Potential of Shear Wave Elastography for Liver Involvement in AL Amyloidosis

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Introduction: Liver involvement is frequently observed in patients with systemic immunoglobulin light-chain (AL) amyloidosis. Although liver biopsy remains the gold standard for diagnosis, it is invasive and associated with a risk of bleeding. In clinical practice, liver involvement is assessed using total liver span and serum alkaline phosphatase (ALP) levels; however, hepatomegaly and elevated serum ALP levels may also occur with different pathologic conditions, including drug-induced liver disease or chronic liver disease. Therefore, a non-invasive and accurate diagnostic approach is needed. Shear wave elastography (SWE) is a non-invasive and repeatable radiation-free technique for the quantitative measurement of tissue elasticity and is currently applied to evaluate liver stiffness. This study was undertaken to evaluate the diagnostic potential of SWE for liver involvement in AL amyloidosis. **Methods:** We retrospectively analyzed 25 patients with biopsy-proven AL amyloidosis who underwent SWE at Tokushima University Hospital between September 2019 and February 2025. Liver involvement was defined according to the current consensus criteria: hepatomegaly (total liver span ≥15 cm) or serum ALP levels >1.5 times the institutional upper limit of normal. Patients with significant ascites, alcohol use, congestive heart failure, or chronic liver disease were excluded. Ultrasound hepatic shear wave velocity (SWV) was measured from the right intercostal space using the C1-6 convex probe on a high-end ultrasound system, Logiq E10. (GE Healthcare, Japan). We also assessed the value of biochemical markers as complementary indicators of liver involvement, including γ-GTP, ALP, AST, ALT, total bilirubin (T-Bil.), albumin (ALB), and prothrombin time (PT). **Results:** Among the 25 patients (median age: 67 years, range: 51–86), 8 had liver involvement. The mean hepatic SWV was significantly higher in patients with liver involvement than those without (1.93 ± 0.39 vs 1.36 ± 0.11 m/s, p = 0.00099). Similarly, γ-GTP levels were elevated in the liver involvement group (165 ± 131 vs 36 ± 28 U/L, p = 0.00222). Both SWV and γ-GTP showed positive correlations with serum ALP levels and total liver span. No significant differences were observed in AST, ALT, T-Bil., ALB, or PT between the groups. Receiver operating characteristic (ROC) curve analysis yielded an area under the curve (AUC) of 0.915 for SWV and 0.886 for γ-GTP. The cut-off value for SWV was 1.62 m/s (sensitivity 1.000, specificity 0.875), and for γ-GTP was 68 U/L (sensitivity 0.882, specificity 0.750), respectively. **Conclusions:** SWE represents an accurate, non-invasive imaging modality for detecting liver involvement in AL amyloidosis. γ-GTP also could have the diagnostic potential alongside conventional criteria. Further multicenter, prospective studies are warranted to validate the clinical applicability of SWE and to explore the pathological basis of increased liver stiffness in patients with AL amyloidosis.

PA-156

Challenges in Diagnosis, Treatment Access, and Quality of Life Among Newly Diagnosed Multiple Myeloma Patients in India: Findings from a Prospective Observational Study

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy with rising incidence in India, where patients often present at a younger age than in Western populations. Although novel therapies have improved survival, many patients experience delays in diagnosis and face significant barriers to accessing care. This prospective single-center study aimed to identify the causes of diagnostic delays, barriers to treatment access, and assess quality of life (QoL) among newly diagnosed MM (NDMM) patients. **Methods:** Between July 2022 and June 2023, 165 NDMM patients were prospectively enrolled. Structured questionnaires were administered at baseline, capturing sociodemographic details, comorbidities, symptom profile, barriers to healthcare access, and QoL using the EQ-5D-5L tool. Diagnostic delay was categorized based on time from symptom onset to initial medical consultation: < 3 months, 3–6 months, and >6 months. Statistical analyses included descriptive statistics, bivariate tests, and logistic regression to identify predictors of diagnostic delay and QoL impairment. **Results:** The median age was 56.7 years (range 28–82), with 63.6% of patients being male. Most resided in rural (61%) or semi-urban areas, and nearly half had comorbidities such as hypertension, diabetes, or cardiovascular disease. Only 12.7% had health insurance, and 42% were unemployed. Presenting symptoms included fatigue (26%), bone pain (22%), and fever (16%), with over 75% reporting multiple symptoms. EQ-5D-5L analysis revealed that pain/discomfort was the most affected domain (mean disutility: 0.126), followed by self-care (0.088) and mobility (0.079). The average EQ-VAS score was 57.8 (SD ± 22.3), and the mean EQ-5D index was 0.58 (range – 0.92 to 1.00), indicating significant QoL impairment. Patients with diagnostic delays >6 months (n = 15) had worse QoL (EQ-VAS 53.2, EQ-5D index 0.52) compared to those diagnosed within 3 months (n = 127; EQ-VAS 58.7, EQ-5D index 0.57). Major reported barriers included lack of symptom awareness (82%), psychological hesitation (24%), and logistical issues such as transport or appointment difficulties (18%). While logistic regression did not identify statistically significant predictors of delays >6 months, trends indicated that lower education and lack of health insurance may contribute to delayed presentation. None of the demographic or CRAB features significantly predicts worse EQ-5D index scores. **Conclusions:** Diagnostic delays and reduced QoL remain prominent issues in the management of MM in India. A lack of awareness and psychosocial barriers contribute significantly to delayed presentation.

Targeted educational interventions and the decentralisation of myeloma care services are essential to improve early diagnosis and patient-centred outcomes in the Indian context.

PA-157

Incidence and Risk Factors of Thromboembolic Events in Chinese Patients with Multiple Myeloma: A Single-Center Retrospective Cohort Study

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Introduction: Patients with multiple myeloma (MM) are at a significantly increased risk of developing thromboembolic events (TEs) compared to the general population, owing to disease-related factors, patient-related factors and treatment-related factors. The incidence of venous thromboembolism (VTE) ranges from 10% to 34% following treatment with immunomodulatory drugs (IMiDs), whereas earlier studies in Chinese patients have reported a lower incidence of 3% to 10%. In contrast, data on arterial thromboembolism (ATE) in MM patients remain limited. Given that TEs may adversely affect both treatment efficacy and overall prognosis, the development of standardized strategies for prevention and management is imperative. **Methods:** This retrospective cohort study included 661 MM patients admitted to the Department of Hematology, Peking Union Medical College Hospital, between January 1, 2018, and June 1, 2024. After excluding 80 patients due to incomplete data or ineligibility, 581 patients were included in the final analysis. Demographic information, disease stage, comorbidities, and treatment data were extracted from the Hospital Information System (HIS). Univariate analysis of VTE risk factors was conducted among 550 patients who received systemic therapy (40 with VTE and 510 without VTE). **Results:** The cumulative incidence of VTE was 10.8% (63/581), with 6.5% occurring within the first six months after diagnosis. The median time to VTE onset was 2.7 months post-diagnosis (IQR: 0–13.6). The cumulative incidence of ATE was 2.9% (17/581), with 1.4% occurring within the first six months and a median onset time of 6.3 months (IQR: 0.2–20.9). Notably, 76% of VTEs and 82% of ATEs occurred during the newly diagnosed MM (NDMM) phase. Univariate analysis revealed significant associations between VTE occurrence and several factors, including older age (median: 67 years [IQR: 61–71] vs. 62 years [IQR: 55–68]; $P < 0.001$), absence of thromboprophylaxis (OR = 2.77), Eastern Cooperative Oncology Group (ECOG) performance status ≥3 (OR = 3.03), chronic kidney disease (CKD) (OR = 3.45), history of cardiovascular or cerebrovascular disease (OR = 2.38), personal history of VTE (OR = 10.16), and family history of VTE (OR = 12.89) (all $P < 0.05$). Thromboprophylaxis use was significantly lower among patients who developed VTE (40.0% vs. 64.9%, $P < 0.01$). The incidence of VTE was 3.2% in patients receiving aspirin prophylaxis compared with 11.9% in those without any prophylaxis. **Conclusions:** The incidence of VTE among MM patients in this cohort exceeds previous reports from China, likely due to the increased use of IMiD-based regimens combined with corticosteroids. In addition to treatment-related risk factors, patient-related risk factors such as CKD and cardiovascular or cerebrovascular disease significantly contribute to VTE risk, highlighting the need for refinement of existing risk assessment models. Aspirin appears to offer meaningful clinical benefit as a baseline thromboprophylaxis agent.

PA-158

The HSCT-BIOME Study: Double-Blinded, Randomized, Placebo-Controlled Trial Using Orally-Administered, Lyophilized Faecal Microbiota Transplantation to Prevent HSCT-Associated Complications

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Introduction: The composition of the gut microbiota both prior to and after haematopoietic stem cell transplantation (HSCT) is increasingly linked to outcomes following HSCT including diarrhea, infections and poor immune reconstitution. Faecal microbiota transplantation (FMT), a method of delivering a healthy gut microbiota to a recipient, therefore offers a potential strategy of promoting gut microbiota stability and improving the adverse effects of HSCT. Although FMT has been investigated in HSCT recipients, it has largely been tested therapeutically for specific indications such as infections or prevention or amelioration of graft versus host disease, following allogenic stem cell transplant. There is limited evidence for the use of FMT in autologous HSCT. **Methods:** The HSCT-BIOME study is designed to determine the tolerability and safety of orally-administered, encapsulated FMT in HSCT recipients, and test its ability to reduce the incidence/severity of complications. Peri-HSCT FMT (i.e. FMT delivered before and after HSCT) will be administered to eligible participants (adults undergoing autologous HSCT for a haematological malignancy) over two courses, with the second starting when ANC >0.8. Following an open-label, safety run in (N = 5), peri-HSCT FMT will be evaluated for its efficacy in N = 51 participants randomised 2:1 to FMT or placebo. The primary outcome is the proportion of participants that develop severe gastrointestinal toxicity - defined as 4 consecutive days of the diarrhea (Bristol Stool Chart 6+) at a frequency of twice daily - within 3 weeks of HSCT. Safety is defined as the incidence of treatment-emergent adverse events (TE-AEs). Tolerability is defined as the incidence of TE-AEs and adherence to FMT. **Results:** The trial has started

recruiting at the Royal Adelaide Hospital, Australia. Final results will be available 18 months after completion. Trial registration ACTRN12624001104549. **Conclusions:** The HSCT-BIOME study is a multi-centre, double-blind, randomized placebo-controlled trial designed to determine the tolerability, safety and efficacy of orally-administered encapsulated FMT to promote the stability of the gastrointestinal microenvironment for autologous HSCT recipients, and therefore improving adverse effects of HSCT in recipients. By utilizing a peri-HSCT schedule and avoiding periods of severe immunosuppression (ANC< 0.8), we hope to demonstrate that FMT can be safely administered to autologous HSCT recipients and reduce personal, clinical and economic burden of HSCT complications.

PA-159

Performance of Deauville Score and Total Lesion Glycolysis as Response Markers for Multiple Myeloma with Extramedullary Disease

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Introduction: Extramedullary disease (EMD) in multiple myeloma (MM) is associated with an aggressive clinical course and poor response to current therapies. The prognostic utility of the Deauville Score (DS) in EMD has not been well characterized, and it remains unclear whether total lesion glycolysis (TLG) provides additional value beyond DS in assessing treatment response. **Methods:** We included patients with EMD who underwent fluorodeoxyglucose (FDG) PET-CT for treatment response assessment between 01/01/2009 and 12/30/2022. DS was assigned per standard criteria: complete response (CR) as DS ≤3, partial response (PR) as DS = 4, and no response/progression (NR/PD) as DS = 5. TLG was calculated as the product of mean standardized uptake value (SUVmean) and the total volume of FDG-avid disease. Metabolic response categories based on TLG reduction were defined as: Deep Metabolic Response (DMR, >90% reduction), Major Metabolic Response (MMR, 50–90%), and Non-significant Metabolic Response (NMR, < 50%). Progression-free survival (PFS) was determined using the 2016 Consensus International Myeloma Working Group criteria. **Results:** Ninety-five patients with response PET scans were included (73 relapsed and 22 newly diagnosed MM). The median interval between response PET-CTs was 3.1 months (IQR: 1.5–4.7) and the median follow-up from the first PET was 78.4 months (95% CI: 55–93). Median PFS for the overall cohort was 4.2 months. By TLG response, median PFS was 16.5 months [5.9–NR] for DMR, 4.8 months [3.6–9.6] for MMR, and 2.2 months [1.7–3.4] for NMR ($p < 0.0001$). Stratified by DS, the median PFS was 22.4 months [95% CI: 11.5–NR] for DS ≤3, 4.3 months [3.6–9.6] for DS = 4, and 2.8 months [2.1–4.0] for DS = 5 ($p < 0.0001$). The difference between DS 4 and DS 5 groups was not statistically significant ($p = 0.3$). In contrary, the difference between MMR and NMR was statistically significant ($p = 0.035$). Among patients with DS ≥4, 23% (n = 16) had discordant responses—worse DS but improved TLG; their median PFS was 4.8 months [3.5–8.2], compared to 2.9 months [1.9–3.8] in the concordant group ($p = 0.057$). In a multivariable analysis, a lower reduction in TLG was independently associated with an inferior PFS [HR 2.3 (95% CI: 1.6–3.1) after adjusting for disease status (de novo versus secondary), triple-class refractoriness (TCR) and high-risk cytogenetics (HRCA). When both DS and TLG were added to the MVA along with TCR status, HRCA and de novo-secondary disease, TLG [HR 1.6 (95% CI: 1.1–2.1), $p = 0.008$] and DS [HR 2.2 (95% CI: 1.5–3.1), $p < 0.0001$] were independently prognostic for PFS. The 18-month OS for patients achieving a DMR was 71% (95% CI: 57–89) vs. 38% (95% CI: 23–65) for MMR and 18% (95% CI: 9–35) for NMR ($p < 0.0001$). **Conclusions:** Both DS-defined complete response and DMR by TLG are associated with significantly improved PFS in EMD. TLG may provide additional discriminatory power for response assessment and should be considered in future response evaluation strategies for EMD.

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Dialysis-Dependence is Associated with Poor Prognosis in Multiple Myeloma: a Multicenter Retrospective Cohort Study

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Introduction: Patients with multiple myeloma (MM) and renal impairment (RI), particularly those requiring dialysis, have historically experienced poor outcomes. Despite advancements in targeted therapies, the prognosis of dialysis-dependent MM and factors influencing dialysis independence remain unclear. **Methods:** This multicenter, retrospective study included 122 MM patients requiring chronic hemodialysis (≥28 days of treatment) at four tertiary hospitals, China from January 2012 to November 2023. Hemodialysis resulting from causes other than MM were excluded. Logistic regression was employed for multivariate analysis of factors

associated with dialysis independence, and Kaplan-Meier survival curves and Cox proportional hazard models were utilized for survival analysis. **Results:** Among the 122 patients, 74 patients (60.7%) were male, with a median age of 65 (39–87) years. Of these, 71.3% (n = 87) had newly diagnosed MM (NDMM), and 28.7% (n = 35) had relapsed/refractory MM (RRMM). Among 94 patients with available fluorescence in situ hybridization (FISH) test results, 51 patients (54.3%) had high-risk cytogenetic abnormalities. Proteasome inhibitors were used in 80.3% of patients (n = 98), while 13.9% (n = 17) received daratumumab-based regimens. Dialysis independence was achieved in 27 patients (22 with NDMM and 5 with RRMM), with a median time of 2.2 (1.2–29.3) months. This group exhibited significantly better hematologic responses (≥very good partial response [VGPR]: 77.8% vs. 24.2%, P < 0.001). Multivariate analysis showed that achieving at least VGPR (P = 0.005), receiving daratumumab-based treatment (P = 0.032), reduction in serum free light chain (sFLC)≥80% after one cycle of chemotherapy (P = 0.010), and age< 65 years (P = 0.015) were associated with dialysis independence. During a median follow-up of 43.7 months (2.1–113.0 months), the median PFS and OS of the whole cohort were 14.4 and 27.4 months (95% CI, 3.6–25.2 and 6.9–47.9 months). Compared to NDMM, RRMM requiring hemodialysis showed poorer PFS (2.6 vs. 24.4 months, P < 0.001) and OS (4.2 vs. 43.0 months, P < 0.001). Reversal of dialysis dependence were associated with significantly better outcomes (PFS: 36.7 vs. 9.4 months, P = 0.006; OS: 62.6 vs. 17.7 months, P < 0.001). Poor prognosis factors included high-risk cytogenetic abnormalities, elevated LDH (≥250 U/L), and high bone marrow plasma cell (BMPC) ratio (≥50%), while ≥80% sFLC reduction after the first chemotherapy cycle was favorable. Further multivariate analysis identified reversal from dialysis (P = 0.039 and P = 0.027) as an independent predictor of improved OS in both NDMM and RRMM patients. **Conclusions:** The prognosis of dialysis-dependent MM patients was poor. Achieving dialysis independence following standard anti-myeloma therapy is associated with improved outcomes. Importantly, RRMM patients who require dialysis had a worse prognosis, but this might be reversed with aggressive treatment strategies.

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Assessing the Clinical Implications and Prognostic Value of Light-Chain N-Glycosylation in 781 Multiple Myeloma Patients at Diagnosis

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Introduction: Light-chain (LC) N-glycosylation, a post-translational modification where glycans bind to monoclonal LC, is detectable by mass spectrometry. While associated with an increased risk of progression in monoclonal gammopathy of uncertain significance (MGUS) its clinical implications in newly diagnosed multiple myeloma (MM) are mostly unknown. **Objective:** To investigate the clinical associations and prognostic impact of LC N-glycosylation at diagnosis in MM and high-risk smoldering MM (SMM) patients included in 3 clinical trials of the Spanish Myeloma Group. **Methods:** A total of 781 baseline serum samples obtained from patients enrolled in the GEM2012MENOS65 (n = 336), GEM2017FIT (n = 368) and GEMCESAR (n = 77) trials were analyzed. LC N-glycosylation was assessed using Quantitative Immunoprecipitation Mass Spectrometry with anti-IgG/A/M, total κ, and total λ beads via the EXENT® system. High-risk cytogenetic abnormalities (HRCA) were defined as the presence of t(4;14), t (14;16) and/or del17p. Measurable residual disease (MRD) was

assessed by flow cytometry following EuroFlow guidelines. **Results:** LC N-glycosylation was present in 70 patients (9.0%) and was more frequent in those older than 75 years (21.4% vs. 12.4%; P = 0.036), with kappa isotype (74.3% vs. 64.8%; P = 0.081), hypoalbuminemia (<3.5 mg/dL: 44.1% vs. 30.7%; P = 0.025) and HRCA (41.3% vs. 27.4%, P = 0.049). No association was observed with ISS or bone marrow infiltration. In the multivariate analysis, age > 75 years and HRCA were independently associated with LC N-glycosylation (P = 0.035 and P = 0.043, respectively). In terms of prognostic value, after a median follow-up of 52 months (range, 3–291), no significant differences in progression-free survival (PFS) or overall survival were seen between patients with and without LC N-glycosylation, either in the overall cohort or stratified by age. Interestingly, among patients with undetectable disease by next-generation flow, those with LC N-glycosylation showed a significantly lower rate of complete response (59.5% vs. 75.0%; P = 0.032). Given that PFS was similar regardless of immunofixation status, these findings suggest that glycosylation may interfere with monoclonal protein (MP) clearance or impact the interpretation of the immunofixation. **Conclusions:** LC N-glycosylation was observed in 8–9% of newly diagnosed MM patients, more frequently in older individuals, those with kappa isotype, and HRCA. Glycosylation was not associated with treatment response or progression-free survival. Its higher prevalence among MRD-negative but immunofixation-positive cases suggests interference with MP clearance or assay interpretation and deserves further investigation.

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Cytokine Dysregulation in Multiple Myeloma: A Comprehensive, Comparative Analysis of Blood and Bone Marrow Profiles

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Introduction: In multiple myeloma (MM), the bone marrow (BM) microenvironment fosters immune dysfunction through cytokine-driven signaling that promotes tumor survival and progression. Cytokines have direct effects on both MM cells and immune cells, including those mediating responses to immunotherapy such as NK cells. Previous studies quantifying cytokine levels in MM patients frequently examined small numbers of cytokines; and often examined only blood levels, without direct comparison to BM levels, clouding interpretation. Comparison of cytokine levels between MM and controls generally uses blood samples, as bone marrow from controls is not routinely available. Gaining a more comprehensive understanding of the cytokine milieu in MM will inform the development of novel therapeutic strategies. To address existing knowledge gaps, we quantitated and compared the levels of a panel of cytokines in the blood and BM of MM patients and the blood of control subjects. **Methods:** We analyzed cytokine expression in 62 blood and 34 BM plasma samples obtained from MM patients at diagnosis or in various phases of follow-up, alongside 15 age-matched control blood samples. Using a Bio-Rad Bio-Plex 200 system, we quantified 23 cytokines. Selection prioritized cytokines implicated in immune surveillance and NK cell function as well as those known to directly impact MM cells. Data analysis involved standard curve calibration, quality control measures, and replicate assessments. Among the samples, 25 pairs of blood and BM specimens were obtained simultaneously from the same patients, allowing for matched analysis. **Results:** MM patients exhibited significantly ($p < 0.05$) increased expression of several cytokines in blood compared to controls, notably TGF-β1, IL-8, IL-16, IL-12p70, G-CSF, IL1 β and IFN-γ. IL-18 was higher in controls ($p < 0.05$). BM samples showed significantly ($p < 0.05$) higher levels of 15 cytokines compared to blood, including IL-8, IL-10, TNF-a, IL-7, TGF-β isoforms, and RANTES. In paired matched samples, 11 cytokines were significantly elevated in BM, highlighting its role as an immunosuppressive environment. Cytokine levels in MM blood and BM were highly correlated, validating the comparison between MM and control blood samples. There were no significant correlations seen between cytokine profiles and disease or treatment characteristics in this small study. **Conclusions:** This study is the first to our knowledge to quantify >20 relevant cytokines in both MM blood and BM as well as in control BL. Our analysis characterizes an environment that, based on the known functions of these cytokines, could potentially enable immune evasion and therapy resistance and promote MM cell survival. These results suggest possible new avenues for therapeutic cytokine modulation in MM in conjunction with other immunotherapies and warrant further translational exploration.

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Characteristics of Long-Term Survivors in Multiple Myeloma: Exploring Factors for Cure After Extended Follow-Up

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Introduction: Multiple myeloma (MM) is typically characterized by successive relapses, with cure rarely considered. Clinical trials often have limited follow-up due to costs, and real-world studies face challenges like small sample sizes or heterogeneous management. Thus, data on long-term MM survivors are scarce, and late relapses challenge the concept of operational cure. This study analyzes factors associated with long-term survival in a large, homogeneously treated cohort with extended follow-up. **Methods:** We analyzed 1,018 transplant-eligible, newly diagnosed MM patients treated from 1999–2004 with polychemotherapy (VBMCP/VBAD), transplant, and 2-year maintenance (interferon/prednisone) under the GEM2000 protocol. Clinical and biological data were collected and updated to the last follow-up. **Results:** With a median follow-up of 180 months (95%CI 156–256), median overall survival (OS) was 69 months (95%CI 62–74), with 10-, 15-, and 20-year OS probabilities of 30%, 20%, and 12%. The probability of being alive and disease-free at 10 and 15 years was 14% and 6%. In multivariate Cox regression, factors associated with better OS included age <65 years, ECOG <2, standard-risk cytogenetics, hemoglobin >10 g/dL, and platelet count >150,000/µL. These factors, plus female sex, predicted long-term survival (≥15 years) in multivariate logistic regression. Achieving undetectable minimal residual disease (MRD, $\geq 10^{-4}$ sensitivity) post-transplant was the strongest predictor when included in both analyses, with median progression-free survival of 74.4 months (HR 0.47; 95%CI 0.35–0.64) and OS of 193.2 months (HR 0.48; 95% CI 0.35–0.65). Relative survival was lower than the age-, sex-, and date-adjusted Spanish population, with excess mortality persisting at 10 and 15 years. Of 806 deceased patients, 40.7% died from progression, 21.8% from MM-related causes (mainly infections), 11.3% from unrelated causes, and 26.2% had unknown causes. Non-MM-related mortality was 9.4% in those dying within 5 years vs. 35.6% beyond 15 years (OR 7.67; 95%CI 3.35–18.20). **Conclusions:** This series, with one of the longest follow-ups reported, identifies a long-term survivor population, mainly driven by MRD negativity, whose characterization may optimize treatment intensity and costs. Nevertheless, excess mortality persists even in long-term survivors, suggesting true cure remains rare in the pre-novel therapy era.

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Serum Cholesterol Levels Demonstrate Dynamic Changes Following Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a hematological malignancy dependent on the bone marrow microenvironment, where adipocytes play a critical role in disease progression. Cholesterol metabolism and lipoprotein levels are emerging prognostic factors in MM, but long-term data on lipid dynamics remain scarce. This study analyzed long-term follow-up data from 115 autograft patients over the past 7.5 years to investigate the long-term changes in lipid metabolism during the course of MM. **Methods:** A retrospective analysis was conducted on 115 MM patients undergoing ASCT between 2016–2023. Lipid parameters and vitamin D levels were measured at diagnosis, pre-transplant, 100 days post-transplant, and up to 2 years post-transplant or relapse. **Results:** This study analyzed 115 multiple myeloma patients (66 males, 49 females) with a median age of 55.8 years. Immunoglobulin type distribution showed IgG (45 cases), IgA (27), IgD (5), light chain (33), and non-secretory (5). Most patients had ISS stage I disease. Genetic risk stratification revealed 38 patients (33.93%) without high-risk abnormalities, 54 with one, and 20 with two high-risk abnormalities. Pretransplant treatment response rates included 85.22% achieving CR/VGPR and 14.78% PR, with a median PFS of 51.43 months. Notable metabolic findings showed consistently subnormal lipid profiles (total cholesterol, triglycerides, HDL, LDL) and vitamin D levels at initial diagnosis. At diagnosis, cholesterol levels were low in 20%, elevated in 20%, and normal in 60% of patients. Post-induction therapy, cholesterol normalized in 62%, while 38% remained elevated. The

proportion of vitamin D deficiency (< 20 ng/ml) further increased after induction therapy. Induction therapy correlated with improved cholesterol normalization but exacerbated vitamin D deficiency. Cholesterol, triglycerides, and LDL levels were significantly higher at both the pre-transplantation and 100-day post-transplantation time points compared to baseline values. However, no significant changes were observed in serum vitamin D levels or in HDL, Apo A1, and Apo B levels. Cholesterol levels were tracked at 100 days, 1 year, and 2 years post-transplant. Patients with early relapse (within 2 years) showed significantly lower cholesterol levels at 2 years compared to 100-day post-transplant levels In contrast, non-relapsed patients maintained stable, higher cholesterol levels over the same period, with a statistically significant difference observed. **Conclusions:** This study is the first to characterize dynamic post-transplant cholesterol variations in MM. Relapsed patients displayed declining cholesterol levels, while sustained higher cholesterol levels during remission were associated with improved outcomes, suggesting that elevated cholesterol levels during remission may indicate a favorable prognosis. Our findings advocate for incorporating lipid metabolism monitoring into the long-term management of MM to guide personalized therapeutic approaches and enhance survival outcomes.

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Testing and Validating a Mass Spectrometry Based Algorithm for Response Assessment in Myeloma

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Introduction: Bone marrow aspirate (BMA) at day 100 post-autologous stem cell transplantation (ASCT) is a standard assessment for residual disease in multiple myeloma, but is invasive, resource-intensive, and prone to sampling variability. As deeper responses are increasingly seen a less invasive but sensitive test is needed. Serum mass spectrometry (MS) offers a highly sensitive, non-invasive alternative. We evaluated the EXENT MALDI-TOF MS assay as a potential replacement for BMA at day 100 post-ASCT. **Methods:** A two-phase study of 67 clinical patients post-ASCT was conducted, incorporating an initial prediction phase and secondary validation phase. All had day 100 BMA and serum samples. A diagnostic serum sample established the M-protein isotype and unique m/z for each patient. MS positivity was defined as a peak matching the diagnostic m/z (±4 m/z) and isotype. BMA was classified as negative if plasma cells were < 5% (IMWG). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using BMA as reference. **Results:** In the initial cohort (n = 20), all MS-negative patients were BMA-negative (n = 4), and all BMA-positive patients were also MS-positive (n = 4). MS-positive/BMA-positive patients had a mean M-protein of 7.76 g/L vs. 1.94 g/L in MS-positive/BMA-negative patients. From this, three predictive rules were proposed: (1) MS-negative = BMA-negative, (2) MS-positive ≥5 g/L = BMA-positive, (3) BMA-positive = MS-positive. These rules were tested in a validation cohort (n = 47). All 23 MS-negative patients were BMA-negative, reaffirming the 100% NPV. Of 24 MS-positive patients, 3 were BMA-positive, all with M-protein levels ≥5 g/L, supporting the proposed threshold. All BMA-positive samples were also MS-positive (n = 7), validating rule (3). When combining both cohorts (n = 67), the overall concordance between MS and BMA was 51%. 67% of the MS-positive samples were negative by CZE. Cohort metrics were as follows when using BMA as gold standard: sensitivity 100%, specificity 45%, PPV 18%, NPV 100%. From this cohort we have proposed an MS testing pathway for ASCT patients: Perform baseline serum MS at diagnosis to identify M-protein m/z. Perform serum MS at day 100 post-ASCT for all patients as first-line test. If MS-negative: omit BMA and continue routine surveillance. If MS-positive ≥5 g/L: interpret as highly likely BMA-positive and consider treatment options. If MS-positive <5 g/L: review in clinical context and perform serial MS monitoring to closely track M-protein changes. **Conclusions:** The EXENT MS assay shows 100% NPV for BMA-defined residual disease at day 100 post-ASCT, identifying all patients with negative BMA while avoiding invasive procedures. We propose replacing routine BMA with serum MS for CR assessment, reserving BMA only for MRD assessment by more sensitive methods.

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Gene-Expression-Profiling Plus Integrated Multidisciplinary Approach to Detect New-Generation Risk-Adapted Prognostic Index in Smoldering Myeloma and Multiple Myeloma (GIMPI): A New Prognostic Score

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Introduction: In our Institution, a prospective study to test the combination of gene-expression-profiling (SKY92 gene signature) and new generation imaging (PET/CT + Whole body MRI) was applied to all consecutive patients affected by smoldering (SMM), newly diagnosed (NDMM) and relapsed/refractory (RRMM) MM and evaluated its potential to predict or correlate with established HR markers of this disease and potentially defining new basis for a personalized treatment. **Methods:** Patients' bone marrow aspirate,

plasma, imaging and clinical data were collected in our Institute under approved protocol and according to the Declaration of Helsinki guidelines. **Results:** In this study a cohort of 139 patients referring to our Institute was enrolled (SMM n = 47, NDMM n = 54 and RRMM n = 38): here we present only the molecular part of the study, combination with imaging analysis is currently ongoing. Proportion of patients with SKY92 HR increased from SMM (8.4%) to NDMM (36.7%) and RRMM (53.3%, p = 0.0162). Virtual FISH in NDMM patients showed 100% accuracy (95% CI) (100.0–100.0) for both t (4;14) and gain(1q) and of 90.0 (71.4–100.0) for del(17p), and this could be really useful for the daily clinical practice. The concentration of sBCMA was measured in our patients' cohort and in healthy subjects (n = 12, control) with a statistically significant increase of sBCMA in the blood of NDMM and RRMM with respect to SMM (p = 0.0009, p = 0.0222) and control (p < 0.0001, p = 0.0010). Consistently with the literature, no statistically significant differences were observed among NDMM and RRMM. Thus, we hypothesize that SKY92 HR could capture patients with high levels of sBCMA. We compared the concentration of this disease biomarker among SR and HR including SMM, NDMM and RRMM patients and we observed increased levels of sBCMA in HR patients with respect to SR (p = 0.0049). A risk-based intragroup comparison showed a similar trend in SMM and RRMM and, importantly, this result was confirmed in NDMM patients (p = 0.0445). However, in this category of MM patients ISS could partially recapitulate differences in sBCMA among risk classes with the only statistically significant difference between Class I and III (p = 0.0381). Therefore, we combined ISS with SKY92 and we observed that n = 11 patients considered as LR by ISS (Class I), were relocated to the IR from this analysis with an overall improvement in the distribution of sBCMA levels according to risk categories (SR vs HR p = 0.0011, IR vs HR p = 0.0036). **Conclusions:** The results of this first pilot Italian study, that in the next future will be framed in a national network contest, strengthen the prognostic relevance of SKY92 based on its potential to (i) predict HR cytogenetic markers of disease; (ii) capture MM patients with high levels of sBCMA supporting the introduction of this GEP-based tool in the clinical diagnostic practice.

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Measurable Residual Disease (MRD) Dynamics Reveals a Therapeutic Vulnerability State for Early Immunotherapy Interception in Multiple Myeloma (MM)

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Introduction: Understanding the underlying dynamics of MRD resistance could help in the design of tailored strategies empowered to eradicate MRD and improve survival of MM patients (pts). **Methods:** MRD dynamics were defined using NGF and Connector in 539 MM pts with ≥3 assessments in the GEM2012-2014 and GEM2017FIT trials. Validation was performed in a real-world cohort of 249 Greek pts. WES and RNA seq was performed to compare MRD with paired diagnostic and relapse tumors FACSorted from 107 MM pts. The bone marrow cell composition in matched diagnostic and MRD samples was analyzed using NGF. For experimental validation, MIcγ1huCRBN immunocompetent mice, which carry humanized CRBNI391V and progressively develop human-like MM, were treated with VRD (as in the GEM2012-2014 trial) until persistent MRD, which drove relapse upon treatment discontinuation. To evaluate the impact in OS, murine anti-BCMA CAR T cells were injected i.v. at MRD vs relapse. **Results:** A total of 3892 assessments from 788 pts were computed to identify three subgroups with different MRD dynamics: sustained undetectable (29.5%), positive/stable (46%) and positive/evolving levels (24.5%). The respective PFS rates at 6 years were 83%, 74% and 11%, and of OS were 89%, 91% and 28%. Positive/evolving MRD levels was the strongest risk-factor for PFS (HR: 9.1, p < .001) and OS (HR: 31.6, p < .001) in multivariate models including transplant-eligibility and the R-ISS. Identical results were observed in trial and real-world cohorts. MRD genomic divergency increased with high-dose chemotherapy when compared to induction. Further genomic complexity was observed in paired tumors sequenced at relapsed vs MRD vs diagnosis. WGS of mouse MM cells revealed increased number of genetic alterations after

VRD therapy, including mutations in Trp53, DNA repair, CRBN, and CRBN-target genes. These results showcase MRD as potentially more vulnerable to therapy than relapsed tumors. MRD transcriptional adaption also peaked after high-dose chemotherapy when compared to induction. Both human and mouse MRD cells were enriched in hallmarks linked to cell cycle, KRAS signaling, TNFα signaling and inflammatory response. In parallel, there was evolving distribution of immune cells in the tumor microenvironment at diagnosis vs MRD vs relapse, including the expansion of clonal and dysfunctional CD8 T cells. In line with the genomic findings, transcriptional and immune dynamics point to MRD as an optimal state for early intervention. Accordingly, deeper and prolonged responses were observed in MIcγ1huCRBN mice following MRD interception using anti-BCMA CAR T cells vs identical treatment at relapse, which led to improved OS (median 12 vs 9.5 months; $p < .001$). **Conclusions:** This study presents MRD kinetics as the most relevant prognostic factor in MM, which could be intercepted with T-cell redirecting therapy to prevent continuous genomic evolution and immune modulation from MRD to relapse.

PA-168

Advancing Soluble BCMA Quantification in Immunotherapy: Analytical Validation of ELLA Versus ELISA for Predicting Toxicity and Response

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Introduction: Serum soluble B-cell maturation antigen (sBCMA) is a validated biomarker associated with treatment response and toxicity in patients receiving BCMA-directed therapies. Elevated baseline sBCMA has been linked to inferior outcomes following chimeric antigen receptor T-cell (CAR-T) therapy and bispecific T-cell engagers (BiTE), while pre-treatment sBCMA reduction correlates with improved outcomes (Freeman et al., 2025; Lee et al., 2024). Recent data support its role in identifying patients who achieve deep responses with long term disease control (Voorhees et al., ASCO 2025, Abstract 7507). Despite its promise, widespread integration into clinical workflows has been limited by technical constraints of ELISA-based platforms, including high inter-assay variability and limited throughput. **Methods:** This retrospective study was approved by the IRB at H. Lee Moffitt Cancer Center and an external IRB (Advarra) and conducted in accordance with the Declaration of Helsinki. Patients were included if they received FDA-approved BCMA CAR-T therapy, consented to the biospecimen protocol (Pro00021733) and had baseline pre-lymphodepletion serum sample available. ELISA assays (R&D Systems) were performed using Cytation3 readers and Gen5 software, with concentrations calculated in GraphPad. A subset of 40 samples underwent parallel testing via ELLA following manufacturers protocol (Protein Simple). Paired sBCMA values were compared using Pearson correlation, linear regression, Bland–Altman analysis, and categorical agreement by clinically relevant thresholds. Residual and agreement analyses assessed reproducibility, bias, and overall assay performance to support clinical translation. **Results:** sBCMA values measured via ELLA and ELISA were strongly correlated (Pearson $r = 0.94$, $p < 0.0001$). Linear regression yielded an R^2 of 0.93, with residuals demonstrating no evidence of heteroscedasticity. Bland–Altman analysis showed a consistent minor bias in ELLA over ELISA ($+0.26$ $\log_{10}$ units), with 95% of values within agreement limits. At a CAR-T–relevant cutoff (≥100,000 pg/mL), ELLA and ELISA demonstrated substantial concordance (Cohen's $\kappa = 0.79$), with ELLA identifying 4 additional high-risk cases. At a BiTE threshold (≥400,000 pg/mL), agreement improved further ($\kappa = 0.89$), with only 2 ELLA-classified highs missed by ELISA. No false negatives were observed in either comparison. ELLA demonstrated superior reproducibility, automation, and reduced hands-on time compared to ELISA. **Conclusions:** This analytical validation supports the clinical use of ELLA for sBCMA quantification. Given sBCMA's growing utility in predicting both response and toxicity to BCMA-targeted immunotherapies—and its emerging role in identifying patients likely to experience long-term disease control—accurate, scalable measurement is critical. ELLA enables timely, reproducible integration of sBCMA into prospective trials and practice, improving biomarker-guided treatment decisions in cellular therapy.

PA-169

Mass Spectrometry vs. 10-5 MRD Detection by Next-Generation Flow and Sequencing in Multiple Myeloma: Results from the Cassiopeia Clinical Trial

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Introduction: The detection of minimal residual disease(MRD) is crucial for evaluating treatment response in Multiple Myeloma(MM). Achieving 10-5 MRD sensitivity is recommended by the IMWG for accurate disease remission assessment, correlating with better long-term outcomes and sustained remission. Recently, mass spectrometry (MS) has emerged as a promising tool for MRD detection, offering a significant clinical advantage by being less invasive as it can be performed on peripheral blood. **Methods:** Our goal is to compare the impact of MS versus MRD detected by NGF and NGS with a sensitivity level of 10-5 on patient outcomes post-treatment in a cohort from the Cassiopeia clinical trial, a Phase 3 study evaluating the addition of daratumumab to bortezomib, thalidomide, and dexamethasone (VTd) induction/consolidation and with daratumumab maintenance vs. observation in transplant-eligible newly diagnosed MM. This study examines MRD detection in paired samples (with NGF/NGS and MS available) at +100 days post-ASCT (n = 162) and at weeks 25 (n = 160), 52 (n = 130), and 105 (n = 112), providing a longitudinal perspective on MRD's prognostic significance. MS was assessed by MALDI-ToF with the EXENT® Analyser (The Binding Site, part of Thermo Fisher Scientific). **Results:** At +100 days, the MS + group had a median progression-free survival (mPFS) of 38.1 months (mo) (HR 0.42, 95% CI:0.27–0.64, p < 0.0001). The NGF +10-5 group had a mPFS of 42.1 mo (HR 0.58, 95% CI:0.37–0.91, p = 0.0124), and the NGS+10-5 group had a mPFS of 42.9 mo (HR 0.59, 95% CI:0.38–0.92, p = 0.0164). At week 52, the MS+ group had a mPFS of 21.6 mo (HR 0.20, 95% CI:0.11–0.39, p < 0.0001). The NGF+10-5 group showed a mPFS of 19.8 mo (HR 0.17, 95% CI:0.09–0.33, p < 0.0001), and the NGS+10-5 group had a mPFS of 21.4 mon (HR 0.15, 95% CI:0.08–0.29, p < 0.0001). At other time points (week 25 and week 105), the MS+, NGF+10-5, and NGS+10-5 groups showed similar significant inferior mPFS. However, at all time points, mPFS was not yet reached for patients achieving MS- and 10-5 NGF-/NGS-. The MS negative predictive value (NPV) at +100 days and week 52, compared to 10-5 NGF and NGS, was 0.90 (CI:0.82–0.94) and 0.87 (CI:0.78–0.92), respectively. The MS positive predictive value (PPV) at +100 days and week 52, compared to 10-5 NGF and NGS, was 0.83 (CI:0.67–0.91) and 0.90 (CI:0.78–0.92), respectively. **Conclusions:** These findings highlight the prognostic significance of MRD using MS and NGF/NGS at a 10-5 sensitivity level across multiple time points in the Cassiopeia clinical trial. Not reaching mPFS for the MS- and 10-5MRD- groups underscores the potential for prolonged remission, indicating the high efficacy of these methods in predicting better long-term outcomes.

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Whole Genome Sequencing of Cell-free DNA for Assessment of Minimal Residual Disease in High-Risk Smoldering Multiple Myeloma

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Introduction: In multiple myeloma (MM), assessment of minimal residual disease (MRD) is limited by the need for serial bone marrow (BM) biopsies. Furthermore, single-site assessment of MRD (e.g., by flow cytometry) may be limited with extramedullary/systemic manifestation. We therefore performed a longitudinal analysis of MRD assessed by whole genome sequencing (WGS) of cell-free (cf)DNA from an interventional trial for high-risk smoldering MM. **Methods:** MRDetect is an ultra-sensitive tumor-informed detection approach for MRD. First, 80X WGS of baseline BM tumor samples (with 40x normal match) was performed on CD138+ plasma cells. Serial blood plasma (Streck tubes) from timepoints including pre-treatment baseline (BL), BM MRD assessment, and progression of disease (PD) were then subjected to 40x WGS and cfDNA reads supporting single nucleotide variants (SNV) corresponding to SNVs from BM WGS were used to estimate tumor fraction (TF) in blood. Patient-specific limits of detection (LOD) were computed by comparing detection rates in plasma to control SNV compendium detection rates derived from tumor-supporting reads in unrelated plasma samples. Results were compared to standard flow MRD in BM (10-5). **Results:** We assayed 71 plasma samples with 25 BL BM samples from 25 patients (n = 96 WGS; median follow-up 53 months). The median TF of BL plasma samples was 6×10^{-4} (range; 1×10^{-4}–9×10^{-3}). The median LOD across patients was 1.2×10^{-4} (range 2×10^{-4}–9×10^{-5}) and 60/71 (84.5%) plasma samples had detectable disease. Tumors with genomic complexity (e.g., chromothripsis and APOBEC activity) had higher BL TF (p = 0.007). In line with this, a higher TF at BL was associated with biochemical/clinical PD (p = 0.01). In longitudinal analysis, cfDNA WGS recapitulated MRD+ for 14/15 (93%) BM MRD+ assays. Representing a limitation with low mutational burden, one case with the lowest SNV count (~2000) could not be detected in plasma. However, 15/21 (71%) BM MRD- timepoints were seen to instead be MRD+ in plasma. Most discrepancies occurred in cases where BM MRD+ conversion or PD later occurred, or in cases where flanking MRD BM assessments were MRD+ (10/15, 75%), suggesting superiority of cfDNA over BM assessment. For cases with BM MRD+ conversion or PD, plasma collected three and six months prior detected early MRD resurgence in 4/6 (75%), representing a logistical advantage. Furthermore, incremental growth of TF in serial measurements foreshadowed PD. Finally, all patients with PD (n = 5) had MRD+ in

plasma at end of combination therapy, but only 2 were BM MRD+ at the same time point. No concordant plasma/BM MRD- patients experienced PD (HR; inf, p = 0.035). **Conclusions:** MRD+ by cfDNA WGS recapitulates MRD+ BM flow cytometry. Despite the deeper LOD of localized BM flow, cfDNA WGS can detect MRD+ where BM flow did not, representing an advantage to the addition of this peripheral approach. LOD is expected to be deeper in newly diagnosed and relapsed MM, where SNV burden is higher.

PA-171

Subclonal and Clonal Progression of Previously Characterized Mutations and Variants of Unknown Significance (VUS) Across a Cohort of Plasma Cell Dyscrasia Patients

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Introduction: Plasma cell dyscrasias (PCD) are genetically diverse, and key oncogenic drivers have been identified. In multiple myeloma (MM), subclonal RAS mutations, in 50–61% of cases, are known to promote progression. Alterations in TP53, DIS3, FAM46C, and NF-κB regulators add complexity, and IGH translocations remain central to risk stratification. Yet, few markers predict MGUS or smoldering MM progression. Current research targets mutational burden, cytogenetic shifts, and clonal diversity. Variant allele frequency (VAF) serves as a clonality proxy (Boscolo Bielo et al 2023), with higher VAF indicating founder clones and lower VAF (commonly <10%) suggesting subclones. Subclonal diversity may signal progression and resistance, as clonal shifts under treatment correlate with poor prognosis. Understanding clonal evolution is key to defining progression in PCDs. **Methods:** We analyzed genomic variants from 252 PCD samples using the Tempus xT® 648-gene NGS panel. Samples included bone marrow (n = 228), tissue (n = 5), and blood (n = 19), collected from Jan 2020 to May 2025. Diagnoses confirmed by chart review included MGUS (n = 84), SMM (n = 23), MM (n = 102), AL amyloidosis (n = 14), and other PCDs (n = 29). NGS reports were digitized as sample-specific CSVs and analyzed using Python in Jupyter (v7.3.2) and Excel (v16.96.1). COSMIC (v102) web platform identified cancer-associated single nucleotide variants (SNVs). **Results:** We identified 332 VUS and 81 oncogenic variants in 252 PCD samples. The malignant cohort had higher oncogenic mutations per sample than the premalignant cohort (Welch's t-test, p < 0.0001), though VUS counts did not differ significantly (p = 0.2276). Among VUS, most frequently observed mutations were in KMT2C, ARID1B, NOTCH1, ZFHX3, and ATM. Notably, all ARID1B, NOTCH1, and ATM SNVs were clonal (VAF >10%). Of 19 ARID1B SNVs, 12 have not been previously associated with any cancer; only one (c.1016_1021dup) was previously linked to hematologic malignancy. Seven of 12 NOTCH1 and 3 of 11 ATM SNVs were not previously reported. Among clonal VUS, the malignant cohort harbored 217 unique genes (574 SNVs; 399 unique). Mean SNVs per gene were higher in malignant samples (1.44 vs. 1.09, p < 0.0001). Most frequent oncogenic mutations occurred in DNMT3A, TP53, MYD88, TET2, and CXCR4, with most DNMT3A, MYD88, and CXCR4 variants being subclonal. Mean VAF was higher in VUS versus oncogenic groups across malignancy status (One-way ANOVA p < 0.0001 then Tukey's test with Benjamini-Hochberg adjusted p-values). VAF did not differ between oncogenic premalignant and malignant samples (p = 0.9848). **Conclusions:** Our analysis reveals distinct clonal patterns and mutational profiles across PCDs. Subclonal oncogenic mutations were more common in malignant states, while VUS were often clonal. Further studies on longitudinal clonal dynamics are needed.

PA-172

The Role of CHIP Mutations in Plasma Cell Dyscrasias: Implications for Clonal Evolution and Risk Stratification

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Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is a premalignant state defined by somatic mutations in hematopoietic stem cells. DNMT3A, TET2, and ASXL1 are common mutations. CHIP occurs in ~19% of plasma cell disorders (PCD), such as multiple myeloma (MM), smoldering MM and MGUS. Prevalence rises with age and is linked to cardiovascular disease and prior chemotherapy/radiation exposure and CHIP may promote progression in MGUS/SMM through age-related genomic instability and therapy-induced clonal selection. In MM, CHIP may predict poorer outcomes, particularly post-autologous stem cell transplant (ASCT). High-throughput single-cell sequencing has detected CHIP mutations in nearly half of ASCT patients. Longitudinal studies suggest CHIP drives high-fitness clonal expansion and may impair treatment response. **Methods:** We analyzed genomic variants from 252 PCD samples using a Tempus xT® 648-gene next generation sequencing (NGS) panel. Samples included bone marrow (n = 228), tissue (n = 5), and blood (n = 19), collected from Jan 2020 to May 2025. NGS reports were digitized and analyzed using Python in Jupyter (v7.3.2) and Excel (v16.96.1). COSMIC (v102) web platform identified cancer-associated SNVs. Diagnoses confirmed by chart review included MGUS (n = 84), SMM (n = 23), MM (n = 102), AL amyloidosis (n = 14) and other PCDs (n = 29). **Results:** We identified 161 mutations across 12 CHIP-associated genes. DNMT3A carried the highest number of mutations (n = 57), 44 of which were unique single nucleotide variants (SNV). 12 SNVs had not been previously identified as

cancer-associated, and only 3 were known to be associated with PCDs. 58% of malignant and 50% of premalignant DNMT3A SNVs were associated with acute myeloid leukemia. The most common SNV seen in this cohort was c.2645G >A (n = 4). Number of DNMT3A mutations did not differ between malignant and premalignant cohorts (Mann-Whitney U, p = 0.7715). CHIP-positive was older than CHIP-negative in the overall cohort (70.8 versus 67.4 years; Welch's t-test, p = 0.0002), and distribution curves highlight this shift. Unique SNV counts for DNMT3A, TET2, and ASXL1 were similar or the same in premalignant and malignant samples (22 and 24, 10 and 9, 4 and 4, respectively). Overall, no significant difference in unique SNVs per CHIP gene was found between premalignant, malignant, treatment-naive MM, and treatment-exposed MM groups (one-way ANOVA, p = 0.6079). **Conclusions:** CHIP mutations occurred across all disease states, most often in DNMT3A. Similar mutation burdens in premalignant and malignant samples support CHIP as a parallel clonal process, not a precursor. Our analysis did not support prior reports of increased CHIP mutations post-treatment; however, it is limited by a sample size. Stratifying by post-ASCT may yield more insight, given its role as a potential contributor to disease complexity and resistance. Further study is needed to clarify the role of CHIP in disease progression.

PA-173

Quantitative CD38 Expression and Clinical Response to Anti-CD38 Therapy in Multiple Myeloma: A Retrospective Cohort Analysis

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Introduction: Anti-CD38 monoclonal antibodies have become essential in treating multiple myeloma (MM), with consistent efficacy across lines of therapy. However, responses vary substantially among patients. Early studies have suggested that baseline CD38 expression may influence treatment outcomes, but supporting clinical evidence remains limited. This study explored whether quantitative CD38 expression correlates with response and survival in MM, and assessed its potential as a predictive biomarker for treatment selection. **Methods:** We retrospectively analyzed 40 MM patients treated with anti-CD38 antibodies (daratumumab or isatuximab) between 2019 and 2025, all receiving ≥4 treatment cycles. CD38 expression on plasma cells was quantified using multiparameter flow cytometry, reporting median fluorescence intensity (MFI) and antigen density (molecules/cell). Treatment regimens included combinations with dexamethasone alone (n = 2), proteasome inhibitors (PIs, n = 11), immunomodulatory drugs (IMiDs, n = 14), both PIs and IMiDs (n = 9), or other agents (n = 4). Patients were treated in first (57.5%), second (25.0%), third (10.0%), or later lines (7.5%). Primary endpoints were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Prognostic factors were assessed by multivariate Cox regression. **Results:** At a median follow-up of 22.1 months (data cutoff: May 2025), the ORR was 75.0%, with 30.0% achieving complete or stringent complete response. Median PFS and OS were 23.8 months (95% CI: 14.0–33.7) and 32.6 months (95% CI: 32.3–140.1), respectively. Response rates were higher in newly diagnosed patients (78.3%) than in relapsed/refractory MM (70.6%). Median CD38 MFI was 27,370 (IQR: 15,417–46,255), and antigen density was 39,671.5 molecules/cell (IQR: 20,771.3–72,516.5). Patients with ≥PR had significantly higher CD38 expression than non-responders (MFI: 47,010.4 vs. 11,019.0, p = 0.0107; antigen density: 68,338.3 vs. 26,880.6, p = 0.0109). Multivariate analysis identified high tumor burden, high-risk cytogenetics, and t(14;16) as independent predictors of worse survival (all p < 0.05). **Conclusions:** Higher CD38 expression was strongly associated with deeper responses and improved survival in MM patients receiving anti-CD38 therapy. These findings support incorporating CD38 quantification into baseline assessment to better predict treatment benefit. As biomarker-driven strategies in MM continue to evolve, this study provides real-world evidence for the potential of CD38 as a clinically meaningful predictive marker. Further prospective validation is warranted.

PA-174

Patient Perceptions of MRD Negativity as a Treatment Outcome and Regulatory Endpoint in Multiple Myeloma

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Introduction: Minimal residual disease (MRD) negativity has emerged as a surrogate marker in multiple myeloma (MM), correlating with deeper responses and improved progression-free survival. In April 2024, the FDA's Oncologic Drugs Advisory Committee (ODAC) endorsed MRD negativity as an early endpoint for accelerated treatment approval in MM. While this regulatory shift may shorten drug approval timelines, patient perspectives on MRD as a treatment goal and trial endpoint remain underexplored. Understanding these views is critical to aligning clinical trial design, regulatory strategies, and patient values. **Methods:** A cross-sectional online survey was conducted among adult MM patients (≥18 years)

enrolled in the HealthTree Cure Hub registry. The IRB-approved survey included 13 MRD-related questions and six demographic questions. Patients were asked about MRD testing experience, treatment perceptions, and regulatory awareness. The survey included a comparative evaluation of the patient's insights regarding MRD-based accelerated approval, both prior to and following their awareness of the ODAC vote concerning MRD. Responses were de-identified and analyzed descriptively. **Results:** Among 192 respondents, 163 (85%) reported an MM diagnosis. Of 149 patients who answered the testing question, 106 (71%) had undergone MRD testing. Among those tested, 42 (41%) achieved 10^{-6} sensitivity, 19 (19%) reached 10^{-5}, and 24 (24%) did not achieve MRD negativity. Regarding efficacy perceptions, 105 of 136 (77%) rated sustained MRD negativity (≥12 months) as "excellent," while only 1 (1%) rated it "below average" or worse. Despite achieving complete response, 58 of 134 (43%) indicated they would be "above average likely" or more to discuss changing therapy to pursue MRD negativity. After being informed of MRD-based regulatory approval by an expert, 87 of 128 (68%) rated it as "very important," compared to 64 of 130 (49%) before reading the explanation. Sixty-three of 127 (50%) said the decision gave them "a great deal" of hope; 55 (44%) believed it would greatly accelerate treatment access. When considering future therapies, 106 of 124 (85%) said MRD negativity held "a lot" or "a great deal" of importance, despite recognizing the limited long-term safety data. **Conclusions:** Patients with MM strongly view MRD negativity, particularly when sustained, as a meaningful indicator of efficacy. A substantial proportion reported willingness to modify treatment strategies to achieve MRD negativity, and educational content significantly increased support for MRD-based regulatory pathways. These findings highlight the importance of incorporating patient-reported preferences into clinical trial endpoints and regulatory decision-making, reinforcing MRD's relevance not only as a biomarker but as a patient-valued measure of treatment success.

PA-175

Comprehensive Characterization and Pharmacological Targeting of Stem-Like Side Population Compartment in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is sustained by a discrete subpopulation of stem-like cells that drive tumor propagation, foster therapeutic resistance, and precipitate relapse. These tumor-initiating cells are characterized by high drug-efflux capacity, prolonged quiescence, and robust self-renewal and confers enhanced clonogenicity and tumorigenicity on side population (SP)-enriched MM cells compared to their non-SP counterparts. **Methods:** We performed flow cytometry to quantify and isolate SP cells from MM cell lines and patient-derived bone marrow samples, applied mass cytometry and immunoblotting to delineate molecular signatures in SP versus non-SP subsets. **Results:** In this study, western blot analysis of key components of the Wnt/β-catenin, SHH-GLI-NANOG (Ptch1, Ptch2, Gli1, Gli2, Sufu), and Notch1 pathways in SP-enriched MM cell lines revealed no significant differential protein expression compared to non-SP cells, with the only exception being a modest change in β-catenin levels. Furthermore, through combined flow cytometry (Nanog, Nestin, Oct3/4, Sox2, CD24, CXCR4) and immunoblotting (Sox2, KLF-4, Oct3/4, ABCG2/BCRP1), we confirmed that SP and non-SP cells share analogous stemness and pluripotency marker profiles, underscoring the need for advanced techniques to resolve phenotypic distinctions. Nevertheless, the frequency, molecular features, and functional properties of SP in patient-derived MM samples remain poorly characterized. To address this, we quantified SP frequency within malignant plasma cell populations in clinically annotated bone marrow specimens from MGUS, newly diagnosed MM, and relapsed/refractory MM patients, revealing marked heterogeneity across disease stages. To define the cellular and molecular signatures that distinguish SP from non-SP cells, we employ mass cytometry to profile stemness and pluripotency factors alongside key developmental pathways, disease-specific signaling pathways, and plasma cell-associated antigens, and will present the resulting data. Furthermore, we pharmacologically targeted SP-enriched MM cells by evaluating small-molecule inhibitors, including vismodegib (Hedgehog pathway inhibitor), plumbagin (PI3K/Akt/mTOR pathway suppressor), deguelin (oxidative stress inducer via SOD and GSH upregulation), parthenolide (NF-κB pathway inhibitor), and the polyether ionophores salinomycin and monensin, to assess their capacity to deplete SP cells and elucidate their mechanisms of action. **Conclusions:** Systematic interrogation of this stem-like SP thus provides a compelling strategy for biomarker discovery and preclinical evaluation of novel therapeutics, with the ultimate goal of eradicating relapse-initiating cells and substantially improving patient outcomes. This study was supported by the Scientific Grant Agency VEGA 2/0088/23 (JJ), VEGA 2/0087/23 (DC), the SRDA grants APVV-20-0183 (JJ), APVV-19-0212 (DC), APVV-21-0215 (JJ), APVV-23-0482 (DC) and the NextGenerationEU project No.09I03-03-V04-00451 (JJ) and No. 09I03-03-V02-00031 (DC & KS).

PA-176

Comparative Evaluation of Advanced Serum-Based Techniques for the Sensitive Detection of Monoclonal Proteins in Multiple Myeloma – A Pilot Study

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy characterized by the production of monoclonal immunoglobulins (mAbs). Effective monitoring of measurable residual disease (MRD) and emerging clonal populations is essential for disease management but remains limited by the invasiveness and infrequency of bone marrow examinations. To address these limitations, novel serum-based techniques have been developed and we conducted their comparative evaluation - including MALDI-TOF mass spectrometry, our novel in-house method named MQ-Sense and high-resolution LC-MS targeting clonotypic peptides of immunoglobulins. **Methods:** A cohort of ≥15 serum samples from MM patients or samples artificially spiked with monoclonal antibodies in a polyclonal serum background was analyzed. The performance of MALDI-TOF, represented by the EXENT System (Binding Site), and our newly developed MQ-Sense method—based on affinity-based isolation and HPLC detection of antibodies—was benchmarked to conventional immunofixation electrophoresis (IFE). Selected samples were further analyzed using a high-resolution nanoLC-MS/MS workflow targeting specific peptides derived from myeloma cell DNA or known sequence of standards. Each method was evaluated for analytical sensitivity, M-protein classification, and the ability to distinguish therapeutic mAbs. **Results:** IFE exhibited limited sensitivity, particularly for low-abundance monoclonal proteins e.g. post-treatment samples. Both MALDI-TOF and MQ-Sense demonstrated improved sensitivity. MQ-Sense achieved very low limit of detection (LOD) of ≤30 $mg{\cdot}L^{-1}$ in polyclonal backgrounds. It also showed capability to differentiate therapeutic mAbs as compared to IFE and MALDI-TOF. Targeted LC-MS/MS significantly have even more sensitivity (LOD ≤1 $mg{\cdot}L^{-1}$), enabling precise detection and longitudinal monitoring of individual clonal populations but is known for limited ability of detection newly emerging subclone. This drawback can be further improved with combination with MQ-Sense, rather than IFE, that had suboptimal LOD (175 $mg{\cdot}L^{-1}$). The performance of MQ-Sense is comparable to MALDI-TOF, but it is more cost-effective. MALDI-TOF systems (such as EXENT) are similarly priced to a full nanoLC-MS system used for detecting clonotypic peptides. **Conclusions:** This pilot study demonstrates that MQ-Sense offers enhanced sensitivity and specificity for serum-based detection of M-proteins in MM. Compared to conventional IFE, MQ-Sense serves as a robust intermediate method and, when combined with high-resolution LC-MS/MS, enables complex and non-invasive clonal monitoring. These findings support the implementation of advanced serum-based workflows for improved MRD assessment and disease surveillance in MM. Supported by Ministry of Health of the Czech Republic, grant nr. NW24-03-00347.

PA-177

Circulating Plasma Cells as an Independent Prognostic Marker in Newly Diagnosed Multiple Myeloma: Clinical Correlation and Immunophenotypic Insights

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Introduction: Circulating plasma cells (CPCs) reflect the dissemination potential of malignant clones in multiple myeloma (MM) and may serve as a surrogate for tumor aggressiveness and microenvironmental independence. However, the prognostic value of baseline CPC levels and their immunophenotypic characteristics relative to bone marrow plasma cells (BMPCs) remains incompletely defined. This study aimed to investigate the clinical and prognostic significance of CPCs at diagnosis and explore their distinct immunophenotypic profile. **Methods:** A total of 212 newly diagnosed MM patients were retrospectively analyzed. Clinical and laboratory parameters, cytogenetic risk, treatment regimens, and outcomes were collected. CPC levels at diagnosis were assessed using two-tube, eight-color multiparametric flow cytometry or next-generation flow cytometry. Progression-free survival (PFS) was defined from treatment initiation to progression, death, or last follow-up. **Results:** The cohort had a median age of 60 years (range: 52–67); 122 (57.5%) were male. Most patients presented with advanced disease: 155 (73.2%) were ISS stage II/III and 166 (83%) were R-ISS stage II/III. Among patients with detectable circulating plasma cells (CPCs), the median CPC level was 0.16% (IQR: 0.04–0.52%). Regarding treatment, 168 patients (79.2%) received a PIs plus IMiDs-based regimen as first-line therapy, and 70 patients (33%) underwent autologous stem cell transplantation (ASCT). Patients in the CPC-high group (> 0.0096%) had significantly higher tumor

burden, including more advanced stage, lower platelet and hemoglobin levels, elevated β2-microglobulin and LDH, and more frequent high-risk cytogenetic abnormalities. CPC levels were moderately correlated with PBMC percentage ($p = 0.51$, $p < 0.001$). CPC-high patients also showed significantly shorter PFS ($p = 0.035$). In multivariable analysis adjusting for ISS stage, cytogenetics, LDH, and extramedullary disease, increased CPC levels remained independently associated with inferior PFS (HR = 1.60; 95% CI: 1.09–2.33; $p = 0.011$). Subgroup analysis showed that ASCT significantly mitigated the adverse impact of elevated CPCs. Immunophenotypic comparison revealed significant differences in the expression intensity of CD200, CD28, CD117, and CD81 between CPCs and BMPCs. Moreover, CD28 and CD117 demonstrated lower positivity rates in CPCs. These findings suggest that CPCs may represent a more aggressive subpopulation with reduced microenvironmental dependence, enhanced migratory capacity, and potential treatment resistance, thereby contributing to systemic disease dissemination. **Conclusions:** Baseline CPC levels are significantly associated with high-risk disease features and inferior PFS in newly diagnosed MM. Their distinct immunophenotypic profile supports a biologically aggressive and microenvironment-independent phenotype. CPCs may serve as a valuable biomarker for early risk stratification and therapeutic guidance in MM.

PA-178

Integrating p53 Protein Expression with Mutation and Copy Number Status Enhances Risk Assessment in Myeloma

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Introduction: Deletion of (17p) in ≥20% neoplastic cells or TP53 mutation (TP53mut) regardless of VAF level are defined as high-risk factors in the newly proposed IMS/IMWG model. It remains unclear if the risk can be further stratified based on the scale and context of these alterations. We hypothesized that further assessment of p53 protein expression may allow an integrated risk assessment. In wild type TP53, p53 expression by immunostaining is weak and heterogenous while mutations or deletions typically result in abnormal p53 expression as overexpression (HI) or total absence (Null). **Methods:** The TP53 copy number changes, del17/(17p), were determined by conventional karyotyping and/or fluorescence in situ hybridization (FISH) using CD138 enriched plasma cells. TP53mut was detected by targeted next generation sequencing (NGS) using whole bone marrow aspirate. Bone marrow trephine samples were stained using a monoclonal anti-p53 antibody clone DO-7 (Dako, Carpinteria, CA) which recognizes both wild-type and the mutant forms. Clinical data were collected from chart review. **Results:** The study included 45 patients with adequate samples and documented TP53 mutations collected from 2012 to 2024. There were 31 men and 14 women, age 38 to 90 (median: 67yrs). All patients had persistent or relapsed diseases. In 20 patients, >1 TP53 mutations were detected. The mutations were characterized as missense (n = 34), nonsense (n = 4), both missense and nonsense (n = 2), frameshift (n = 2), splice site (n = 3). The VAF levels ranged from < 5% to 57.6% (median < 5%), despite a much higher tumur burden (median: 60%, range 10–100%) determined by CD138 staining. Del17/(17p) was detected in a background of complex karyotype in 17 of 26 (65.4%) patients with a complex karyotype (57.8%), or by FISH in a background of a simple or normal karyotype in 11 (24.4%). A p53 overexpression (HI) or a null pattern were seen in 29 (64.4%) and 7 (15.6%) respectively. Of the 9 (20%) cases with a normal p53 pattern, both missense and nonsense were seen, VAF < 10. With a median follow up of 47 month (range 3–171), 29 died and 16 were alive with a median OS of 62 months. The normal pattern was more associated with a normal or simple karyotype than the abnormal pattern (66.7% vs. 30.5%, $p = 0.04$), though in this small cohort, the OS between the normal and abnormal expression groups was not significantly different. **Conclusions:** TP53 missense mutation is most common type of mutation, usually present at a low VAF, and frequently coexists with del17/17p, in a background of complex karyotype, resulting in abnormal p53 expression. A normal pattern of p53 expression, however, was observed in approximately 20% of patients who are more likely to have a normal or simple karyotype, compared to patients with abnormal p53 expression, suggesting that integrating p53 protein expression may enhance risk stratification beyond mutation and copy number changes.

PA-179

Verification and Optimization of VTE Risk Stratification System for Multiple Myeloma in China Based on Review Cohort

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Introduction: Venous thromboembolism (VTE) is a common complications in multiple myeloma (MM), linked to poor prognosis. The International Myeloma Working Group (IMWG) recommends stratified prevention for MM patients via VTE risk assessment models. Validating and optimizing a VTE risk assessment model for MM is crucial for hematologists to better identify the VTE risk in MM patients. **Methods:** This study is retrospective. (1) Derivation cohort: We selected 332 NDMM patients admitted to Fu Xing Hospital, Capital Medical University from January 2017 to April 2024. Patients were categorized into VTE and non-VTE groups based on the occurrence of VTE within six months following the initiation of chemotherapy. We identified independent risk factors for VTE in

NDMM through univariate and multivariate analyses. Further optimize the VTE risk stratification system in China based on the identified independent risk factors. (2) Validation cohort: 101 NDMM patients who visited the hospital from May 2024 to November 2024. The predictive efficacy of the VTE risk stratification system in China, before and after optimization, will be compared for their ability to predict the occurrence of VTE in NDMM using the area under the receiver operating characteristic curve (AUC). **Results:** The patients in the validation cohort and derivation cohort were similar with respect to age, gender, BMI, and ECOG score. This validation cohort included 332 NDMM, median age of 65.50 years (95% CI: 57.27~72.00). There were 201 male (60.54%) and 131 female (39.46%). Notably, 84.94% (282/332) received thromboprophylaxis before the initiation of chemotherapy, and VTE occurred within six months was 8.43% (28/332). Factors associated with the occurrence of VTE in patients with NDMM include female ($P < 0.001$), bed rest at diagnosis ($P < 0.001$), platelet count above the upper limit of normal (ULN) ($P = 0.003$), and D-dimer >0.5 mg/L ($P = 0.009$). The results of the multivariate analysis indicated that female gender, bed rest at diagnosis, and platelet count above the ULN are independent risk factors for VTE. It is recommended to optimize the VTE risk stratification system in China with these independent risk factors and thrombosis prevention treatments. The AUCs of the IMWG score and the VTE risk stratification system in China, both before and after optimization, were 0.605 (95% CI: 0.483~0.728), 0.660 (95% CI: 0.555~0.766), and 0.742 (95% CI: 0.649~0.835), respectively. The validation cohort includes 101NDMM, the incidence of VTE within 6 months was 7.92% (8/101) , and the AUCs of the VTE risk stratification system in China before and after optimization were 0.659 (95%CI: 0.490~0.970) and 0.730 (95%CI: 0.420~0.898), respectively. **Conclusions:** MM-related VTE predominantly occurred within the first 6 months following chemotherapy initiation. Lower extremity deep vein thrombosis constituted the most common VTE manifestation. The optimized VTE risk stratification system in China demonstrated enhanced capability in accurately identifying high-risk populations.

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Revealing Clonal Evolution and Assessing Immune Reconstitution in Multiple Myeloma Using Next-Generation Sequencing-Based Minimal Residual Disease (NGS-MRD) Analysis

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Introduction: It is generally believed that clonal CDR3 sequences identified at baseline for MRD detection are stable and unique throughout the disease course. However, Munshi et al. reported the emergence of evolved clones post-treatment, though the prognostic significance of these findings remains undefined. Recently, Martinez-Lopez et al. proposed "clonal diversity" from NGS-MRD as a surrogate for immune competence to evaluate immune system reconstitution in MM patients. **Methods:** A total of 183 NDMM patients who underwent at least 1 NGS-MRD assessment were enrolled, including 109 patients with ≥2 time points. Clonotypes fulfilling clonal rearrangement criteria were defined as malignant, which called index clone at baseline. Clonal evolution was defined as either the emergence of new malignant Ig clonotypes or a discordant change in the relative frequency of the index clone between baseline and post-treatment samples. To assess immune reconstitution, BCR diversity was quantified by the number and Shannon index of unique IGH, IGK, and IGL clonotypes. **Results:** Among 109 patients, 8 patients exhibited new Ig clones post-treatment, while 5 showed discordant change in the relative frequency of the index clone. All 13 cases were persistent/recurrent MRD-positive. For example, in patient P07, new clones emerged after achieving CR with a residual MRD level of 10–3, while the original index clone diminished. Among persistent/recurrent MRD-positive patients, those with clonal evolution had significantly shorter PFS (1-year PFS: 40.0% vs. 86.5%, $P = 0.022$). Higher BCR diversity was found to be associated with better immune reconstitution. High IGH-Shannon index correlated with increased serum IgM levels ($P = 0.001$) and a higher proportion of normal plasma cells in the bone marrow ($P < 0.001$). High BCR diversity at the start of maintenance therapy showed a trend toward association with better PFS (IGH-counts: $P = 0.18$; IGK-counts: $P = 0.034$; IGL-counts: $P = 0.15$; IGH-Shannon: $P = 0.077$; IGK-Shannon: $P = 0.0012$; IGL-Shannon: $P = 0.019$). Among patients who experienced disease progression, those with clonal evolution exhibited higher BCR diversity ($P < 0.05$), which may be explained by the presence of a broader spectrum of low-frequency tumor subclones. This observation suggests that BCR diversity may not accurately represent the immune status in patients with clonal evolution. Among persistent/recurrent MRD-positive patients, low BCR diversity at the start of maintenance—indicative of incomplete immune reconstitution—effectively identified a subgroup with poor prognosis independent of clonal evolution (all $P < 0.05$ for Shannon index and clonotype count of IGH, IGK, and IGL). **Conclusions:** NGS-MRD provides insights into clonal evolution and immune status, both of which contribute to risk stratification in MRD-positive multiple myeloma patients. The complementary information provided by NGS-MRD may facilitate earlier identification and intervention for patients at higher risk of relapse.

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The New IMS/IMWG Consensus Risk Definition Predicts Outcomes with Daratumumab-Based Quadruplet Regimens for Multiple Myeloma

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Introduction: In 2024, the IMS and IMWG presented a new consensus risk definition for newly diagnosed myeloma (NDMM), including TP53 mutations and the co-occurrence of IgH translocations with chromosome 1 aberrations. However, as most centers assess NDMM using FISH rather than NGS, TP53 mutation status is not yet routinely available. Here, we apply the consensus definition to patients treated with daratumumab-based quadruplet induction (dara-quads) at MSKCC. **Methods:** We assessed all patients treated with daratumumab-revlimid-dexamethasone plus bortezomib (DVRd) or carfilzomib (DKRd), with at least 3 months of follow-up data available. Genomic information included FISH, SNP-array and MSK-IMPACT-Heme targeted sequencing. MRD-status was compared by Fisher exact test. Survival analysis used Kaplan-Meier estimates, with event-free survival (EFS) including progression and therapy change for suboptimal response. **Results:** 506 patients were treated with DKRd (n = 150) or DVRd (n = 356). Median follow-up was 1.8 years (y, IQR 0.9–3.0, max 7.5y), with 484/506 (96%) having genomic data available. The distribution of individual high-risk (HR) features was 14% with del17p/TP53mut, 11% with IgH translocation + del1p/gain1q, 7% with del1p + gain1q, and 6% with B2M >5.5 mg/dL + creatinine <1.2 mg/dL. Interestingly, of 86/461 (19%) with ISS III, 57 were no longer HR if considering creatinine level. Overall, 33% were defined as HR by at least one consensus criteria, higher than when defining by ISS (19%), R-ISS (8%) or R2-ISS (7%), thereby better delineating patients at intermediate risk by other prognostic scores. EFS and OS did not differ between DVRd and DKRd, with HR patients comprising 30% of DVRd-treated, and 40% of DKRd-treated, possibly reflecting physician preference in this real-world cohort. MRD-status after 4–6 cycles did not differ by risk ($p = 0.4$), however 1y- and 2y-EFS in HR were 81% and 70% respectively, compared with 94% and 90% in standard risk (SR). Of note, patients who were HR by ISS but not by the new definition had shorter EFS compared with SR, while those HR by both ISS and the consensus definition had even shorter EFS. EFS based on each of t(4;14), t(14;16), and gain1q were significant at a univariate level ($p < 0.005$), however, these risk factors mainly occurred in combination, and none retained significance when excluding patients harboring multiple risk factors. **Conclusions:** Dara-quad induction overcomes individual prognostic features in NDMM, however the cumulative impact of HR features remains adverse. Consensus HR status did not predict early MRD status but did predict EFS, suggesting that any MRD-directed approaches should also consider genomic risk. Given that the new IMWG/IMS risk criteria accurately predict survival in the setting of dara-quads, they are a good basis for harmonizing NDMM clinical trial inclusion and stratification. Future trials may benefit from considering risk definition by IMWG/IMS consensus criteria together with HR by ISS staging.

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Minimal Residual Disease Kinetics in Patients with Multiple Myeloma Receiving First Line Treatment and the Association with their Progression-Free Survival; A Retrospective Study of 323 Patients

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Introduction: Minimal residual disease (MRD) has emerged as a highly sensitive tool for evaluating treatment response in multiple myeloma (MM) and is associated with prolonged PFS and OS. Consecutive MRD testing provides critical insight into the depth and durability of response and it drives possible therapeutic decisions. **Methods:** In this retrospective study we evaluated patients with newly diagnosed MM (NDMM), who were assessed with at least 3 consecutive MRD evaluations in the first line of treatment, irrespective of their transplant status. The first MRD evaluation was performed at the time of complete response and consecutive MRD measurements were done every 6–12 months. Four subgroups of patients were identified: sustained MRD positive (sMRDpos), sustained MRD negative (sMRDneg), converted to MRD negative (conMRDneg) and converted to MRD positive (conMRDpos). The aim of the study was to compare PFS among these groups. **Results:** In our center, a total of 323 NDMM patients had at least 3 MRD assessments and were included in the analysis. The median age of these patients at diagnosis was 59 years (range 35–87) and 55.1% were male. As per risk stratification, our cohort was mostly represented by low-risk patients, and only 16.7% were classified as ISS-3, 7.7% as R-ISS-3 and 4% as R2-ISS-4. The median number of MRD samples assessed was 5 (3–13). 25% of patients received a quadruplet as their first line regimen, and 32.3% received treatment with an anti-CD38 antibody. The distribution of the four subgroups was as follows: 165 patients were sMRDneg (51.1%), 41 were sMRDpos (12.7%), 52 were conMRDneg (16.1%), 65 patients were conMRDpos (20.1%). The median follow-up was 3.9 years (95% CI: 3.6–4.2 years). Median PFS has not been reached yet in all studied subgroups. Sustained MRD negativity was associated with superior PFS compared to the other subgroups, as expected by current knowledge.

Sustained MRD positivity was associated with significantly inferior PFS compared to the sMRDneg subgroup (HR = 5.92; 95% CI: 1.53–22.94; p = 0.01). The subgroup that converted from MRD negative to MRD positive during follow-up was also associated with inferior PFS compared to the sMRDneg subgroup (HR = 5.19; 95% CI: 1.58–17.05, p = 0.007). Patients who converted to MRD negative were also associated with a worse prognosis compared to those with sustained MRD negativity, but this difference did not reach a statistical significance to-date (HR = 2.85; 95% CI: 0.58–14.0; p = 0.196]. The presence of at least one MRD positive result, at any time-point, was associated with inferior PFS compared to the sMRDneg subgroup (HR = 5.93; 95% CI: 1.73–20.30; p = 0.0046). **Conclusions:** We conclude that sustained MRD negativity is associated with prolonged PFS, whereas the presence of even one MRD positive result impaired PFS in NDMM patients who have achieved CR during their first line therapy. These data further solidify the role of MRD assessment in MM patients and confirm the significance of sustained MRD negativity over time.

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Bridging the Gap: Conversion of Siemens N-Latex to Binding Site Freelite for Accurate Multiple Myeloma Diagnosis and Risk Stratification

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Introduction: The International Myeloma Working Group (IMWG) defines myeloma-defining events (MDEs) using thresholds based on the Binding Site Freelite assay, including a free light chain (FLC) ratio >100. However, many institutions employ alternative assays, such as Siemens N Latex, which yield systematically lower values. Applying IMWG criteria directly to Siemens results may lead to underdiagnosis of active multiple myeloma. It also leads misclassification of risk of smoldering myeloma (SMM) which also uses a ratio of >20 as one of the risk factors, delaying necessary treatment. **Methods:** We prospectively collected 2,094 paired FLC measurements from 1,772 patients between December 2023 and February 2024 using Siemens N Latex (BNII) and Binding Site Freelite (Optilite) platforms. After outlier exclusion, regression models were generated. Nonparametric comparisons and correlation matrices were used to validate concordance. **Results:** Linear conversion equations were established for kappa (r = 0.93), lambda (r = 0.77), and kappa/lambda ratio (r = 0.86). Regression analysis yielded the following: Kappa: Siemens = 0.65 × Freelite + 0.44, Lambda: Siemens = 0.79 × Freelite + 1.07, Ratio: Siemens = 0.49 × Freelite + 0.34. A Freelite FLC ratio of 100 corresponds to approximately 50 using Siemens. Involved FLC thresholds of 10 mg/dL align with 7 mg/dL (kappa) and 9 mg/dL (lambda) on Siemens. Without assay-specific thresholds, nearly 50% of patients meeting IMWG diagnostic criteria using Freelite were misclassified with Siemens. Similarly, high-risk SMM patients with Freelite ratios >20 were under-identified on Siemens, potentially delaying early therapeutic intervention. **Conclusions:** Using Freelite-based IMWG criteria with Siemens N Latex assay results introduces a substantial risk of missed multiple myeloma diagnoses and under-recognition of high-risk smoldering myeloma. A Siemens FLC ratio >50 should prompt confirmatory testing with the Binding Site Freelite assay before ruling out active disease. For SMM risk stratification, a Siemens FLC ratio >10 should be considered equivalent to a Freelite ratio >20 to ensure appropriate identification of patients who may benefit from early intervention. These findings highlight the urgent need for IMWG endorsed, assay-specific thresholds or mandatory reporting of assay platform to ensure consistent and accurate clinical decision-making.

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Stem Cell Autograft Minimal Residual Disease Negativity Predicts Improved Outcomes After Autologous Stem Cell Transplant for Multiple Myeloma

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Introduction: Autologous stem cell transplantation (ASCT) remains a standard-of-care for newly diagnosed multiple myeloma (NDMM). Advances in induction regimens have improved rates of bone marrow (BM) minimal residual disease (MRD) negativity and survival. However, the prognostic relevance of MRD status in stem cell autografts (AG) remains unclear. **Methods:** We evaluated 659 NDMM patients who underwent up-front ASCT at our institution between Sept 2027 and Dec 2023, with AG and BM MRD assessments using next-generation flow (NGF). AG MRD was tested at stem cell collection. BM MRD was assessed post-induction/pre-collection and at 3 months post-ASCT. Kaplan-Meier methods, log-rank tests, and Cox models were used to evaluate progression-free survival (PFS) and overall survival (OS) from ASCT. **Results:** Baseline characteristics were comparable between the MRD-negative and positive groups with a median age 63 and 56% male. ISS III and R-ISS III stages were seen in 22% and 33%, respectively; 56% had high-risk cytogenetics. The median number of induction cycles was 6: 55%

received lenalidomide/proteasome inhibitor-based triplets (RVd, KRd), 29% daratumumab-based quadruplets (D-RVd, D-KRd), and 26% other regimens. VGPR or better was highest with D-KRd (86.5%), followed by D-RVd (82%), KRd (75.8%), RVd (62.5%), and others (60%). AG MRD-negativity was observed in 72.7% of matched cases, compared to 22% in BM post-induction samples. All MRD-negative BMs had MRD-negative AGs. Among MRD-positive BMs, 65% had MRD-negative AGs, while the remaining 35% had MRD-positive AGs. Importantly, no MRD-negative BMs had MRD-positive AGs. Most patients (95%) received post-ASCT maintenance, primarily single agent lenalidomide. Multi-drug post-ASCT consolidation therapy was more common in the AG MRD-positive group (28% vs. 6.8%). With a median follow-up among survivors of 32 months, AG MRD-negativity was associated with improved PFS (3-year: 76% vs. 50%, log-rank $p < 0.002$) and OS (3-year: 92% vs. 69%, $p < 0.002$). This benefit extended across BM MRD and cytogenetic subgroups. At 3 years, OS was 95% in AG-/BM-, 93% in AG-/BM+, and 76% in AG+/BM+. Among high-risk cytogenetics, OS at 3 years was 95% (AG-/HR-), 93% (AG-/HR+), 82% (AG+/HR-), and 72% (AG+/HR+). In univariable analysis, AG MRD-positivity (HR 3.37, 95% CI 2.55–5.65), BM MRD-positivity (HR 2.09, 95% CI 2.26–3.56), ISS > I, and high-risk cytogenetics were associated with shorter PFS. In multivariable analysis, AG MRD-positivity (HR 2.28, 95% CI 2.57–3.25) and ISS > I remained significant. Importantly, AG MRD status retained prognostic impact for both PSF and OS in delayed ASCT recipients ($n = 78$). **Conclusions:** MRD-negativity in autografts is independently associated with superior PFS and OS following ASCT. These findings support AG MRD status as a valuable prognostic marker beyond conventional post-induction BM MRD status, with potential implications for tailoring post-ASCT therapy.

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Towards the Identification of Novel Circulating Biomarkers Associated with Bone Disease in Multiple Myeloma

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Introduction: Myeloma bone disease (MBD) remains a debilitating complication of multiple myeloma (MM), yet its early molecular determinants remain incompletely understood. Previously, we identified bone marrow semaphorin 4D (Sema4D), periostin, and activin-A as markers linked to bone resorption and extensive bone disease (BD). In this study, we aimed to examine these markers in plasma to assess their utility for early detection of deregulation of bone microenvironment in patients with smoldering MM (SMM) progressing to MM, with or without clinically evident BD. Furthermore, we sought to identify novel circulating biomarkers associated with MBD through high-throughput plasma proteomics. **Methods:** We analyzed $n = 44$ newly diagnosed MM patients (median age: 68.1 years; 62.7% female), of whom 35% were ISS-1 and 27.5% ISS-2; 42.5% harbored high-risk cytogenetics. Plasma samples underwent filter-aided sample preparation (FASP) and mass spectrometry-based proteomics to identify BD-associated proteins. In $n = 24$ matched cases, plasma Sema4D, periostin, and activin-A were quantified by ELISA at MM diagnosis and at a preceding SMM timepoint. Multivariate general linear models (GLMs) assessed associations between biomarkers, MBD, and clinical parameters (e.g., ISS, bone lesions). Cox regression was used for survival analyses, and ROC curves assessed diagnostic utility. **Results:** Among established markers, circulating levels of activin A and Sema4D at the SMM stage trended towards an association ($p = 0.08$) with BD at MM stage. Activin A showed promising diagnostic performance (sensitivity: 0.80, specificity: 0.73), whereas sema4D showed promising sensitivity (0.85), but limited specificity (0.36). At MM diagnosis, proteomics revealed that TUFT1 (Tuftelin 1)—a protein implicated in mineralization—was significantly associated with MBD presence ($p = 0.002$). The extent of osteolytic lesions as seen in low-dose whole-body computed tomography correlated with circulating IGFALS (insulin-like growth factor-binding protein complex acid labile subunit) levels ($r = 0.488$, $p = 0.008$), suggesting a role for IGFALS in osteolytic activity. In exploratory survival analyses, IGFALS was identified as the most prominent prognostic indicator, albeit results were marginally not significant ($HR_OS = 6.12$, $p = 0.081$), followed by TUFT1. ROC-derived cutoffs for both IGFALS and TUFT1 yielded AUC >0.70, and corresponding odds ratios suggested moderate to strong associations with MBD. **Conclusions:** This study supports the use of circulating activin A and Sema4D as early predictors of MBD progression in SMM. In addition, we report IGFALS and TUFT1 as promising novel biomarkers of MBD presence and prognosis at the MM stage. These findings merit further validation in larger cohorts to support their utility in early risk stratification and personalized bone-directed therapies.

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Deciphering Genomic Correlates of Differential Treatment Response Kinetics in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is an incurable blood cancer often marked by treatment resistance. Emerging evidence suggests that differential treatment response kinetics (DTRK) – the rate of patients' response – can predict outcomes, with slower responders faring better. This study investigates the prognostic value of DTRK and its underlying genetic drivers. **Methods:** Patients were classified as fast (≤4 months) or slow (>4 months) responders based on time to achieve a partial response or better during first-line therapy, consistent with clinical investigations into DTRK. Clinical and genomic data were used from CoMMpass, and an independent clinical dataset was used to validate the clinical outcomes. Kaplan-Meier survival analysis and multivariate Cox regression, adjusting for age, sex, ISS stage, cytogenetics, drug classes (i.e., IMID, PI, PI +IMID), an upfront autologous transplant, and response depth, were used to compare progression-free survival (PFS) and overall survival (OS) between response groups. To investigate the molecular correlates of DTRK, a robust bioinformatics pipeline was used to analyze mutation, structural variant, copy number alteration, and gene expression data. Machine learning based analysis of single-cell RNA sequencing data was performed to characterize the tumor microenvironment. **Results:** Patients were classified into fast (n = 284) and slow (n = 425) responders and their clinical outcomes were compared. Analysis shows that slow responders have significantly longer PFS and OS compared to fast responders (HR = 0.68, 95% CI 0.52–0.89, p = 0.005; and HR = 0.66, 95% CI 0.50–0.89, p = 0.006, respectively). These results were independently validated in a separate real-world clinical cohort. Genomic analysis identified alterations in myeloma driver genes; such as fast responders exhibiting a higher frequency of TP53 aberrations (Chi-squared test, p value <0.05), which may contribute to worse outcomes. Pathway analysis revealed upregulation of stemness-associated and lineage differentiation pathways in fast responders, suggesting a more aggressive tumor phenotype. Machine learning based exploration of immune microenvironment identified that that slow responders were enriched for natural killer cells and $CD4^+$ and $CD8^+$ T cells, indicating distinct immune landscapes. **Conclusions:** Our findings demonstrate that slower treatment response is associated with significantly improved prognosis in multiple myeloma, independent of covariates. Multi-omics analyses identify DTRK to be associated with differences in tumor stemness, differentiation status, and immune microenvironment composition. These findings underscore the clinical relevance of response kinetics as a biomarker and provide insights into the underlying mechanisms, which may inform more personalized therapeutic strategies in MM.

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Peripheral Blood Clonotypic Mass Spectrometry-Based MRD Stratification Identifies Patients at Increased Risk of Progression After Quadruplet Therapy in NDMM

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Introduction: In newly diagnosed multiple myeloma (NDMM), many patients achieve complete or stringent complete response (CR/sCR) following quadruplet induction. Measurable residual disease (MRD) testing helps to further stratify outcomes but traditionally requires painful bone marrow (BM) sampling, highlighting the need for sensitive, minimally invasive biomarkers of MRD. M-inSight mass spectrometry allows non-invasive, longitudinal detection of clonotypic monoclonal proteins in peripheral blood (PB). Unlike binary tests, M-inSight provides continuous quantitative readouts, but clinically validated thresholds remain undefined. **Methods:** We analyzed patients in CR/sCR from two prospective trials (EloKRD and DaraKRD without transplant). Eligibility for this post-hoc analysis required samples with M-protein concentrations sufficient for clonotypic peptide tracking. The lowest clonotypic protein concentration across all timepoints was used to define each patient's best MRD response. Receiver operating characteristic (ROC) curve analysis using 48-month progression status identified an optimal threshold by Youden's index, which was used to classify patients as MRD-negative or positive. Survival was analyzed using Kaplan-Meier and Cox models. BM MRD was assessed via next-generation sequencing (NGS) at 10–5 sensitivity, and patients were further categorized as "double-negative" (negative by both methods) or "positive" (positive by one or both). **Results:** Among 64 CR/sCR patients, 33 were included in the M-inSight analysis. Baseline characteristics, PFS, and OS did not differ between included and excluded patients. ROC analysis identified a cutoff with strong prognostic value (AUC = 0.77; sensitivity 75%; specificity 76%). Patients above this threshold had significantly shorter PFS (p = 0.002; HR = 8.76; 95% CI: 1.7–45.1). Addition of BM MRD further refined risk stratification. Patients not achieving double-negativity (M-inSight PB positive or BM MRD-positive) had worse outcomes (HR = 8.12; 95% CI: 0.94–70.2; p = 0.057; C-index = 0.713). Although not statistically significant, the survival curves were clearly separated (log-rank p = 0.02), potentially indicating meaningful clinical differentiation in this small cohort. Agreement between PB M-inSight and BM NGS MRD at 10-5 was low (Cohen's

kappa = 0.043; p = 0.82), suggesting potential complementarity, though further investigation is warranted. **Conclusions:** A ROC-derived M-inSight threshold identifies patients in CR/sCR with increased risk of progression after quadruplet therapy. Integration with BM MRD enhances stratification, supporting the role of PB clonotypic mass spectrometry as a non-invasive, clinically meaningful tool in MRD-guided monitoring.

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Light Chain Escape in Multiple Myeloma: A Not-So-Unusual Phenomenon

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Introduction: Light chain (LC) escape, traditionally measured by light chain (Bence Jones –BJ-) proteinuria, is a phenomenon that indicates the need for urine monitoring during the follow-up of patients with multiple myeloma (MM). However, 24-hour urinary LC monitoring has some limitations, as it is influenced by renal function, incomplete urine collection, and the presence of intact immunoglobulin in the urine, which interferes with LC measurement in a significant proportion of patients. In contrast, serum free light chains (sFLC) have a higher sensitivity and constitute an early marker of progression. It is estimated that 10% of patients relapse in the form of LC escape. However, since the routine implementation of sFLC measurement, there are few data on its actual frequency. The aim of our study is to describe the frequency of different relapse patterns, including LC escape, in patients with MM after autologous stem cell transplant (ASCT). **Methods:** A retrospective study was conducted in 55 patients diagnosed with MM who relapsed after ASCT performed at our center between 2010 and 2020. Serum monoclonal component (sMC), BJ proteinuria, sFLC, and the presence of plasmacytomas were assessed. Four relapse patterns were established: isolated LC escape, increase in sMC plus BJ proteinuria and/or sFLC, isolated increase in sMC, and oligosecretory relapse. The relapse pattern was analyzed at the first, second, third, and fourth relapses. Patients without BJ or sFLC measurements at the time of relapse, as well as pure light chain myelomas (Bence-Jones myelomas), were excluded from the analysis. **Results:** in our series, 63%, 43%, and 29% of patients experienced a second, third, and fourth relapse, respectively. Between 10% and 15% of patients relapsed with LC escape at each successive relapse. Approximately 30% relapsed with concomitant increases in sMC and LC, 33% with isolated increases in sMC, and approximately 15% had an oligosecretory relapse. sFLC were more sensitive than BJ proteinuria in detecting LC escape. Thus, between 45% and 100% of patients with isolated LC escape and 30%-60% of patients with concomitant increases in sMC and LC had progression of sFLC without measurable BJ proteinuria. Overall, the proportion of patients with measurable sFLC without BJ proteinuria increased from 29% at first relapse to 41% at fourth relapse. The incidence of plasmacytomas according to the relapse pattern shows that plasmacytomas are frequent in all patterns, regardless of the increase in LC. **Conclusions:** Approximately 15% of patients in our series relapsed as LC escape, with 30% relapsing with increased sMC and LC. Increased LC, whether isolated or accompanied by sMC, is not associated with an increased incidence of plasmacytomas, which are common in all relapse patterns. These findings underscore the importance of routine sFLC measurement in the follow-up of patients with MM, even in those with measurable disease, since they may represent the only biochemical manifestation of progression.

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Peripheral Residual Disease (PRD) Monitoring by Clonotypic Mass Spectrometry (EASYM) in patients with Newly Diagnosed Multiple Myeloma

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Introduction: Minimal Residual Disease (MRD) assessment using next generation sequencing (NGS) or next generation flow cytometry (NGF) is a robust predictor of survival outcomes but relies on serial, invasive bone marrow (BM) aspirates, often limited by patchy disease and suboptimal sampling. EASYM (Rapid Novor) is a clonotypic mass spectrometry assay that employs de novo sequencing of the serum M-protein to identify a 'patient-specific peptide fingerprint" allowing for the quantitative tracking of peripheral residual disease (PRD) (Liyasova 2021). **Methods:** This is a prospective, investigator-initiated study in transplant eligible (TE) and transplant ineligible (TIE) newly diagnosed multiple myeloma (NDMM). The study enrols patients within 4 months of treatment initiation; with M protein of >2 g/L and/or involved free light chains (iFLC) of> 2000 mg/L at screening. Conventional myeloma tests are performed monthly; EASYM is done at screening (visit 1), and q3 months (visit 2+) for TIE patients, or post-induction (visit 2), at day100 post-autologous stem cell transplant (ASCT; visit 3) and q3

monthly (visit 4+) thereafter for TE patients. We aim to prospectively compare conventional myeloma assessments, PRD by EASYM and BM MRD by NGF to establish the role of EASYM in clinical practice. **Results:** As of April 30, 2025, 33 patients had undergone baseline EASYM testing. At screening, the median concentration of M protein was 14.35 (range 2.9–52.9) g/L in 26 patients with measurable intact paraprotein (IgG 67% (n = 22) IgA 12% (n = 4)) and 2616 (range 22.9–9381) mg/L for the iFLC in 7 light chain myeloma (LC) 21%; kappa = 3; lambda = 4) patients. All patients (n = 32) meeting eligibility criteria had successful baseline identification of a clonotypic peptide, including 6 LC MM. One screen failure was due to iFLC levels lower than detection limit. 28 of 32 patients (85%) were TE. At the time of analysis, 17 (61%) had completed ASCT (15 single, 2 tandem) and 2 had received induction therapy followed by CAR T-cell therapy. Three patients (9%) were TIE, and 1 patient had not yet initiated treatment. At a median follow up of 5 (range 1–13.7) months, 22 and 11 patients had completed the 2nd and 3rd visit assessments, respectively. At visit 2, 68% (15/22) had achieved >VGPR, with 9 SPEP(−), 1 SIFE(−) and no PRD(−) by EASYM. At visit 3, 72% (8/11) were in >VGPR with 5 SPEP(−), 3 SIFE(−) and 2 PRD(−) by EASYM highlighting that PRD could still detect M protein in 2 SIFE(−) patients at different time points. At early follow-up, 2 patients had concordant negative PRD and matched marrow MRD (10-5) by NGF (done within 30 days), 1 patient had both PRD(+) and MRD(+) while 2 MRD(−) patient were still SIFE(+) and PRD(+). To date, no patient has experienced disease progression by conventional assessments or EASYM. **Conclusions:** This ongoing trial explores the potential of EASYM as a sensitive, non-invasive serum-based method for reliably detecting PRD and predicting BM MRD status. Data with longer follow up data will be presented.

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3D Telomere Profiling of MRD in Liquid Biopsy as a Predictive Marker of Disease Stability or Progression

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Introduction: Post-treatment, minimal residual disease (MRD) is an FDA-approved endpoint in multiple myeloma (MM) patients. The ability to accurately assess the biological behavior of MRD is limited, as current technologies primarily focus on detecting and quantifying unique DNA sequences or surface antigens of tumor cells isolated from bone marrow specimens, and are unable to predict the biological patterns of these tumor cells. The evaluation of circulating tumor cells (CTCs) from peripheral blood, rather than bone marrow, offers a promising, less invasive biomarker for MM that allows for continuous monitoring of patients. However, due to the heterogeneity of MM, CTC enumeration alone cannot give a precise indication of MRD stability/progression. We recently demonstrated that the 3-dimensional (3D) profiles of telomeres, a known marker of cancer-associated genome instability, can accurately predict disease progression in patients with smoldering multiple myeloma (PMID: 38747543). Our current study describes a new workflow for MRD evaluation that combines the enumeration and immunophenotyping of individual MM CTCs with 3D telomere profiling to characterize the residual MM cells or clones, determine MRD negativity or positivity, predict disease progression, and enable continuous non-invasive follow-up. **Methods:** We report a technique for isolating intact circulating myeloma plasma cells from the peripheral blood of MM patients at the point of diagnosis, post-induction, and 3 months post-transplant/treatment, with subsequent enumeration and immunophenotyping using CD56 and CD138 markers combined with 3D telomere profiling using the TeloView software platform. **Results:** Enumeration of MM CTCs demonstrated a high number of detectable myeloma plasma cells in the peripheral blood samples of MM patients at the point of diagnosis. In contrast, the number of detectable CTCs was dramatically lower post-induction and further decreased 3 months post-transplant/treatment. 3D telomere analysis of the isolated CTCs demonstrated 3D telomere profiles characteristic of MM (PMI D: 33921898, 24466378). The captured CTCs were confirmed through pathology review and immunophenotyping. **Conclusions:** The proposed unique workflow integrates the isolation of circulating tumor cells (CTC) from peripheral blood with quantitative enumeration, detailed immunophenotypic characterization, and high-resolution 3D telomere architecture profiling. This allows for longitudinal and minimally invasive monitoring of MRD in multiple myeloma patients from the time of treatment. Unlike conventional approaches, this platform yields functionally and biologically actionable data on CTCs, providing insights into disease stability or progression beyond simple enumeration, while avoiding the need for repeated bone marrow biopsies.

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Lymphocyte to Monocyte Ratio at Minimal Residual Disease Assessment Predicted Survival Time Among Myeloma Patients in Complete Response

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Introduction: Minimal residual disease (MRD) has already established as a surrogate marker for survival in myeloma patients who achieved complete response (CR), whereas the clinical

significance of lymphocyte to monocyte ratio (LMR), serve as a prognostic factor associated with the immunological, has not investigated as prognostic markers. In this study, we evaluated the clinical impact of MRD negativity (MRD-ve) and LMR at MRD assessment. **Methods:** MRD was analyzed by multicolor flow cytometry (threshold, 1×10^{-5}). Sustained MRD-ve (sus-MRD-ve) was defined as continuing MRD-ve for 1year or longer. LMR was calculated at the time point when MRD was assessed. The cutoff of LMR was 3.75, which was a median value. **Results:** A total of 155 patients who achieved CR were included in this study, with a median age of 70 years. The number of patients treated with autologous stem cell transplantation (ASCT), daratumumab treatment, and other treatments were 72, 58, and 25, respectively. 108 patients (69.7%) achieved MRD negative. In a median follow-up time of 36.1 months, 3-year time to next treatment (TTNT) and overall survival (OS) rates from the first MRD assessment were 73.0% and 92.9%, respectively. The 3-year TTNT in the patients with sus-MRD-ve was significantly higher than in those without sus-MRD-ve (79.0% vs 73.0%, P = 0.017) while there was no significant difference of 3-year TTNT between the patients with and without MRD-ve (74.0% vs 69.4%, P = 0.478). LMR >3.75 was observed in the patients whose MRD assessment was done after ASCT compared to those after non-ASCT (59.5% vs 32.9%, P = 0.012). Additionally, LMR >3.75 tended to be related with not MRD-ve but sus-MRD-ve (P = 0.221 and 0.064). The 3-year TTNT in the LMR >3.75 was significantly higher than those in the LMR< 3.75 (87.2% vs 56.8%, P < 0.001). LMR >3.75 was a significant prognostic factor for TTNT (HR 0.448, P = 0.014) while sus-MRD-ve, which predicted TTNT significantly using univariate analysis, was not identified as a significant predictor (HR 0.549, P = 0.115) using multivariate analysis. The 3-year OS in the LMR >3.75 was significantly higher than those in the LMR< 3.75 (98.3% vs 87.1%, P = 0.012), whereas there was no significant difference of OS between the patients with and without sus-MRD-ve (3-year OS 96.5% vs 97.0%, P = 0.853). LMR >3.75 was a significant prognostic factor for OS (HR 0.288, P = 0.033) while MRD assessment after ASCT, which predicted OS significantly using univariate analysis, was not identified as a significant predictor (HR 0.366, P = 0.096) using multivariate analysis. **Conclusions:** LMR >3.75 at MRD assessment tended to be associated with sus-MRD-ve and could be identified as a predictor of long TTNT and OS, suggesting that immunological status might improve survival time by contribution to continuous deep response. Therefore, we should pay attention not only treatment response but also immunological status in myeloma patients in CR to predict survival time.

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Refining MRD Surveillance in Multiple Myeloma: Predictive Insights from Ultrasensitive Bone Marrow Analysis

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Introduction: Measurable residual disease (MRD) is a key prognostic marker in multiple myeloma (MM), guiding treatment, predicting relapse, and serving as a clinical trial endpoint. The widely adopted EuroFlow MRD method offers standardized protocols with a sensitivity of 10^{-5} to 10^{-6}. However, higher sensitivity is still required for detecting low-level disease following potent immunotherapies, such as CAR T-cell therapy, bispecifics, and monoclonal antibodies, which can reduce tumor burden below conventional detection thresholds. To investigate whether an ultrasensitive MRD method using enriched $CD138^+$ plasma cells more effectively identifies patients at risk of disease progression and relapse, we compared it with conventional EuroFlow MRD in bone marrow samples from 277 MM patients. **Methods:** Conventional MRD was performed following EuroFlow guidelines. For ultrasensitive MRD, $CD138^+$ plasma cells were enriched using MACSprep™ CD138 MicroBeads with AutoMACS® system. Conventional MRD was analyzed using Infinicyt's automated gating and identification tools, while ultrasensitive MRD was manually analyzed using Infinicyt software. **Results:** Among the 277 samples analyzed, conventional MRD detected positivity in 116 cases, all of which were confirmed by the ultrasensitive method. Of the 161 samples classified as MRD-negative by conventional assessment, 150 (93%) were also confirmed as negative by ultrasensitive MRD. However, 11 cases (7%) were reclassified as MRD-positive by the ultrasensitive method, with limits of detection (LODs) ranging from 0.000010 to 0.000036, and a median of 0.000019. During follow-up, four of the 11 discordant cases later converted to MRD-positive by conventional assessment. Patient 1 became positive by conventional MRD 24 months after initial detection by the ultrasensitive method, while patients 2 and 3 converted within five months, and patient 4 at 18 months. Patients 1, 3, and 4 did not exhibit serological progression. Patients 5, 7, 8, and 9 remained MRD-negative by conventional assessment throughout follow-up, spanning 3–15 months after ultrasensitive detection. They exhibited no signs of serological progression during subsequent evaluations. Follow-up data were unavailable for patient 11. Patients 2, 6, and 10 showed serological progression within two to five months after ultrasensitive assessment. Notably, patients 2 and 6 experienced relapse. **Conclusions:** Ultrasensitive MRD, with a detection threshold of up to 10^{-8}, identified additional cases of residual disease and effectively anticipated disease progression and relapse. While conventional MRD, with a sensitivity of 10^{-6}, remains a robust tool, these findings support incorporating ultrasensitive MRD into routine monitoring to enhance relapse prediction and guide timely therapeutic decisions, particularly for patients receiving high-efficacy immunotherapies.

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Absolute Lymphocyte Count (ALC) ≥1,000 IS AS A Surrogate of Car-T Cell Expansion and a Readily Available Biomarker to Predict Outcomes in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Following the approval of anti-BCMA CAR-T cells as living drugs, there is an urgent need to identify biomarkers that enable tailored strategies to improve post-infusion outcomes. While measuring CAR-T cell expansion is informative, it remains technically challenging in most centers. We aim to evaluate whether the absolute lymphocyte count (ALC) during the first 14 days after CAR-T infusion could serve as a practical surrogate for CAR-T cell expansion and predict clinical outcomes. **Methods:** We retrospectively analyzed 65 relapsed/refractory multiple myeloma patients treated with anti-BCMA CAR-T cells at our center between April 2018 and November 2024. ALC was recorded at baseline and daily for the first 14 days post-infusion. Patients were stratified into those reaching at any time point a maximum ALC ≥ 1,000 cells/mm³ vs those who did not. **Results:** Patients had received a median of 3 prior lines of therapy (range, 1–10) before CAR-T treatment. The overall median progression-free survival (PFS) was 11.3 months (95% CI, 6.8–12.9). Of the 65 patients, 37 (56.9%) achieved ALCmax ≥ 1,000 cells/mm³, while 28 (43.1%) did not. Baseline characteristics were largely similar between groups, except that the ALCmax < 1,000 cohort had received more prior therapies (> 3 lines: 54% vs. 27%; P = .03) and exhibited a higher rate of extramedullary disease (EMD: 18% vs. 3%; P = .048). No significant differences were observed in terms of cytogenetic risk, ISS stage, triple-class refractoriness, bone marrow plasma cell infiltration (BMPC) >50%, marrow B- or T-cell populations, or the CD27−/CD27+ T-cell ratio. At one month post-infusion, 59% of patients in the ALCmax < 1,000 group achieved MRD negativity vs 94% in the ALCmax ≥ 1,000 group (P = .001). No significant differences were found for the occurrence of CRS (86% vs 97%; P = .083) or ICANS (18% vs 16%; P = .86), neither in terms of frequency or severity of the episodes. Patients with ALCmax <1,000 had markedly inferior outcomes: median PFS of 6.8 months (95% CI, 2.5–11.2) versus 17.5 months (95% CI, 11.4–23.6); HR 3.4 (95% CI, 1.9–6.1) (P < .001) and median overall survival (OS) of 11.7 months (95% CI, 7.8–15.7) versus not reached; HR 3.1 (95% CI, 1.6–6.2) (P = .001). In multivariate Cox regression adjusting for high-risk cytogenetics, EMD at screening, BMPC > 50%, triple-class refractoriness, and ISS stage III, ALCmax < 1,000 remained an independent predictor of poorer outcomes. The HR for PFS was 2.4 (95%CI 1.8–5.1; P = .017), and for OS was 3.1 (95%CI 1.2–7.6; P = .017). **Conclusions:** Early post-infusion ALC serves as a reliable surrogate for CAR-T cell expansion, stratifying patients into two groups with significantly different survival outcomes despite comparable baseline profiles. Patients failing to achieve ALCmax ≥ 1,000 cells/mm³ may warrant early, tailored interventions to mitigate progression risk associated with suboptimal CAR-T expansion.

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Detectable Peripheral Blood Measurable Residual Disease (PBMRD) is Strongly Associated with Early Progression in Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: Bone marrow (BM) measurable residual disease (MRD) is a key biomarker in multiple myeloma (MM), but its invasive/painful nature limits serial monitoring. It also risks false negatives from haemodilution, patchy disease, or extramedullary involvement. Peripheral blood MRD (PBMRD) offers a minimally invasive, and convenient alternative, though its clinical relevance in newly diagnosed MM (NDMM) remains unclear. We assessed the clinical value of PBMRD alongside BMMRD post-initial therapy in NDMM. **Methods:** We prospectively enrolled 94 NDMM patients who completed 8 VRd cycles followed by BM/PB MRD assessment. Post-induction, patients were randomized to MRD-guided consolidation (VRd/KPd) or standard maintenance (Lenalidomide or Bortezomib-Lenalidomide; CTRI/2021/11/037702). MRD was evaluated using a highly sensitive 13-color flow cytometry method. Any detectable MRD was defined as positive. Levels of M-protein, FLC and Serum immunofixation (sIF) were measured. **Results:** Of 94 patients (age: median-53.5 years; range-32–75 years; M:F-3), ISS-I, II and III included 21 (22.34%), 26 (27.6%), and 47 (50%), respectively. RISS staging was available in 86 patients where RISS-I, II and III included 11 (12.8%), 48 (55.8%), and 27 (31.4%), respectively. Best response at the end of 8-cycles of VRd included stringent-CR-29.03%, CR-31.33%, VGPR-26.88%, PR-10.75%, patients. The sIF was done in 92 patients with sIF(+) in 59 (64.13%) at 8 cycles of VRd. BMMRD was detectable in (median-0.019%; range-0.0002–4.5%) in 60/94 (63.8%) patients. PBMRD was detectable (median-0.0016%; range-0.00007–0.09%) in 18/94 (19.15%) patients and 18/60 (30%) of BMMRD-positive patients. Median follow-up was 36 weeks (25–92 weeks) and 14 of 94 patients

progressed after 8 cycles of VRd during this follow-up. On Kaplan Meier analysis, detectable PBMRD was strongly associated with PFS (26 weeks vs. not reached; HR-14; p < 0.0001). Detectable BMMRD also demonstrated an association with PFS with HR-5.9 (p = 0.0076), and sIF+ status with HR-2.6 (p = 0.047), but the median was not reached for both i.e. positive versus negative patients for BMMRD and sIF. ISS, R-ISS, high-risk cytogenetics and the best initial response did not reveal any association with early progression on univariate analysis. PBMRD status showed a strong independent association (HR-12; p = 0.0012), with early progression in multivariate analysis. **Conclusions:** PBMRD using highly sensitive flow cytometry is detectable in one-third of NDMM patients with detectable BMMRD. Thus, PBMRD positivity serves as a surrogate for BMMRD and can help to design a staged approach to reduce number of BM procedures thereby improving its acceptance. Most importantly, positive PBMRD is strongly associated with early myeloma progression and identifies ultra-high-risk NDMM patients, providing a rationale for immediate therapeutic intervention.

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Profiling Minimal Residual Disease with Single-Cell Whole-Genome Sequencing of Circulating Tumor Cells in Patients Receiving BCMA- or GPRC5D-Targeted Agents

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Introduction: Genetic profiling can guide the use of targeted therapies in relapsed/refractory multiple myeloma (RRMM); however, it typically requires bone marrow (BM) biopsies, which are often not performed in advanced stages of the disease. Consequently, the use of immunotherapies like anti-BCMA or GPRC5D CAR-T cells and bispecific T-cell engagers (TCEs) is rarely informed by relevant somatic mutations. To address this critical unmet need, we explored whole-genome sequencing (WGS) on (single) circulating tumor cells (CTCs) isolated from peripheral blood (PB) of RRMM patients before and during therapy, aiming to generate clinically relevant genomic data without relying on invasive BM sampling. **Methods:** CTCs were enriched for CD138+ cells using autoMACS® columns and sorted by 9-color FACS based on abnormal immunophenotypes. DNA was extracted from single cells and mini-pools (up to 25 cells) using primary template-directed amplification (ResolveDNA®, Bioskryb Genomics), or directly from pools of >50 CTCs. Libraries were sequenced on NovaSeq X10B flowcells, and tumor-specific variants were identified via comparison to matched germline controls. Clinical data were assessed at baseline; response was assessed by IMWG Uniform Response Criteria. **Results:** We profiled CTCs from 16 RRMM patients (median 6 prior lines; range 3–12), treated with anti-BCMA CAR-T (n = 8), anti-BCMA TCE (n = 5), or anti-GPRC5D TCE (n = 3). Tumor origin of CTCs was confirmed in all cases (median tumor purity 99% [22–100%]), and clonotypic BCRs were detected in 88% (14/17). Initiating events —translocations and hyperdiploidy—were observed in 81% (13/17). Somatic driver mutations were identified in 81% (13/17), including NRAS/KRAS (6/17), TP53 (3/17), DIS3 (3/17), SP140 (1/17). Of note, no mutations in GPRC5D or TNFRSF17 (BCMA) were found, even among those previously treated with anti-BCMA CAR-T (ide-cel n = 4, cilta-cel n = 1). The absence of mutation in immunotherapy targets aligned with treatment response (CR n = 13; SD n = 1; PD n = 2; non-relapsed death n = 1), suggesting that previous lines of treatment did not select for resistant clones. To investigate whether resistant clones were present before disease relapse, we longitudinally characterized CTCs in 5 patients and 7 timepoints undergoing treatment with immunotherapies. In one anti-BCMA TCE-treated patient (SD), a TP53 R342* clone with complex karyotype expanded (cancer cell fraction 16% to 45%) despite reduced CTC counts. In another post-CAR-T patient (MRD+ at 10^{-6}, CR), WGS of 7 and 30 single CTCs at 10 and 18 months post-infusion revealed persistent tumor-derived cells lacking BCMA mutations and driving relapse after 20 months. **Conclusions:** Single-cell WGS of CTCs enables high-resolution, longitudinal genomic monitoring in RRMM. This approach enables the detection of mutant clones, tracking of increasing subclones, and supports treatment adaptation, all without requiring a bone marrow biopsy.

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Clinical Utility of Quantitative, Mass Spectrometry-Based EasyM for MRD Monitoring in Multiple Myeloma: Integration with Established MRD Detection Techniques in a Pan-Canadian Real-World Cohort Study

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Introduction: Minimal residual disease (MRD) in the bone marrow (BM) following multiple myeloma (MM) treatment is an adverse prognostic factor and an emerging clinical trials endpoint. Blood-based MRD assays could reduce invasive BM testing and overcome spatial heterogeneity in the BM and BM hemodilution. The EasyM assay uses a mass spectrometry-based approach to identify and track patient-specific, clonotypic M-protein peptides in peripheral blood (PB), facilitating frequent, non-invasive MRD monitoring. The optimal integration of different MRD tests remains unclear. **Methods:** We evaluated MRD in a pan-Canadian cohort of 91 newly diagnosed, transplant-eligible MM patients using EasyM (N = 59 patients), next-generation sequencing (NGS) of immunoglobulin clonotypes from BM (10^{-5} and 10^{-6} sensitivity, N = 42 patients), multiparameter flow cytometry of BM (MFC, sensitivity between 10^{-4} and 10^{-6}, N = 48 patients), and 18F-FDG PET/CT (PET, N = 18 patients) (sample collection from Nov 2017–Sept 2024). Samples were analyzed prior to the initiation of therapy and at one or more follow up timepoints: after induction chemotherapy, 100 days post-ASCT, after 12 months of maintenance therapy, and every 6 months until progression. PET was done after 12 months of maintenance therapy if in VGPR or better. We compared EasyM with NGS, MFC and PET and assessed their prediction of subsequent relapse. **Results:** Over the follow-up period (range 114–1961 days, median = 920 days), MRD negative status was achieved by 18% (11/59) of patients by EasyM, 21% (9/42) by NGS at 10^{-6}, 57% (24/42) by NGS at 10^{-5}, 58% (28/48) by MFC, and 83% (15/18) by PET. Among matched EasyM and BM samples, concordance was highest between EasyM and NGS at 10^{-6} (70%, N = 30 matched samples), followed by MFC (58%, N = 60), NGS at 10^{-5} (53%, N = 38), and then PET (37%, N = 16). The majority of discordant samples were positive by EasyM and negative by other methods (range of 23% with NGS at 10-6-63% with PET). The percentage of residual M-protein by EasyM was strongly correlated with the percentage of clonal plasma cells from MFC, MRD quantitation via NGS, and serum protein electrophoresis (SPEP) results (Spearman $r \geq 0.8$, $p < 0.01$). None of the patients that achieved MRD negativity by EasyM have progressed to date. By Sept 2024, 20 patients progressed and for the 13 progressing patients with serial data, 9 demonstrated rising M-protein by EasyM 2–12 months before clinical progression. A two-variable logistic model combining percent residual M-protein via EasyM with NGS MRD quantitation at 10-6 yielded the best relapse prediction (AUC = 0.84 within 1 year of sample collection; 0.80 within 2 years). **Conclusions:** EasyM is a sensitive, non-invasive tool for frequent MRD monitoring in MM that correlates with established MRD assays and can detect recurrent disease earlier than conventional methods. Combining EasyM with established assays could enhance relapse prediction and inform future development of response adapted trials with MRD negativity as the endpoint.

PA-197

Utilization and Preferences of MRD Testing for patients with Multiple Myeloma: Insights from a Survey of 251 North American Hematologists and/or Oncologists

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Introduction: Minimal Residual Disease (MRD) testing in Multiple Myeloma (MM) patients provides insights into treatment efficacy and disease prognosis. MRD negativity has been considered an early endpoint that is reasonably likely to predict clinical benefit in clinical trials for accelerated approval of drugs by the FDA. Despite its significance, the routine utilization of and preferences for MRD testing among North American (NA) hematologists and/or oncologists (specialists) remain underexplored. **Methods:** A comprehensive survey was designed to gather quantitative and qualitative insights about the current utilization of MRD assessment tools, preferred testing methods, barriers to MRD testing, and opinion on the value and potential future utilization of MRD testing from NA specialists. Eligible specialists must have practiced either in the US or Canada and must have treated at least 5 or more MM patients per year. A life science market research company fielded this survey between October – December 2024, including responses from 202 US and 49 Canadian specialists. **Results:** Survey respondents perceive MRD testing as valuable for early relapse detection (~30%), clinical trials endpoints (~20%), risk stratification (~15%), and personalized treatment planning (~25%), which can improve patient outcomes. However, most specialists do not assess MRD status outside clinical trials, with only 11% (28 out of 251) of respondents actively doing so. The two key barriers to MRD utilization are the reluctance to subject patients to additional bone marrow biopsies (63%) and concerns about cost and insurance coverage (45%). Next-Generation Sequencing (NGS) in the bone marrow is both the most utilized and preferred method among the specialists who do utilize MRD for their myeloma patients (n = 61). Common reasons for favoring NGS-bone marrow compared to other available methods include its sensitivity, specificity, genetic information, and its perceived status as the standard method. The lower limit of detection for 67% of NA specialists' preferred MRD testing is 1 aberrant plasma cell in 10,000 cells (10-5). 94% of surveyed NA specialists would find a biopsy-sparing, sensitive blood-based technique valuable as a surrogate to currently available MRD assessment methods. **Conclusions:** Most

respondents see the transformative potential of MRD testing in advancing personalized medicine and improving clinical outcomes. Addressing barriers such as biopsy invasiveness and cost is critical to broader utilization of MRD outside clinical trials. Respondents perceive methods measuring residual disease in the peripheral blood as a promising alternative for sensitive, non-invasive assessment of MRD in MM.

PA-198

Identification of a CAR–Derived Clone by NGS-Based MRD After Fully Human BCMA CAR T-Cell Therapy in Multiple Myeloma

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Introduction: B cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy has significantly improved survival outcomes in relapsed/refractory multiple myeloma (RRMM), frequently inducing deep responses with high rates of minimal residual disease (MRD) negativity. However, during routine next-generation sequencing (NGS)-based MRD assessments in our real-world cohort, we identified a persistent novel clone signal in a subset of patients, despite sustained remission and clearance of the original myeloma clone. This raises concerns about MRD interpretation in the setting of genetically engineered T cell therapies. **Methods:** We retrospectively analyzed 55 myeloma patients who received BCMA CAR-T cell therapy at our center and had at least one NGS-MRD assessment post-infusion, as part of real-world observational studies or investigator-initiated trials (IIT). NGS-MRD analysis was conducted using the Neo-MRD® assay (Neoimmune, Shenzhen, China), targeting V(D)J rearrangements in IGH, IGK, and IGL genes. Lentiviral vector copy number (VCN) was quantified using digital droplet PCR (ddPCR) in 27 bone marrow (BM) DNA samples collected at MRD timepoints. Single-cell RNA, BCR, and TCR sequencing were performed on bone marrow mononuclear cells from P22 at T4 (D28 post-infusion), to explore the clonal origin of the novel clone. **Results:** Among 55 patients analyzed, 25 (45.5%) exhibited this novel clone following infusion of equecabtagene autoleucel (eque-cel), a fully human-derived BCMA CAR-T product. The sequence was identical across patients and aligned with the single-chain variable fragment (scFv) of the eque-cel construct. It was absent in recipients of non-human-derived CAR-T products. The novel clone abundance strongly correlated with CAR vector copy number quantified by digital droplet PCR ($R = 0.88$, $P < 0.001$). Single-cell multiomic sequencing confirmed its origin from CAR+ T cells, excluding endogenous derivation. This previously unrecognized NGS-MRD artifact reflects CAR transgene persistence rather than residual disease. **Conclusions:** Collectively, our findings demonstrate that persistent novel clone observed post-eque-cel therapy represents an analytical artifact derived from the CAR transgene, not residual disease or secondary lymphoproliferative processes. Awareness of this signal is essential to prevent misinterpretation of disease status and to ensure accurate clinical decision-making in the post-CAR-T setting.

PA-199

Elevated Non-Clonal Bone Marrow Plasma Cell Fraction at Diagnosis is Associated with Improved Outcomes in Multiple Myeloma

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Introduction: Current risk stratification in newly diagnosed multiple myeloma (NDMM) primarily relies on interphase FISH cytogenetics and disease burden. In smoldering myeloma, a clonal/aberrant plasma cell fraction ≥95% is a recognized predictor of early progression, while a higher non-clonal plasma cell fraction (NCPF) is associated with improved outcomes. The prognostic impact of NCPF in NDMM remains understudied in the context of established risk factors. **Methods:** We included patients with newly diagnosed multiple myeloma (NDMM) between 01/01/2013 and 01/31/2023. Non-clonal plasma cell fraction (NCPF), defined as the percentage of non-clonal plasma cells among total plasma cells, was measured using multiparameter flow cytometry (MFC) on baseline bone marrow aspirates. Immunophenotyping used CD19, CD38, CD45, CD138, cytoplasmic kappa/lambda light chains, and DAPI. Clonal plasma cells were identified as CD38+/CD138+, CD19–/CD45–, with light chain restriction and/or ploidy differences by DAPI. An NCPF of ≥5% was considered as NCPF-High and we hypothesized this to be associated with better prognosis. High-risk cytogenetics included del (17p), t(4;14), t(14;16), t(14;20), del(1p), and 1q gain/amplification. An adaptation of the 2024 IMS/IMWG classification was

utilized for risk stratification (without the TP53 mutation data). **Results:** We included 798 patients, out of which 124 patients (15.5%) had a NCPF of ≥5% (NPCF-High). The median follow-up was 6 years and the estimated median overall survival (OS) was 8.2 years (95% CI: 5.6–6.4 years) for the entire cohort. Compared to NCPF-Low patients, the NCPF-High cohort had a lower BM plasma cell burden (median 20% vs. 50%, p < 0.0001), lower t(11;14) rates (14 vs. 24%, p = 0.02) and a higher prevalence of hyperdiploidy (71% vs. 59%, p = 0.025), with comparable rates of high-risk cytogenetics and IMS/IMWG high-risk status (25.2%vs. 25.5%, p = 0.94). The 6-year OS rate was 70.3% (95% CI: 62–79%; median OS not reached) for the NCPF-High cohort and 56.5% [95% CI: 52.2%-61%; median OS 7.6 years) for the NPCF-Low cohort [p = 0.0096; HR 0.64 (95% CI: 0.46–0.9)]. In a multivariable analysis including NCPF-High, age of ≥75 years at diagnosis of MM, IMS/IMWG high-risk status, S-phase ≥2%, bone marrow plasma cells ≥50% and eGFR <45 ml/min, the NCPF-High fraction was independently associated with a better prognosis [HR 0.64 (95% CI: 0.43–0.96), p = 0.03]. The median progression-free survival with frontline therapy was significantly better for the NCPF-High cohort [HR 0.69 (95% CI: 0.53–0.9), p = 0.006], with comparable induction, transplant and maintenance strategies in the two cohorts. **Conclusions:** Among patients with NDMM, a higher non-clonal plasma cell fraction at diagnosis is independently associated with improved overall survival, suggesting its potential as a novel prognostic biomarker. Characterization of the immune microenvironment in these patients would be important to understanding the biologic rationale for these findings.

PA-200

Performance and Additional Benefits of Matrix-Assisted Laser Desorption/Ionization-Time-of-Flight Mass Spectrometry in M-Protein Detection in Plasma Cell Disorders

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Introduction: Current recommendations for detecting monoclonal immunoglobulin component (M-proteins) include immunofixation electrophoresis (IFE) and serum protein electrophoresis (SPEP). However, these methods have been progressively limited in clinical application due to low sensitivity and time-consuming operation. The aim of this study was to examine the feasibility of matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF-MS) to qualitatively detect M-proteins. **Methods:** Peripheral blood samples from 137 newly diagnosed patients with plasma cell disorders (PCDs) were collected for MALDI-TOF-MS analysis. The performance of MALDI-TOF-MS in identifying M-proteins using serum and plasma samples was evaluated with the results of SPEP and IFE as the reference standard. **Results:** Our cohort included 105 MM (89.0%), 13 AL amyloidosis (11.0%), 4 MGUS (2.9%), 3 plasmacytoma (2.5%), 1 POEMS syndrome (0.7%). With SPEP/IFE results as the gold standard, serum-based MALDI-TOF-MS had 96.4% (132/137) agreement in determining the M-proteins, with specificity of 98.5% (132/134). With clinical results as a reference, MALDI-TOF-MS achieved higher accuracy than SPEP/IFE in identifying M proteins (99.3% vs. 97.1%). Meanwhile, detection of M-proteins using plasma samples yielded a concordance of 88.3% (121/137) with SPEP/IFE results as reference. Moreover, MALDI-TOF-MS offered additional benefits, including the identification of light chain (LC) glycosylation in 17 patients and other aberrant peaks associated with post-translational modifications (PTMs) in 4 patients. Interestingly, by monitoring post-treatment changes in M-proteins in some patients via MALDI-TOF-MS, we found that 2 patients who achieved elimination of the glycosylation peak after treatment exhibited complete response, whereas 1 patient with persistent glycosylation peak showed very good partial response. **Conclusions:** MALDI-TOF-MS is a dependable substitute for SPEP/IFE, delivering superior diagnostic and efficacy prediction values by characterizing LC glycosylation and uncovering PTM-associated spectral peaks. Our study provides robust evidence supporting the feasibility of MALDI-TOF-MS for widespread clinical application in the M-protein detection.

PA-201

Delayed and Sustained Minimal Residual Disease Response Predicts Favorable Outcomes in Newly Diagnosed Multiple Myeloma

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Introduction: Minimal residual disease (MRD) negativity is a well-established prognostic marker in multiple myeloma (MM), yet the clinical relevance of the timing and duration of MRD response remains uncertain, especially among patients who never achieve MRD negativity. **Methods:** In this large cohort study, we analyzed 1,048 newly diagnosed MM patients, encompassing 5,406 flow cytometry-based MRD assessments. We assessed the associations of time to best MRD response and duration of MRD response with progression-free survival (PFS) and overall survival (OS) using landmark and time-

dependent analyses. Multivariable Cox regression models were used to evaluate the prognostic impact of MRD response kinetics across clinical and genetic risk factors. **Results:** A longer time to best MRD response (>6 months) was significantly associated with improved PFS and OS, particularly in patients who never achieved MRD negativity but exhibited persistent low-level disease. Early responders were more likely to have higher tumor burden and high-risk cytogenetic abnormalities. Importantly, a prolonged MRD duration (≥36 months) predicted favorable outcomes regardless of MRD status, cytogenetic risk, or transplant eligibility. Patients with a "Late + Long" MRD pattern exhibited the best long-term outcomes, including those who never achieved MRD negativity. **Conclusions:** Our findings demonstrate that MRD kinetics—specifically the timing and duration of response—have independent prognostic value beyond static MRD negativity. A slow but sustained MRD response may offset the adverse impact of MRD positivity or high-risk features and could inform long-term disease monitoring and individualized treatment strategies.

PA-202

Dynamic Changes in Cytogenetic Abnormalities Detected by Serial FISH Predict MRD Status and Outcomes in Multiple Myeloma

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Introduction: Cytogenetic abnormalities (CAs) in multiple myeloma (MM) are known to evolve over time, with clonal shifts commonly observed at relapse. However, few studies have systematically examined the dynamic changes in CAs detected by fluorescence in situ hybridization (FISH) prior to relapse. Although FISH is a standard diagnostic tool at baseline, its role in longitudinal monitoring before disease progression has been underexplored. **Methods:** We retrospectively analyzed 588 MM patients who underwent multiple FISH tests before relapse. We investigated the evolution of high-risk cytogenetic abnormalities (HRCAs) and their association with minimal residual disease (MRD) dynamics and patient outcomes. Patients were stratified based on baseline and follow-up FISH results, and corresponding MRD response patterns were assessed. **Results:** Among patients with progression-free survival (PFS) >3 years, there was no significant survival difference between baseline high-risk and standard-risk groups. However, dynamic FISH assessments revealed prognostically relevant patterns: patients whose HRCAs converted from positive to negative (HR→SR) were more likely to achieve and sustain MRD negativity, whereas patients who converted from negative to positive (SR→HR) had a lower MRD-negative rate and shorter duration of MRD response. Importantly, clonal expansion of HRCAs was observed before MRD progression, indicating that cytogenetic shifts may precede molecular relapse. **Conclusions:** Our findings demonstrate that longitudinal FISH testing captures cytogenetic evolution that correlates with MRD dynamics and clinical outcomes. Compared to single-timepoint FISH, dual FISH assessments provide greater prognostic value and may guide earlier clinical interventions. These results support incorporating a second FISH test before relapse, not just at diagnosis or after relapse, to improve risk stratification and disease monitoring in MM.

PA-203

Ultra-Deep, Cost-Efficient Whole-Genome Sequencing of Cell Free DNA Recovers Most Bone Marrow Mutations in Newly Diagnosed Multiple Myeloma

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Introduction: Cell-free DNA whole-genome sequencing (cfWGS) provides a non-invasive alternative to tumor biopsy for molecular profiling. Standard-depth (~30–40×) cfWGS estimates tumour fraction and broad copy-number alterations but often misses single-nucleotide variants (SNVs) and small indels below 10% variant-allele frequency. Recent studies in solid tumours have shown that pushing cfWGS to ultra-deep coverage (≥100×) can rescue low-frequency somatic mutations, yet this has not been explored in multiple myeloma (MM). With sequencing costs declining, ultra-deep cfWGS now holds promise for the near-complete genomic reconstruction of MM from peripheral blood (PB) cfDNA alone. To determine whether ultra-deep cfWGS can approach the mutational yield of matched bone-marrow (BM) WGS and capture clinically actionable variants, we compared standard-depth (40×) Illumina cfWGS with 200× cfWGS generated on the new, low-cost Ultima Genomics platform. **Methods:** Paired BM and PB cfDNA samples with matched buffy coat germline controls were obtained at diagnosis from eight transplant-eligible MM patients in the Multiple Myeloma

Molecular Monitoring (M4) study. BM CD138+ DNA underwent 30–40× WGS on Illumina NovaSeq 6000. Matched cfDNA libraries were sequenced to 40× on Illumina (aligned with BWA-MEM/GATK with somatic variants called via MuTect2) and 200× on Ultima Solaris™ (prepared with PPM-Seq and processed through Ultima's variant pipeline). cfDNA tumor fraction was estimated using ichorCNA (Adalsteinsson et al., 2017). **Results:** At diagnosis (median age 59, range 41–67; 5M/3F), 3/8 patients were high-risk, 2 standard-risk, and 3 unknown; subtypes included 4 IgG, 3 IgA, and 1 light-chain only. WGS of DNA derived from CD138+ selected plasma cells identified a median of 3,437 somatic mutations (range 633–4,681). In these untreated patients, cfDNA tumor fractions ranged from 4.5% to 33.7% (median 12.0%). Standard 40× cfWGS recovered a median of 1,654 mutations, while 200× cfWGS recovered 2,510 (range 455–4,153), representing a 48% median increase (range 13–102%). Relative to tumor-derived DNA, 200× cfWGS captured 80% of mutations and 69% of OncoKB actionable tier 1–2 variants (such as NRAS p.Q61R, KRAS p.A146V and TP53 p.M237I), compared to 56% and 46% at 40×, respectively. The percent increase in mutation recovery with ultra-deep sequencing correlated inversely with cfDNA tumor fraction (Spearman's $\rho = -0.88$; $p < 0.01$). In all three samples with ≤5% tumor fraction, 200× cfWGS recovered at least 50% more tumor-identified mutations than 40×, with gains up to 102%. **Conclusions:** Ultra-deep cfWGS using Ultima sequencing recovered a median of 80% of tumor-derived mutations (range 65% to 89%) in this pilot cohort, supporting cfDNA as a standalone substrate for comprehensive MM genomic profiling and potentially reducing invasive BM sampling. Future work will validate these findings in larger cohorts and extend the analysis to other variant types including translocations.

PA-204

Daratumumab-Based Quadruplet Therapy in Functional High-Risk RRMM (fRRMM) Patients Promotes CD8 T Cell Activation and Expansion in the Immune Microenvironment

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Introduction: The Multiple Myeloma Research Foundation (MMRF) and its partners launched the MyDRUG platform clinical trial (NCT03732703) to evaluate the safety and efficacy of genomically-guided treatments for functional relapsed/refractory myeloma patients (fRRMM). fHRMM patients with no discernible activating mutations and who had received 1–3 prior therapies (exposed to at least one proteasome inhibitor and an IMiD) were given a combination of daratumumab (D), ixazomib (I), pomalidomide (P) and dexamethasone (d) (D-IPd) quadruplet therapy. The goal of this study is to evaluate the immunomodulatory effects of daratumumab-(anti-CD38)-based therapy on fHRMM patients enrolled in the MMRF-sponsored MyDRUG umbrella clinical trial over the duration of therapy and to correlate immune changes with patient response immediately following the first two cycles of therapy. **Methods:** Bone marrow (BM) aspirates were then collected from patients prior to therapy (BL), after 2 cycles (EOC2), after 4 cycles (EOC4) of the quadruplet therapy and at the end of treatment or disease progression (EOT). Immune and tumor fractions were enriched by CD138 selection. Here, CD138- bone marrow mononuclear cells were isolated and transcriptionally profiled by scRNAseq and scTCRseq. **Results:** Single-cell RNA and TCR profiles were generated from ~90,000 cells across 41 samples from 16 subjects. scRNAseq identified CD3+ T cells, NK cells, classical and non-classical monocytes and B cells. CD8+ T cells were further resolved into their subsets including precursor (TPEX) and terminally exhausted T cells (TEX) within the bone marrow microenvironment. Within the CD8+ T cell compartment, an expansion of the effector memory (TEM) cell population was observed following 2-cycles of therapy (EOC2). However, this TEM expansion was not sustained at timepoint EOC4. Towards the end of therapy, enrichment of precursors to exhausted and terminal dysfunctional effector memory cells (TEMRA) was observed. Subjects with partial (PR), very good partial (VGPR) and complete (CR) best overall responses showed an initial increase in TEM cells followed by a slow expansion of TEX and TEMRA cells over time. Longitudinal tracking of T cell clonality showed preferential progressive expansion of TEMRA cells after the therapy. We mapped hyperexpanded (more than 16 copies) clonotypes, presumed to be tumor-reactive, to various CD8+ T cell subsets. These hyperexpanded clonotypes mapped to the TEMRA, TEX and TEM CD8+ T cells. Analysis of TCR repertoires clonality and diversity also demonstrated a reduced richness and increased clonality of CD8+ TCRs in responders. **Conclusions:** These data indicate that paired single cell RNA and TCR sequencing of BM T cells from RRMM patients receiving D-IPd quadruplet therapy revealed a selective expansion of clonotypic CD8+ T cells. These results support further explorations of rational combinations of targeted and immune therapies for greater efficacy in this disease.

PA-205

CoMMpass Explorer: An Interactive Platform to Explore Clinico-Genomic Data from Newly Diagnosed Multiple Myeloma Patients from the CoMMpass Observational Trial

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Introduction: The CoMMpass study (NCT01454297) was a prospective, longitudinal trial of treatment naïve, newly diagnosed multiple myeloma (NDMM) patients (n = 1,141). Tumor samples were characterized using whole-exome sequencing and bulk RNA-seq at diagnosis and progression. Additionally, immune microenvironment of a subset of patients was assessed at single cell resolution (3′ scRNA-seq). To facilitate data accessibility and exploration of this multi-omic dataset, we developed CoMMpass Explorer (CE), a user-friendly platform that enables real-time exploration of clinico-genomic data from patient samples enrolled in the study. **Methods:** CE provides four functional views – a) Overall Summary displays clinical feature distribution, and Kaplan–Meier survival curves b) Mutational Profile provides somatic mutation visualization and comparison, c) Tumor Profile shows expression-level analysis including differential expression and gene set enrichment and d) Immune Microenvironment compares cell type abundance and cell cycle distributions between cohorts using scRNA-seq data. **Results:** CE centers around the idea of cohort building by allowing users to filter on the rich set of clinical, survival, and genomic data elements from CoMMpass dataset to create custom cohorts. As proof of concept, we demonstrate the validity of CE by reproducing results from two previously published studies that used CoMMpass datasets. In our first use case, we reproduced results from Simhal et al by building cohorts based on WEE1 gene expression as described by the authors. We were able to reproduce the results from the study by showing patient stratification on the basis of WEE1 gene expression and associate it with progression-free survival (PFS) using Kaplan–Meier survival curves. In our second use case, we reproduced results from Manojlovic et al by building cohorts based on self-reported race, one cohort has only African Americans and the second cohort with only Caucasians. We also demonstrate the value of CE by comparing two cohorts of patients at baseline – NDMM patients that received triplet therapy up front (Cohort 1; N = 241) vs that did not (Cohort 2; N = 139). Additionally, the patients in these two cohorts did not receive any transplant. While there is no statistical difference in the PFS or overall survival between these two groups, CE identified distinct mutational patterns in TENT5C in Cohort 1, which is less differentially expressed compared to patients in Cohort 2. Cohort 1 is also characterized by a high EMT, PI3K/AKT/MTOR signal along with a lower abundance of CD8+ T ($p < 0.05$) and NK ($p = 0.01$) cells. **Conclusions:** CE democratizes access to clinico-genomic data, empowering the myeloma research community with an intuitive tool for data exploration. Using an example, CE demonstrates significant differences in gene expression, mutational landscape and cell type abundance between patients that received triplet up front vs patients that did not within a non-programmatic framework.

PA-206

Comprehensive Characterization of Myeloma Genomes from Bone Marrow and Peripheral Blood Using a Novel Clinical Assay

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Introduction: Detecting genetic abnormalities is crucial for risk stratification and tailored interventions in multiple myeloma (MM) and its precursor conditions. This currently requires invasive bone marrow (BM) aspirates, which poses a challenge for serial monitoring of genomic evolution and causes discomfort to patients. The current standard for detecting genetic alterations in MM is fluorescence in situ hybridization (FISH), which cannot detect mutations and other clinically relevant events. As a result, the recently updated IMS-IMWG guidelines require next-generation sequencing for the classification of high-risk MM. Moreover, identification of mutations/deletions in therapeutic targets (e.g., BCMA, GPRC5D) is critical for guiding immunotherapies. Here, we enable routine assessment of MM genomes by comprehensively and robustly characterizing with whole genome sequencing (WGS) a minimum of ~50 circulating tumor cells (CTCs) isolated from peripheral blood (PB), in a novel CLIA-approved Laboratory Developed Test called GenoPredicta. We demonstrate complete concordance between WGS on CTCs and BM tumor cells, corroborated by independent clinical FISH results on BM. **Methods:** Tumor cells were isolated from paired BM and PB samples using fluorescence-activated cell sorting (FACS) (after CD138+ enrichment for PB) and subjected to WGS, from which we identified copy number alterations, structural variants, and single nucleotide variants and indels. For a subset of samples, the BM was also characterized by FISH, using a standard clinical panel for characterizing MM. **Results:** In a retrospective cohort of >60 viably frozen samples from >30 patients, we show excellent concordance between genomic abnormalities detected in BM and PB, with all clinically relevant events (11 translocations and 125 CNVs) observed in BM recapitulated in PB (100% recall). These abnormalities included high-risk events not assayed by FISH, including biallelic TP53 loss (Del 17p coupled with a deleterious TP53 mutation, observed in 4 patients) and MYC::IGL translocations (2 patients). Moreover, all events identified by FISH in 14 samples (8 translocations and 30 CNVs) were also identified in the BM and PB (100% recall), with 50 translocations and 30 CNVs not detected by FISH also absent in the WGS data (100% precision). Importantly,

the sensitivity of our methods distinguished events that were subclonal in PB but clonal in the paired BM sample, suggestive of multi-focal or extramedullary disease. For example, we identified subclonal translocations (MYC::IGH) that were only detectable in PB, including in a longitudinal sample post-treatment, suggesting emergence of a resistant clone. **Conclusions:** We demonstrate that WGS-based characterization of MM from BM or CTCs is a viable replacement for FISH for clinical diagnosis, with blood-based measurements enabling more dynamic and minimally invasive monitoring of the myeloma cancer genome.

PA-207

Single-Cell RNA-Seq Studies Underline the Influence at Baseline of the BM Immune Composition in Promoting Resistance to CAR-T Therapies in Multiple Myeloma

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Introduction: BCMA- and GPRC5D-directed chimeric antigen receptor T-cell (CAR-T) therapies induce high response rates in multiple myeloma (MM) patients. However, clinical relapses occur in most cases. While the quality of T cells is known to influence responses to CAR-T, the impact of the bone marrow (BM) niche on patients' outcomes is not fully known. In this study, we used single-cell transcriptomics analysis to evaluate how at baseline the composition of the immune microenvironment correlates with response to CAR-T therapies. **Methods:** BM aspirates were collected from MM patients treated with anti-BCMA (n = 4) or -GPRC5D (n = 4) CAR-T. Patients were defined as responders (R; n = 4) if achieved ≥ partial response (PR) for at least 4 months. Following Ficoll separation and magnetic sorting the CD138- immune and CD138+ MM cells were isolated and used to perform unbiased single-cell mRNA profiling (10x GemCode, NextSeq 1000). CellRanger and Seurat were used for sample de-multiplexing, barcode processing, single-cell 3′ gene counting, and data analysis. A total of 36,450 cells were annotated based on their gene expression signature using scGate and ProjecTILs packages. **Results:** We first compared the baseline immunome profiling of CD138- cells obtained from R and NR. Notably, in NR we observed a highly inflammatory microenvironment characterized by an enrichment of dysfunctional NK cells (CCL3+, CX3CR1+, HAVCR2+, GZMH+) and a higher number of tolerogenic cDC1 (IDO1+) cells together with pDC and monoDC with inflammatory features. In contrast, an activated innate immune microenvironment with significant enrichment of highly cytotoxic NK cells (GZMK+, CXCR4+, CD160+, NCR3+) and an increased number of cDC1 and cDC2 cells promoting type 1 and 2 immune responses were observed in R. Among the T cells in NR we identified an increased number of regulatory CD4 T cells (TIGIT+, FOXP3+, ICOS+), dysregulated CD4 Th17 cells (CTLA4+, CD28+, GZMA+, IFNG+), and exhausted CD8 T cells (HAVCR2+, LAG3+, TIGIT+, TOX+) contributing to a dysfunctional microenvironment. In contrast, enrichment of naïve and effector memory T cells was observed in R to support the cytotoxicity and persistence of CAR-T cells. Lastly, the analysis of the MM cells transcriptome of NR confirmed the expression of BCMA and GPRC5D on tumor cells and excluded antigenic escape as a cause of resistance. Analysis of cell-cell interactions between tumor and immune cells using CellChat is currently ongoing and will be updated at the meeting. **Conclusions:** In conclusion, through single-cell transcriptomic studies we have characterized the BM niche of patients treated with CAR-T cells and identified in NR a tolerogenic, dysfunctional, and pro-inflammatory BM microenvironment that promotes tumor progression. Our findings underline the influence of the BM immune composition in promoting resistance to CAR-T and support the integration of novel therapeutic strategies able to overcome the negative effects of BM niche and improve the anti-tumor effect of CAR-T in MM.

PA-208

Multi-Omic Profiling of NK Cell Dysfunction and Tumor Immune Escape in Multiple Myeloma Evolution

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Introduction: Natural killer (NK) cells play a key role in immune surveillance of multiple myeloma (MM), targeting malignant plasma cells. Genome-wide CRISPR-Cas9 screening has identified genes regulating tumor susceptibility or resistance to NK-mediated killing, highlighting mechanisms of immune escape. Thus,this study aims to characterize NK cells dynamics and tumor immune visibility in MM through integrated functional genomic screening, single-cell transcriptomics, and multiparametric flow cytometry across disease stages. **Methods:** We analyzed a published genome-wide CRISPR-Cas9 screen in NK-tumor co-cultures to define gene signatures linked to NK sensitivity or resistance in MM cell lines. These signatures were applied to single-cell RNA-seq data from 209 patients, profiling

209,175 malignant plasma cells and 48,614 NK cells (Resting, Cytokine-activated, Adaptive, Type I, Activated). Healthy donor (HD) samples served as reference. Additionally, we performed fresh bone marrow sampling from 46 MM patients and conducted multiparametric flow cytometry. FlowCT was used for cytometric analysis and unsupervised clustering. **Results:** Both NK sensitivity and resistance gene signatures declined with disease progression, indicating reduced tumor immune visibility and impaired NK recognition. NK cells showed marked inter-patient heterogeneity and different functional states. Clustering of integrated tumor and NK profiles revealed seven transcriptional clusters. Cluster 1 (68% MM) showed cytokine-responsive NKs (e.g., IFNG, CD69), while Cluster 4 (mainly HD) retained resting NK features (e.g., NKG2A, GZMK) and higher tumor immunogenicity. Clusters 5–6 (mostly MM) showed low susceptibility and expression of immunoregulatory genes (e.g., TIGIT, CD96). Cluster 7 (relapsed MM) exhibited adaptive NK features (e.g., KLRC2, IL32). MGUS and SMM aligned more closely with HD profiles, indicating preserved immune control in early disease. Flow cytometry confirmed progressive downregulation of TIGIT and NKG2A in NK cells with disease progression. In MM patients with osteolytic lesions, we observed expansion of activated NK subsets ($TIM3^+$ $CD57^{+/-}$ $TIGIT^-$ $PD1^-$ $NKG2A^{+/-}$) in bone marrow, suggesting a local immune response to inflammation and bone damage. **Conclusions:** MM progression involves loss of tumor immunogenicity and remodeling of NK cell states, with emergence of suppressive phenotypes in advanced stages and expansion of activated NKs in osteolytic disease. MGUS and SMM retain more physiological NK-tumor interactions. These findings offer a multi-omic framework for understanding NK dysfunction in MM and support the development of NK-based immunotherapies and monitoring strategies across disease stages.

PA-209

Single Cell RNA and Whole Genome Sequencing Analysis Reveal Distinct Immune and Genomic Signatures in WM Patients Resistant to Ibrutinib Therapy

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Introduction: Even though our understanding of the pathobiology of Waldenström's macroglobulinemia (WM) has grown significantly over the last few years, there is limited data on the heterogeneity that is observed in terms of the depth of response to ibrutinib therapy in clinical responses that allude to mechanisms beyond mere tumor debulking and mechanisms of resistance and treatment failure. The aim of this study was to identify and characterize the mechanisms of resistance of previously untreated WM patients uniformly treated with standard BTK therapy, ibrutinib (IBR), by integrating single cell RNA seq (scRNAseq), B cell receptor (BCR) and whole genome sequencing (WGS) profiling approaches. **Methods:** We performed scRNA combined with BCR sequencing on bone marrow mononuclear cells (BMNCs) from 62 bone marrow aspirates of 27 WM patients and 2 healthy donors; 27 samples at the time of diagnosis and at 6 moths post-IBR therapy (n = 54 samples total), 3 samples at 12 months post-IBR and 3 samples from patients that developed progressive disease on IBR therapy. The responder group (RG) who achieved at least partial response consisted of 17 patients while the non-responder group (NRG) consisted of 10 patients. After filtering out cells using standard quality controls, we proceeded to the analysis of a total of ~260,000 BMNCs. **Results:** Our results showed significantly more clonal B cell population in the NRG at diagnosis compared to the RG ($p = 0.03$) and identified genes such as CHST15, EIF4E3, GSDME, IL17RB upregulated in RG and genes such as EGR1, S100A4, S100A6 upregulated in NRG. Regarding the immune microenvironment, IFN+ monocytes in NRG were significantly increased compared to the RG ($p = 0.005$) at diagnosis, and SELL+ NK subpopulation was more prominent. CD4 and CD8 T naive cells were significantly enriched in the RG while subpopulations exhibiting more exhausted phenotype, such as the GZMB+, were more common in the NRG. We also observed significant increases of the GZMK+ T cell effector subpopulation post-IBR in NRG ($p = 0.005$) while a significant decrease of the naïve CD8 T cells and Tregs was observed post-IBR in the RG only. Mutational analysis identified highly mutated genes in the RG including KMT2C (25%), CAST (25%), and SLC10A3 (25%) while in the NRG included CXCR4 (44%), NOTCH1 (33%), KMT2D (33%), ARID1A (22%) and ARID1B (22%). Amplifications of chromosomes 12 (40% in NR group) and 18 (25% in NR group) were only seen in the NRG while del6q was observed in about 40% of the NRG compared to 25% in the RG. **Conclusions:** In conclusion, our results show distinct transcriptomic, genomic and immune profiles between WM patients with different responses to ibrutinib therapy, highlighting potential mechanisms of resistance that could serve for the identification of predictive biomarkers for BTK-based therapy in WM.

PA-210

Single-Nucleus Profiling Reveals Aberrant Osteoclast Differentiation in MM

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Introduction: Osteolytic bone lesions are a defining feature of multiple myeloma (MM), affecting up to 80% of patients and leading to chronic pain, pathological fractures, and neurological impairment. These lesions result from an imbalance between bone forming osteoblasts (OBs) and bone resorbing osteoclasts (OCs), driven by MM-induced changes in the bone marrow microenvironment. Current therapies, such as bisphosphonates and RANKL inhibitors, fail to promote bone repair, lead to a low bone turnover state, and carry side effects. A key gap is our limited understanding of how MM alters OC differentiation. **Methods:** To model MM bone disease, murine Vk*MYC MM cells were intrafemorally transplanted into C57BL/6 mouse femurs. MM development and bone lesions were confirmed via serum protein electrophoresis and μ-CT imaging. The number and spatial distribution of OCs were assessed using tartrate-resistant acid phosphatase (TRAP) staining in FFPE femur sections. In parallel, an in vitro model was developed and validated to differentiate OCs from bone marrow mononuclear cells (BMMNCs). BMMNCs were cultured with M-CSF and RANKL for five days, promoting the expansion and fusion of OC precursors (OCPs) into mature OCs, while MM cells were present in the supernatant of the culture. Single-nucleus RNA sequencing (snRNA-seq) was optimized and performed at two key time points: day two (OCP stage) and day five (OC stage) cells differentiated from Vk*MYC and PBS-injected (control) mice, using 10X Genomics Chromium 3′ platform to identify transcriptional signatures. **Results:** TRAP and H&E staining of Vk*MYC bone sections confirmed aberrant osteoclast distribution, cortical and trabecular bone loss, and extensive MM infiltration. Unlike single-cell RNA-seq, which excludes large multinucleated OCs due to size limitations during droplet encapsulation, snRNA-seq enabled capture of all OCs. No differences were detected in the composition of cell types between Vk*MYC and control samples. Our data analysis indicated that at day two (OCP population), the culture system was primarily composed of macrophage subtypes, along with the presence of immune cells such as B cells and dendritic cells. By day five, distinct macrophage-like pre-OCs and mature OCs had emerged. Differential gene expression analysis revealed that macrophage clusters exhibited increased expression of genes linked to phagocytosis, adhesion, and mononuclear cell differentiation, suggesting accelerated OC differentiation in the presence of MM cells. Furthermore, the Vk*MYC OC cluster exhibited a distinct immune-inflammatory transcriptional signature along with upregulation of ribosome biogenesis pathways, consistent with increased functional activation. **Conclusions:** In summary, we observed similar cell populations within the OC culture system in both Vk*MYC and control samples; however, OCPs and OCs displayed altered gene expression profiles, suggesting accelerated differentiation, increased activity, and an inflammatory signature.

PA-211

Cyclin D1 Beyond the Cell Cycle: A New Role in t (11;14) MM

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Introduction: Cyclin D1, encoded by CCND1, is a cell cycle regulator, overexpressed in ~15% of multiple myeloma (MM) cases via CCND1-IGH super-enhancer juxtaposition through t(11;14). Cyclin D1 also plays a non-canonical role in transcriptional regulation, but its function in gene regulation in t(11;14) MM remains undefined. We investigated the global transcriptional and epigenomic consequences of cyclin D1 overexpression in t(11;14) MM. **Methods:** Two CCND1 knockout (KO) t(11;14) MM U266B1 clones were generated by CRISPR/Cas9, introducing a frameshift insertion (A) after chr11:69641478 (hg38, exon 1). ChIP-seq (H3K4me3, H3K4me1, H3K27ac) was performed in KO and wild-type in duplicates, RNA-seq in triplicates. Libraries were sequenced on Illumina NextSeq 2000 (2 × 51 bp for ChIP/ATAC, 2 × 150 bp for RNA-seq). Reads were mapped to hg38 by BWA (ChIP/ATAC) or STAR (RNA-seq), peaks called by MACS2 (FDR< 0.01), gene counts by featureCounts. Differential peaks and differentially expressed genes were identified by edgeR (FDR<0.05, fold-change ≥2), including peaks in ≥2 samples and genes with transcript-per-million (TPM) ≥0.1 in ≥1 sample. Pathway analysis performed using Enrichr. To define a CCND1 signature, RNA-seq from two independent cohorts was compared (high CCND1 t(11;14) (≥300 TPM, n = 271) vs. low CCND1 hyperdiploid cases (< 30 TPM, n = 233). Co-immunoprecipitation was done in t(11;14) KMS12BM cells. **Results:** Differential expression comparing CCND1-high t(11;14) and CCND1-low MM cases identified 22 upregulated and 21 downregulated genes associated with CCND1 expression in 2 patient cohorts and CCND1-modified U266 cells. Enriched pathways ($p < 0.05$) included Notch signaling, early/late estrogen response, epithelial-mesenchymal transition and reduced mitotic spindle and myogenesis. Dysregulated genes included those related to apoptosis, ubiquitin-proteosome, extracellular matrix, adhesion, and immune response, demonstrating a broader role for cyclin D1 beyond cell cycle control. To explore the epigenomic basis of this regulation, we examined histone marks in the U266 KO model. Among differentially expressed genes, 6 (27%; ASS1, PMAIP1, MAN1C1, MYEOV, CCR7, DTX1) and 5 (24%; UACA, RASAL2, PTPRZ1, PPT2, IL23R) showed visually distinct changes in histone marks, suggesting a chromatin-mediated

mechanism of gene regulation by cyclin D1. The most prominent changes involved H3K27ac, mirroring the gene expression changes. As H3K27ac is deposited by histone acetyltransferases CBP, we tested for cyclin D1-CBP interaction. Co-IP confirmed this interaction, suggesting a role for this complex in chromatin remodeling and transcriptional control in t(11;14) MM. **Conclusions:** A cyclin D1-associated gene signature was identified supporting its role in t(11;14) MM beyond the cell cycle. These findings highlight cyclin D1 as a therapeutic vulnerability and open new avenues for personalized treatment strategies.

PA-212

Spatial Transcriptomics in Extramedullary Multiple Myeloma Reveals an M2 Macrophage Prominent TME

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Introduction: Extramedullary disease (EMD) in multiple myeloma (MM) is associated with poor prognosis due to aggressive disease kinetics and therapy resistance. Bone marrow (BM) restricted MM is highly dependent on the BM microenvironment for survival, putatively contributing to drug-resistance. In EMD, the biology and particularly the role of the tumour microenvironment (TME) is unknown. **Methods:** Eight biopsies from 8 patients with haematogenous EMD were analysed using 10x Xenium In Situ Prime 5K. Subsequent analysis utilised the recently described high resolution ProSeg cell segmentation algorithm (Jones D et al, Nat Methods 2025). **Results:** A total of 499,726 cells from 8 samples were included. Plasma cells (PC) in EMD maintain a PC transcriptome with expression of transcription factors XBP1, IRF4 and PRDM1 without significant expression of PAX5, FOXP1. After dimensionality reduction, like BM-restricted MM, PC clustering was driven primarily by inter-patient variability. The TME was assessed. The most numerous immune cells were macrophages, specifically those with an immune-suppressive M2 phenotype, demonstrated by expression of markers such as CD163 and MRC1. Myeloma infiltration by T-cells was associated with proximity to M1 macrophages. Infiltrating CD8+ T-cells co-expressed cytotoxicity and exhaustion genes. Cancer associated fibroblasts were the most common non-immune cell in the TME. Spatial analysis was performed with recurrent microenvironments identified. Perivascular niches, characterised by fibroblasts and endothelial cells, were enriched for immune cells and more proliferative PC subsets. The bulk of tumours were characterized by immune-excluded regions with a high proportion of PC (>80%). Rarer areas with increased T-cells, presumed immune-permissive regions, were also present. Predicted cell-cell interactions identified a complex, bidirectional network. PC interactions with the TME via signals including prostaglandin E2 and VEGFB were evident, predicted to drive M2 macrophage differentiation. Conversely, macrophages in the TME expressing APRIL and BAFF are predicted to promote PC survival via canonical ligands including BCMA, CXCR4 and CD38. This bidirectional signalling between suppressive myeloid cells in the TME and PC thus putatively promote myeloma growth directly whilst concurrently constraining anti-myeloma immunity. Across all samples, subsets of PC showed upregulation of cell cycle genes, consistent with proliferative transcriptional programs. There was also an enrichment of SOST, SNHG15 and LENG8, genes implicated in bone formation and oncogenesis. While described in BM-restricted MM, the presence of these clusters in all samples suggests an important role in EMD biology. **Conclusions:** Our findings provide new insights into the spatial organisation of MM EMD and identify prominent M2 macrophage rich niches in the context of T cell exclusion within the TME, together with proliferative signalling networks in PC, that represent new clinically tractable targets.

PA-213

Single-Cell Transcriptomic Stratification of Multiple Myeloma Reveals Oxidative Stress-Driven Subtypes and Cytogenetic Correlates

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy characterized by bone marrow infiltration and high genomic instability. Clonal plasma cells (cPCs) in MM exhibit elevated oxidative stress (OS) due to intense metabolic activity and protein synthesis, resulting in the production of reactive oxygen species (ROS). To survive, these cells rely on antioxidant systems such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and thioredoxin reductase (TrxR). Upregulation of these pathways has been linked to drug resistance and poor prognosis. We aimed to define OS-related molecular subtypes of MM by analyzing a large collection of single-cell transcriptomic profiles, with the goal of uncovering

stress-linked vulnerabilities and identifying immune and genetic correlates of malignant plasma cell states. **Methods:** We integrated raw scRNA-seq data from 10 publicly available GEO datasets (n = 64 patients), extracting 93,071 bone marrow plasma cell profiles. Data underwent individual quality control, normalization, and reference-based annotation. A curated panel of 210 OS-related genes was used to cluster cells via PCA, UMAP, and the Leiden algorithm. This revealed seven OS-related clusters (O2_clusters) reflecting distinct transcriptional stress signatures. Patients were assigned to O2_clusters based on the dominant stress phenotype in their plasma cells. We created pseudobulk profiles for each patient to assess expression of genes linked to major cytogenetic events in MM (FGFR3, CCND1, MCL1, etc.), allowing cytogenetic stratification. The complete cellular dataset was also used to evaluate immune cell-type differences between O2_clusters. **Results:** Seven transcriptionally distinct O2_clusters were identified. 52 patients showed a dominant plasma cell cluster, suggesting monoclonality of the OS phenotype. O2_cluster_1 was associated with t(4;14) translocations, marked by FGFR3 and MCL1 upregulation. O2_cluster_2 was linked to t (11;14), defined by CCND1 and MCL1 expression. Other clusters revealed potentially novel cytogenetic states. Immune landscape analysis showed cluster-specific traits with distinct profiles across O2_clusters. O2_cluster_1_ t(4;14) patients had increased Prog-B cell fractions and reduced MAIT. O2_cluster_2_ t(11;14) showed lower cDC2 and pDC content. O2_cluster_3, marked by chaperones like CCT3 and BAG1, had elevated Naive B cells. O2_cluster_4 exhibited enrichment in Memory B, Lymphoid-Primed Multipotent Progenitors. **Conclusions:** This study introduces a scalable bioinformatics pipeline for MM patient stratification based on OS-related transcriptional programs. Cross-cohort integration of scRNA-seq data revealed distinct stress-driven plasma cell subtypes with specific genetic and immune correlates. These findings highlight the utility of large-scale single-cell analyses for identifying clinically relevant MM biomarkers and stress-related therapeutic targets, underscoring the potential of bioinformatics in precision oncology.

PA-214

Expression Profile–Based Dissemination Score for Myeloma Prognostication

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Introduction: Disseminated myeloma, defined by the presence of circulating plasma cells (CPCs) and/or extramedullary disease (EMD), is associated with poor prognosis and resistance to standard therapies. Epithelial-to-mesenchymal transition (EMT) is marked by the downregulation of adhesion molecules such as CD138, CD56, and integrins. EMT has been implicated in both CPCs and EMD by previous studies and unifies the understanding of disseminated myeloma. **Methods:** We analyzed baseline RNA-seq data from 754 newly diagnosed multiple myeloma patients enrolled in the MMRF CoMMpass study. A total of 1,357 candidate genes were selected by integrating the EMTome gene set (1,114 genes) with genes differentially expressed in association with CPC percentage (n = 243) and PET-CT–confirmed plasmacytomas (n = 34), identified using the limma-voom pipeline (FDR ≤0.05, effect size >5 SD). Among these, 365 genes demonstrated significant associations with overall survival ($p \leq 0.05$ in univariate Cox regression) and were entered into an Elastic Net Cox model ($\alpha = 0.5$), yielding a 30-gene signature to compute the weighted Dissemination Score(D-S). **Results:** The D-S included positively weighted genes: PHF19, FABP5, APOBEC3B, TOP2A, HTR2C, FOXM1, Novel lnRNA(ENSG00000237422), BUB1, NAP1L3, WEE1, PFKP, SHROOM3, KIR3DX1, KIF21B, PKDCC, JAG2, FOXD1, MAGEA1, CDCA7, ELOVL6, HHAT, CRIP2, SCRIB, and ADAM15., and negatively weighted genes: LTBP1, DENND2D, GRHL1, LAMA5, TJP1, and KIAA1191, representing a balance between mesenchymal and epithelial traits. The D-S demonstrated strong prognostic discrimination with a C-statistic of 0.71 (SE = 0.02). Median overall survival (OS) was 55.5 months (95% CI: 47.2–65.0) in the high D-S group, versus 102.5 months (95% CI: 89.3–NA) in the low D-S group. The score further stratified patients within IMWG risk groups (log-rank $\chi^2 = 77.83$, $df = 3$, $p < 0.001$), with the worst outcomes seen in those with both high DS and high IMWG risk (median OS: 52.3 months, 95% CI: 37.8–70.9). Incorporating the D-S into existing genomic models improved performance: C-statistics increased from 0.68 to 0.76 for EMC92 and from 0.69 to 0.75 for UAMS70 when D-S was added alongside age and R2-ISS ($p < 0.001$ for both comparisons, Wilcoxon signed-rank test, 1,000 bootstraps). Dissemination Score was significantly elevated in patients harboring high-risk cytogenetic lesions, including 1q21 gain, 17p deletion, t(4;14), and GPRC5D loss (all $p < 0.001$), while it was lower in hyperdiploid cases, suggesting its alignment with aggressive biological subtypes. In multivariable Cox regression, the D-S remained an independent predictor of overall survival (HR 1.09, 95% CI: 1.05–1.14, $p < 0.001$), outperforming other gene expression–based scores including UAMS70 and EMC92. **Conclusions:** The Dissemination Score is a robust metric that captures the biology of plasma cell dissemination, a phenotype analogous to metastatic behavior in solid tumors and may help guide therapeutic decisions.

PA-215

Defining a Novel Cytokine Combination to Optimize in Vitro Culture Conditions for Primary Multiple Myeloma Patient Cells

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Introduction: In vitro culture of primary multiple myeloma (MM) patient cells is very challenging and still poses a major hurdle in MM research. Our goal is to establish a robust, biologically-driven in vitro culture system for primary MM patient samples, enabling downstream applications. **Methods:** We developed our culture cocktail platform in a systematic, data-driven manner cross-referenced with literature to allow the discovery of novel cytokines. Bioinformatic analyses utilized the MMRF-CoMMpass RNA-Seq dataset of 770 MM patients to investigate cytokine and receptor mRNA expression associated with defined MM patient characteristics and clinical outcomes. Based on the 13 resulting cytokines, a high-throughput combinatorial screen of 2- and 3-cytokine combinations was performed on CD138+ MM patient samples (n = 3) over 96 hours. The 10 most viable doublet or triplet cytokine combinations were further validated on more primary CD138+ and whole bone marrow MM patient samples (n = 4) as well as plasma cell leukemia (PCL) patient samples (n = 3) that were previously engrafted in NRG-3GS mice. Readouts by flow cytometry. **Results:** Validation of the top 10 cytokine combinations on primary MM samples (n = 4) and ex vivo patient-derived xenograft (PDX) samples (n = 3) revealed a leading cytokine combination that sustained viability and supported the retention of an MM immunophenotype up to 14 days (patent application pending). Final viability between days 10–14 ranged from 65–73%, showing a significant improvement over the initial thaw viability of 50–60%. Our leading cytokine combination achieved a mean viability of 66.7% ± 2.3% SEM, significantly higher than the negative control (medium only) at day 12 ($p = 0.009$, $n = 4$). Another key indicator of successful culture is the recovery of the MM cell marker CD138, which is often lost during freezing and thawing, and its maintenance in culture. Our candidate cocktail supported a faster recovery of CD138 expression in frozen whole bone marrow PCL patient samples (n = 3) post-thaw, outperforming other cytokine combinations and the negative control. By day 4 post-thaw, our candidate cocktail yielded a CD138 expression of 39.6% versus 18.8% in the negative control (±4.7% SEM, $p = 0.048$), increasing to 64.9% versus 31.2% by day 7 (±5.2% SEM, $p = 0.023$). To evaluate our cytokine combination in a downstream application, we infected a PCL patient sample with a lentivirus carrying an mCherry fluorescent marker. This approach resulted in a transduction efficiency of 44% with a viability of 65%. Ongoing experiments are to compare lentiviral infection rates in freshly-thawed versus cultured MM cells at multiple timepoints. Preliminary data indicate improved transduction after 5 days in culture (89%) compared to immediate post-thaw (40%). **Conclusions:** Our culture system (patent pending) offers broad applications, including drug screening, gene manipulation, and functional studies of primary MM cells, providing a valuable tool for translational research.

PA-216

The PBX1 Protein is Substantially Overexpressed in Patients with Multiple Myeloma Exhibiting Chromosomal 1q Gain or Amplification, and it is Associated with Unfavorable Prognosis

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Introduction: Pre-B cell leukemia factor 1 (PBX1) gene, located at chromosome 1q23.3, is a transcription factor that modulates essential oncogenic pathways in multiple myeloma (MM), serves as a negative prognostic factor, and may function as a therapeutic target. **Methods:** We conducted a retrospective analysis of PBX1 protein expression in bone marrow (BM) biopsies of MM patients with known chromosome 1 abnormalities (1q21+). The immunohistochemical (IH) staining was performed on 3 μm thick sections from paraffin embedded BM biopsies, utilizing a specific PBX1 clone 4A2 monoclonal antibody (Abnova, Taipei, Taiwan, 1 mg/mL, M01). In addition, cytogenetic abnormalities (CA) were assessed using fluorescence in situ hybridization (FISH) on CD138-positive BM plasma cells. FISH analysis and BM IH staining were performed on samples obtained at the same time point. Overall survival (OS) was determined with the Kaplan-Meier method. Fifty-four BM specimens from MM patients were analyzed, comprising 45 individuals with 1q21+ and 9 patients without 1q21+. **Results:** Of the 54 patients, 31 were men (57.4%) and 23 women (42.6%) with a median age at diagnosis of 64 years (range, 42–86 years). Disease stage at diagnosis defined by R-ISS was I in 10 (18.5%) patients, II in 23 (42.6%) patients, III in 19 (35.2%) patients, while for 2 (3.7%) patients it was unknown. Regarding the 45 patients with 1q21+, gain or amplification was present in 29 (64.4%) and 13 (28,9%) patients respectively, while for 3 (6.7%) patients it was unknown. Co-existence of other CA was present in 28 (62.2%) patients. Detection of TP53 was found in 10 (22.2%) patients while t(4;14), t(14;16) and t(11;14) were found in 8 (17.7%), 5 (11.1%) and 5 (11.1%) patients respectively. Lactate dehydrogenase (LDH) at diagnosis was elevated in 17 patients (37.8%). PBX1 protein was expressed in 22 (49%) patients with 1q21+, whereas 23 (51%) were negative. Half of the patients with PBX1 positivity had additional CA and disease stage III R-ISS was found in 10 (10/22, 45.5%) of them. Of the 9 patients lacking 1q21+, PBX1 protein was expressed in 2 (2/9, 22.2%) patients. The estimated 5-year OS for the patients who expressed PBX1 was 34.4% (95% CI: 16.2%-72.8%) versus 48.7% (95% CI: 25.8%-91.9%) for PBX1 negative patients (p 0.54). **Conclusions:** The PBX1 protein expression in BM biopsies of MM patients with 1q21+ appears to correlate with a poor trend in overall survival.

Further research of the effect of PBX1 expression in the clinical outcome of patients with MM is needed.

PA-217

Potential Roles of YBX1-MIF Axis in Promoting Bone Marrow Inflammation and Multiple Myeloma Progression

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Introduction: Bone marrow inflammation is considered as a driver of multiple myeloma (MM) progression; however, underlying mechanisms remain to be elucidated. **Methods:** The bulk RNA-Seq data were downloaded from Multiple Myeloma Research Foundation (MMRF) CoMMpass dataset. Single cell RNA-seq datasets were downloaded from the GeneExpression Omnibus (GEO) database (GSE124310, GSE189460, GSE223060, GSE161801), and ArrayExpress (E-MTAB-9139) covering disease spectrum from MGUS, SMM to NDMM and RRMM as well as healthy condition. Single-cell data was integrated and a total of 1,220,829 cells were captured, downstream analysis was performed majorly using Seurat R package. Each cell cluster was annotated by canonical markers. **Results:** By comparing gene expression profile of myeloma cells and other major cell types including T, NK, B, monocytes, macrophage, neutrophil, DC and erythroid cells, we found that MIF (migration inhibitory factor) showed the strongest expression level in myeloma cells. And its expression gradually increased during disease progression. Cell-cell interactions results indicated that MIF-CD74/CXCR4/CD44 ligand-receptor pairs mediate the most prominent interaction between myeloma cells and myeloid subsets. By exploring the potential factor regulating MIF expression in MM, we found that transcription factor YBX1 showed a positive correlation with MIF, suggesting YBX1 may promote myeloma-derived MIF expression and secretion. YBX1-high MM patients exhibited stronger interaction of MIF-CD74/CXCR4/CD44 between myeloma cells and each myeloid subset. Furthermore, inflammatory pathways (interferon response, inflammatory response, cell adhesion, leukocyte migration) and proinflammatory genes (IL1B, CCL2, CCR2, ISG15, MX1, IL15, IL16, CX3CR1) were significantly enhanced in myeloid subsets from YBX1-high MM patients. **Conclusions:** MM-derived MIF may be regulated by YBX1 and promote myeloid cell-mediated inflammatory response, thus promote disease progression. Detailed mechanisms warrant further exploration.

PA-218

Bortezomib, Lenalidomide, and Dexamethasone Reverses the Inferior Prognostic Effect of KRAS Mutation in Patients with Newly-Diagnosed Multiple Myeloma

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Introduction: Bortezomib, lenalidomide, and dexamethasone (VRD) is a standard regimen for patients with newly diagnosed multiple myeloma (NDMM), which achieves over 90% response rate. The superior efficacy of VRd in triplet regimens is not mechanically explained. This study aims to filtrate subpopulation responding to VRd based on the data of next generation sequencing (NGS) in NDMM patients. **Methods:** We analyzed clinical and NGS data from 121 NDMM patients receiving frontline VRD (June 2019–March 2024, Peking Union Medical College Hospital). Controls included 50 patients receiving bortezomib, cyclophosphamide, dexamethasone (BCD)/BD or ixazomib and dexamethasone (ID) regimens. High-risk cytogenetic abnormalities (HRCA) were defined as 1q21+, del17p, t(4;14), t(14;16). A NGS panel including 290 tumor-related genes was performed in purified plasma cells. High-risk MM (HRMM) was defined by fulfilling any of the following criteria: R-ISS stage III, soft-tissue extramedullary disease, positive circulating plasma cells, at least one HRCA (isolated 1q21 gain excluded), early relapse (progression within 2 years in transplant patinets, or < 18 months in non-transplant ones). **Results:** Median follow-up: 38.8 months.Frequent mutations: KRAS (26.4%), NRAS (15.7%), TP53 (6.6%), IGLL5 (5.8%)and BRAF (3.3%). Survival analysis of patients with the aforementioned genetic alterations revealed that KRAS-mutated patients exhibited significantly longer PFS and OS than wild-type counterparts (2-year PFS 81% vs.61%; 2-year OS 97% vs.87%, $p < 0.05$). Univariate and multivariate analyses incorporating baseline characteristics (sex, age, M-protein type, R-ISS stage III, transplantation status, HRCA) and NGS results identified KRAS as an independent favorable factor for PFS. Among 78 HRMM patients (per defined criteria), 14 harbored KRAS mutations. Although it was not statistically significant, these mutated patients demonstrated survival advantages in both PFS (2-year PFS 64%vs.46%, $p = 0.144$) and OS (2-year OS 93%vs.81%, $p = 0.193$) compared to non-mutated cases. For other gene mutations, the survival differences between the two groups were not statistically significant, likely due to the limited number of cases. In contrast, among 50 patients receiving alternative first-line regimens including BCD/BD/ID, those with KRAS mutations presented significantly worse outcomes than wild-type cases (2-year PFS: 34% vs. 76%, $p = 0.003$). **Conclusions:** The prognostic value of gene mutations other than TP53 is controversial in MM patients. Although KRAS

mutation is associated with inferior outcome in proteosome inhibitor-based regimens not combined with immunomodulator drugs, our findings suggest that VRD regimen may improve the response and survival in KRAS mutated NDMM patients, therefore translating into the improvement of whole population. The synergistic effect of bortezomib and lenalidomide in overcoming stimulation of RAS pathway will be further explored.

PA-219

CD69+ Bone Marrow-Resident CD8+ T Cells Exhibit Functional Exhaustion and Impaired Anti-Tumor Activity in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is characterized by dysfunctional immune microenvironments in the bone marrow (BM), where tumor-induced T cell exhaustion hinders effective immune surveillance. CD69, a canonical marker of tissue-resident memory T cells (TRM), is constitutively expressed on resident CD8+ T cells in various tissues. However, the immunological characteristics and clinical significance of CD69+CD8+ T cells in the MM bone marrow remain poorly understood. **Methods:** Paired BM and peripheral blood samples were collected from 39 newly diagnosed MM patients. Flow cytometry was used to assess surface and intracellular markers, including exhaustion and cytotoxicity markers. CD69+ and CD69− memory CD8+ T cells were sorted from BM and subjected to RNA sequencing and gene set enrichment analysis (GSEA). Functional status was evaluated via intracellular cytokine staining after direct ex vivo stimulation. Antigen-specific CD8+ T cells recognizing NY-ESO-1 or HM1.24 were identified using MHC-multimer technique. Correlations with tumor burden (BM plasma cell % and serum β2-microglobulin) were also analyzed. **Results:** BM-resident CD69+CD8+ T cells were more abundant than their peripheral counterparts and displayed TRM-like transcriptomic profiles, including upregulation of CD69, PDCD1, EOMES, and TOX, and downregulation of S1PR1, GZMB, and GNLY. These cells co-expressed multiple exhaustion markers (PD-1, TIGIT, Lag-3) and showed higher frequencies of terminally exhausted Eomeshi T-betlo phenotypes. Myeloma antigen-specific CD8+ T cells were enriched in the CD69+ subset and expressed higher levels of PD-1 and TIGIT. The frequency of PD-1+ or PD-1+TIGIT+ among CD69+CD8+ T cells significantly correlated with BM plasma cell percentage and serum β2-microglobulin level. Functionally, CD69+ cells exhibited diminished expression of granzyme B, perforin, TNF-α, and IFN-γ. Notably, co-blockade of PD-1 and TIGIT—but not either alone—restored cytokine production in CD69+CD8+ T cells ex vivo. **Conclusions:** CD69+CD8+ T cells in the MM bone marrow represent a distinct tissue-resident and tumor antigen-reactive subset with features of advanced exhaustion and functional impairment. Their phenotype correlates with disease burden, and their function can be partially restored via PD-1/TIGIT dual blockade. These findings support the clinical utility of CD69+CD8+ T cells as a biomarker for anti-myeloma immune activity and potential therapeutic targets in T cell-based immunotherapy.

PA-220

Integrated Multi-Omic Profiling of Immune, Soluble, and Microbial Signatures Identifies Predictors of Multiple Myeloma Evolution

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Introduction: Multiple myeloma (MM) is a clonal plasma cell malignancy that develops through precursor stages, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). Despite well-established clinical criteria, the biological drivers of evolution remain incompletely understood. Here, we applied a multi-omic approach to dissect immune cell phenotypes, cytokine networks, and microbial composition across the MGUS–SMM–MM continuum, aiming to identify early determinants of evolution. **Methods:** We comprehensively characterized the immune landscape by performing scRNAseq and flow cytometric analysis of both BM and peripheral blood (PB) samples from a cohort of 26 and 46 patients, respectively, including MGUS, SMM, and MM. To complement the cellular data, we assessed cytokine and chemokine profiles using 48-plex Luminex assays on 72 patient samples, alongside 4 healthy donors (HDs). Additionally, fecal microbiota profiling was conducted on samples collected from 10 MGUS, 15 SMM, and 16 MM patients. **Results:** scRNAseq analysis revealed a progressive upregulation of immune checkpoint-related genes, including CD266, TIGIT, and members of the KIR family, accompanied by a concomitant downregulation of CD96 expression during MM evolution. In parallel, flow cytometric profiling indicated a significant depletion of PB transitional memory $CD8^+$ T cells in MM patients, accompanied by an increase in both PB and BM TEMRA $CD57^-$ $CD8^+$ T cells, compared to MGUS and SMM. The evaluation of cytokine and chemokine levels revealed a marked reduction of multiple immune mediators (including GM-

CSF, IFN-α2, IFN-γ, IL-1β, IL-2, IL-2Rα, IL-3, IL-10, IL-13, LIF, and MCP-1/CCL2) in BM plasma of MM patients compared to MGUS, SMM, and HDs, indicating impaired T cell activation, reduced immune cell recruitment, and an overall immunosuppressive milieu. A similar profile of immune mediator reduction was observed in PB plasma. Notably, this immune dysfunction is detectable not only in MM but also in MGUS and SMM patients, when compared to HDs. Complementary gut microbiota profiling identified a shift towards dysbiosis in MM patients, characterized by expansion of pro-inflammatory taxa (Proteobacteria, Enterobacteriaceae, Streptococcaceae) and depletion of beneficial microbial families (e.g., Lachnospiraceae, Bifidobacteriaceae). Notably, microbiota composition correlated with disease stage: MGUS samples retained a eubiotic profile, while SMM showed an intermediate state, mirroring the immune alterations observed in systemic compartments. **Conclusions:** Through an integrated multi-omic approach encompassing single-cell transcriptomics, immunophenotyping, cytokine profiling, and gut microbiota analysis, we delineated the progressive immune dysregulation occurring across the spectrum from MGUS to MM. These alterations may serve as predictive biomarkers of evolution and potential targets for preventive or therapeutic interventions.

PA-221

Type I Interferon Pathway Activation Disrupts Monocyte Maturation and Enhances Immune Evasion in Multiple Myeloma

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Introduction: In multiple myeloma (MM) tumor microenvironment, activation of type I interferon pathway and dysregulated expression of major histocompatibility complex type II genes are observed in classical monocytes, which result in loss of antigen presentation of monocytes. The proportions of BAFF+PD-L1+ monocytes in the bone marrow also correlate with survival of myeloma patients following chimeric antigen-receptor T cell therapy. Nevertheless, the mechanisms underlying monocytes defects in MM remain poorly addressed, at least in part by the lack of large scale single-cell RNA sequencing (scRNA-seq) studies. **Methods:** To resolve the heterogeneous bone marrow (BM) and peripheral blood (PB) monocyte subpopulations and their transcriptional factors between healthy donors (HD) and MM patients. We performed scRNA-seq on monocytes of 7 newly diagnosed MM (NDMM) patients and 12 HD. **Results:** We constructed a precise atlas of human PB and BM monocytes, identified seven subpopulations in both BM and PB—including S100A12, HLA, ISG15, CD16, proinflammatory, and intermediate in both BM and PB; megakaryocyte-like in PB; and proliferating subset in BM. Differential expression analysis on the BM and PB monocytes showed that a large number of interferon (IFN) signaling pathway genes (e.g. IFI27, IFI6, ISG15) were overexpressed in MM compared with HD. Genes encoding major complement system components and class II major histocompatibility complex molecules (MHC class II) were more highly expressed in MM compared to HD, indicating higher inflammatory and phagocytic potential of MM monocytes. However, relative to HD, T-cell attraction-related genes (e.g. CCL3 and CCL4) were markedly downregulated in MM, and T-cell suppression-related genes (e.g. IDO1, CD274 and PDCD1LG2) were markedly upregulated in MM. Furthermore, we identified two monocyte differentiation pathways in both BM and PB, and discovered that BM monocyte feature type I IFN-associated alterations in differentiation in patients with MM as well as dysregulated patterns at transcriptome. Quantitative PCR results showed that-human monocytes expressed type I IFN (IFNα and IFNβ), but not type II IFN (IFNγ). Furthermore, we collected conditioned media (CM) from alone culture or cocultured myeloma cell lines and human monocytes at 1:10 ratio, and co-cultured CM significantly promotes myeloma cell line proliferation. Finally, we included 10 MM patients as a validation cohort, by tracking the alterations in transcriptome and differentiation during treatment using scRNA-seq. Our results indicated that type I IFN signaling pathway activation and alterations in differentiation were partially alleviated for BM monocytes in MM by antitumor therapy. **Conclusions:** Our results provided further insight into transcriptional and differentiation alterations occurring in the BM and PB monocytes from patients with MM and explored mechanisms of immune evasion associated with monocytes.

PA-222

Dissecting B Cell Landscape and Receptor Repertoire in Plasma Cell Neoplasms at Single Cell Resolution

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Introduction: B cells are emerging as key contributors to the tumor microenvironment (TME), with growing evidence supporting their functional diversity and prognostic significance. However, their role in plasma cell (PC) dyscrasias' evolution, including monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and MM, remains poorly understood. In

this scenario, our study aims to investigate the functional properties and B cell receptor (BCR) repertoire changes of B cells in the TME of PC neoplasms. **Methods:** Single cell (sc) 5′ RNAseq coupled with scBCRseq was performed on the CD138neg cell fraction of bone marrow (BM) aspirates from 20 patients at diagnosis (7 MGUS and 13 SMM). Paired samples were also obtained from 6 patients at progression to overt MM. A control cohort of 12 healthy donors (HDs) (4 internally sourced, 8 from public repositories) was included. Bioinformatic analysis was conducted using the Seurat pipeline, Gene Set Enrichment Analysis with ClusterProfiler, interactome analysis with Multinichenet, and BCR repertoire profiling applying scRepertoire and Immcantation workflow. **Results:** We analyzed a total of 73,464 CD138neg cells, and a total of 6,890 B cells were annotated according to Fitzsimons et al. B cell atlas. In MM, compared to asymptomatic stages, there was a shift toward an activated B cell phenotype and a decline in naïve B cells. Genes associated with a physiological B cell function (e.g., CD79B, RAG1, CD38) were enriched in HDs and MGUS. In contrast, SMM and MM showed higher levels of activation- (e.g., IFITM1, CD9) and stress-related genes (e.g., HSPs, CD69, JUN, FOS), which increased progressively with disease stage. Pathways related with physiological B cell function, such as OXPHOS, MYC, and mTORC were upregulated in asymptomatic stages while exclusively not-progressed patients were characterized by inflammatory IFN-related pathways. Paired samples analysis revealed that TNFA/NFκB, UV response, and IL2–STAT5 pathways were enriched exclusively at the MM stage, indicating a more activated phenotype. To gain insight into B cell dysfunction, interactome analysis showed a reduced CD40–CD40L interactions with T helper cells in progressive asymptomatic cases, suggesting impaired activation of immune surveillance. In MM, B cells promoted monocyte immunosuppression (e.g., SERPINE1) via TGF-β. In progressing asymptomatic cases, we found lower usage of class-switch recombination and somatic hypermutation ($p < 0.0001$). Finally, BCR diversity, assessed via Hill's index, was highest in MM, suggesting increased reactive polyclonality. **Conclusions:** These findings reveal dynamic changes in the B cell landscape across PC dyscrasias. In asymptomatic stages, B cells retain more physiological function, while in MM they exhibit increased activation, higher polyclonality, and reduced SHM, suggesting a less specific repertoire. This highlights the evolving phenotype of B cells in disease progression.

PA-223

GPRC5D and BCMA Genotypes in Relation to Diagnosis, Prognosis and Lenalidomide-Based Maintenance Therapy in Multiple Myeloma Patients

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Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy, with prognosis prediction and treatment personalization remaining key challenges. This study explores germline genetic variability in MM patients to improve risk stratification, focusing on BCMA and GPRC5D genes that encode for two plasma cell surface proteins relevant for MM biology and targeted therapies. **Methods:** We genotyped polymorphisms of these genes in 305 MM patients and correlated them with MM risk, disease progression, treatment response, and overall survival. **Results:** Among the SNPs evaluated, rs3850997 in the BCMA gene was significantly associated with progression-free survival. Among patients not receiving maintenance therapy, T allele carriers exhibited prolonged PFS (HR = 0.65, 95% CI: 0.35–0.88, p = 0.013). When patients undergoing maintenance therapy were included, the benefit of maintenance appeared limited to those with the G/G genotype, whereas T allele carriers did not derive additional advantage, suggesting a genotype-specific modulation of therapy effectiveness. **Conclusions:** Given the role of BCMA and GPRC5D in plasma cell function and emerging targeted therapies, further research is needed to validate their clinical utility in personalized treatment strategies.

PA-224

Referral of Select Multiple Myeloma Patients for Genetic Evaluation Leads to 5-Fold Increase in Pathogenic Germline Variant Detection

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Introduction: In a prior analysis of 1,681 unselected multiple myeloma (MM) patients, we showed that ~10% carry pathogenic germline variants (PGVs) in hereditary cancer (HC) genes (Thibaud et al, Blood Cancer Discovery 2024). PGV detection offers a powerful tool for reducing cancer burden through tailored, family-centered prevention strategies. However, germline testing is not routinely performed in MM & no guidelines exist to define who should be tested. To guide future testing recommendations, we evaluated whether selective referral of PCD patients with HC risk indicators increases PGV detection relative to unselected cohorts. **Methods:** We retrospectively reviewed patients with PCDs referred for genetic counseling & germline testing at our institution between 2010 & 2025. Referrals were made at the discretion of treating physicians, based on clinical suspicion due to personal or family history of cancer

and/or the presence of mutations in tumor NGS suggestive of germline origin. PGVs were identified through CLIA-certified multigene HC panels. Clinical & genomic data were extracted from the electronic health record. The primary outcome was PGV detection rate. **Results:** 115 PCD patients had a genetic evaluation by a certified genetic counselor. 101 were referred based on personal/family cancer history & 14 due to suspicious tumor NGS findings. Median age at referral was 64 (range 22–88) & 41% were male. 66% were White, 20% Black, 11% Hispanic & 3% Other. 61 patients (53%) had a personal history of other cancers & 104 (90%) had a first- or second-degree relative with cancer. 100 referred patients completed germline testing (87%), including 55 with MM, 18 smoldering MM (SMM) & 27 MGUS. 29 tested patients (29%) carried PGVs associated with HC: 20 MM (36% of all MM cases), 5 SMM (28% of all SMM cases) & 3 MGUS (11% of all MGUS cases). Compared to our previously published unselected MM cohort with a 9.9% PGV prevalence, the 36% detection rate in this selected MM subgroup represents a highly significant enrichment (OR 5.2, 95% CI 2.9–9.2, $p = 2.8 \times 10^{-7}$). 18 of 29 PGVs were in high-penetrance HC genes, including BRCA2 (6), BRCA1 (3), PALB2 (2) & 7 others. The remaining 11 PGVs were low-penetrance founder variants in APC (5), CHEK2 (5) & MUTYH (1). 2 additional MM patients, not included in above calculations, were incidentally found to carry clinically actionable PGVs unrelated to cancer risk (long QT syndrome & hypertrophic cardiomyopathy). 13 PGV carriers (45%) had a personal history of cancer, most commonly colon (4), breast (3) & thyroid (3). 28 PGV carriers had a first-degree relative with cancer (97%), most frequently breast (13), gynecologic (9) & pancreatic (7). **Conclusions:** 1 in 3 MM patients referred for suspected cancer predisposition carried a clinically actionable PGV, representing a fivefold enrichment over unselected MM cases. These findings highlight the feasibility & clinical utility of targeted germline screening in MM. A prospective study is underway to inform future testing guidelines.

PA-225

Development of a Cytogenetic Double-Hit Model for Survival Prediction in Multiple Myeloma

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Introduction: High-risk chromosomal abnormalities (HRCAs) detected by fluorescence in situ hybridization (FISH) have a profoundly adverse impact on the prognosis for patients with multiple myeloma (MM). It is widely acknowledged that the presence of two or more HRCAs significantly increases risk, classifying these cases as double or multiple-hit MM. However, the definition of double-hit MM remains a topic of ongoing debate. In this study, we analyzed a large cohort of newly diagnosed MM (NDMM) with fluorescence in situ hybridization (FISH) examination results for HRCAs. We intended to screen out the most decisive and irreplaceable HRCAs and develop a simplified HRCA model to define double-hit MM. The analysis identified a four HRCA double-hit model after comparing various double-hit definitions in the era of novel therapies. **Methods:** This study was carried out based on the MM database of the National Longitudinal Cohort of Hematological Diseases (NICHE, NCT04645199), a total of 1122 NDMM patients were identified with at least one CA data and enrolled in this study. Among them, 984 patients had the required HRCAs data, including t(4;14), t(14;16), del(17p) and gain(1q). And 757 patients had complete FISH testing data, which, in addition to the aforementioned abnormalities, also included t(14;20) and del(1p), were included in the double-hit model development. **Results:** When analyzing the explained variation of all HRCAs, the top four contributors to survival were gain(1q), del(17p), del(1p), and t(14;16), forming the HBDH model. The HBDH model demonstrated a concordance index of 0.59 for both PFS and OS, comparable to the NCRI model and a model incorporating all six HRCAs. The HBDH model stratified MM patients into three groups: no hit, single-hit, and double-hit, showing significant prognostic differences. Median PFS was 53.3, 32.0, and 20.6 months ($P < 0.001$), and median OS was 84.2, 64.2, and 40.2 months ($P < 0.001$) for no hit, single-hit, and double-hit MM patients, respectively. Furthermore, our results showed that the inclusion of del(13q), t(4;14), and t(11;14) did not add further prognostic value to the model. Multivariate analysis, accounting for aging, LDH abnormalities, ISS stage, and the number of HRCAs, confirmed that HBDH double-hit model can independently predict both PFS and OS. **Conclusions:** Our findings suggest that double-hit MM is associated with a high risk of early progression or death. Further validation of this model in prospective studies is needed to confirm its prognostic utility and refine risk stratification for MM patients.

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MYC Copy Number Variation Detected by FISH Indicates a Similarly Poor Prognosis to MYC Rearrangement in Newly Diagnosed Multiple Myeloma

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Introduction: Cytogenetic abnormality is one of the imperative prognostic factors of multiple myeloma (MM), and help to outline double-hit high-risk patients. Mainstream risk stratification systems included t(4;14), t(14;16), t(14;20), del(17p), gain(1q) and/or del(1p) as high-risk factors. MYC rearrangement detected by FISH is also a confirmed adverse prognostic factor in MM. However, MYC is not under consideration when defining double-hit MM. Another

interesting issue is whether MYC copy number variation indicates inferior outcome, as both rearrangement and amplification may result in MYC overexpression. To answer these questions, we conducted an analysis of a prospective observational cohort. **Methods:** This study was carried out based on the MM database of the National Longitudinal Cohort of Hematological Diseases (NICHE, NCT04645199). 227 newly diagnosed MM patients were enrolled from January 1, 2014 to January 31, 2021. Patients received BCD or VRD induction therapy. Transplant-eligible patients accepted first-line autologous stem cell transplantation. All patients were treated by lenalidomide-based maintenance therapy for at least two years. FISH panel included del(13q), del(17p), del(1p), 1q21 gain/amp, IgH rearrangement, with its translocation partners [t(4;14), t(11;14), t(14;16), and t(14;20)], and MYC (8q24.1) break-apart probe. **Results:** The median follow-up time was 31.2 months. 18.9% of patients had MYC structural variation (SV) and 19.8% of patients had MYC copy number variation (CNV). Only three patients had both MYC abnormalities. Patients with either MYC SV or CNV intended to have higher level of bone marrow plasma cells, and were more likely to had anemia and LDH elevation. Compared to patients without MYC SV or CNV, patients with SV or CNV had a higher incidence rate of del(17p) (4.7%, 15.6% vs. 3.5%) and gain(1q) (60.5%, 71.1% vs. 34.5%). Patients with SV or CNV had an inferior PFS (24.7, 24.2 months) and OS (30.6, 32.7 months), compared to patients without any (PFS 31.1 months, OS 38.2 months). By adding MYC abnormalities on double-hit model [t(4;14), t(14;16), t(14;20), del(17p), gain(1q), del(1p)], concordance index for PFS and OS was increased (0.580 vs. 0.563, 0.608 vs. 0.575). **Conclusions:** Our findings suggest that MYC CNV also exerted an adverse effect on survival as SV did. It may be better if we considered MYC abnormalities (including SV and CNV) as high-risk factors to define double-hit MM. The conclusion should be verified in larger prospective cohort.

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Characterizing the Molecular Impact of DIS3 Mutation-Driven Mechanisms in Multiple Myeloma

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Introduction: DIS3 is the main catalytic subunit of the RNA exosome—a critical complex responsible for degrading most cellular RNA. Mutations in DIS3 occur in 10% of multiple myeloma (MM) patients and can be either recurrent heterozygous hotspot mutations or homozygous non-hotspot mutations, both associated with poor prognosis. Determining the distinct mechanisms by which these mutation subtypes impair RNA exosome function and drive MM pathogenesis is critical for unraveling their biological role in disease progression and advancing targeted therapeutic strategies. **Methods:** We analyzed patient samples from the Multiple Myeloma Research Foundation (MMRF) CoMMpass Study (n = 1,245; DNA and RNA sequencing), combined with Indiana University samples (SMM, n = 14; NDMM, n = 36; RRMM, n = 54; DNA and RNA sequencing), to determine DIS3 mutation rates and downstream effects. Endogenous DIS3 was mutated in both KMS11 and JJN3 cell lines using CRISPR-Cas9 homology directed repair, and mutated colonies were isolated for 4 non-hotspot mutations (Y106C, T262P, L544P, H788Y), 3 hotspot mutations (D479G, D488N, R780K), and controls. We examined the functional impact of these DIS3 mutations via Western blot analysis, total RNA-sequencing for differentially expressed gene (DEG) and pathway analysis, R-loop detection, tandem mass spectrometry (LC-MS/MS), and Olink Explore 3072. **Results:** DEG analysis of MMRF CoMMpass RNA-sequencing data between subsampled DIS3 hotspot (n = 13) and non-hotspot (n = 24) groups with controls (n = 24) resulted in a substantial increase ($p < 0.0001$) of lncRNAs—where non-hotspot mutations had a significantly larger increase than hotspot mutations. This result was also observed in our DIS3-mutated cell lines, therefore validating our experimental approach. Over half of the DEGs in mutated cell lines were found to be regulated by AU-rich elements, suggesting aberrant post-transcriptional regulation contributing to disease pathology. The introduction of endogenous DIS3 mutations did not affect DIS3 mRNA expression, but there was a 25-fold decrease ($p < 0.0001$) in DIS3 protein expression only in non-hotspot mutated cells, validated by Western blot analysis of MM patient CD138+ samples. In contrast, hotspot mutations exhibited no DIS3 protein abundance change in both our DIS3-mutated cell lines and patient samples, as confirmed by mass spectrometry. Lastly, LC-MS/MS analysis revealed non-hotspot mutations resulted in the significant ($p < 0.05$) dysregulation of histone linkers (H1.2-H1.5, H1-10) which may be contributing to the overall downregulation of proteins and transcriptional pathways seen in proteomic and pathway analysis. **Conclusions:** Our findings show DIS3 mutations in MM have unique molecular consequences by subtype, affecting both RNA processing and exosome function. These results advance our understanding of how DIS3 mutations contribute to disease progression and emphasize the importance of considering mutation-specific effects when developing targeted therapies.

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A Novel Hypoxia Gene Signature from the HOVON-65/GMMG-HD4 Phase 3 Study Prognostic of Survival and Associated with Immune Suppression in the Tumor Microenvironment

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Introduction: Multiple myeloma (MM) thrives in the bone marrow, a niche that provides myeloma cells with essential nutrient and growth signals. This hostile immune suppressive tumor microenvironment (TME) limits immune cell function and contributes to poor treatment responses. Hypoxia, a key feature of the TME, regulates cancer cell metabolic homeostasis, differentiation, and progression. We developed a MM hypoxia gene signature using data from the HOVON65/GMMG-HD4 trial that compared bortezomib during induction and maintenance versus standard of care in newly diagnosed transplant eligible MM patient, (Sonneveld et al, JCO 2012), prognostic of poor patient outcome. **Methods:** MM cell lines (U266, JJN-3, RPMI-8226, OPM-2, L363) were cultured under normoxic (20% O_2) and hypoxic (0.02% O_2) conditions. Bulk RNA sequencing identified hypoxia-associated differentially expressed genes (DEGs) with a false discovery rate (FDR) cutoff of 0.01. DEGs common to ≥3 cell lines were selected as "seed" genes for cluster analysis in the HOVON-65/GMMG-HD4 training cohort consisting of 326 patients with 10 year follow up (Mai et al, Hemasphere 2024). To identify a prognostic signature, two machine learning shrinkage algorithms—LASSO and PAMR—were applied independently, and prognostic genes were selected for Cox proportional hazards regression analysis. The signature was validated in publicly available datasets: COMMPASS, GSE57317, and GSE4452. Immune cell infiltration was assessed using MM whole bone marrow RNA data from GSE136324. **Results:** Eighty hypoxia-induced DEGs were identified, with the top Gene Ontology (GO) pathways including "response to hypoxia" and "response to oxygen levels." K-means cluster analysis assigned 121 patients to the hypoxia-high cluster and 205 to the hypoxia-low cluster. Cox proportional hazards regression analysis revealed a median PFS of 34.7 months [95% CI 30.8–38.1], in the hypoxia-low and 20.8 months [95% CI 18.7–26.1], in the hypoxia-high group with significant overall survival (OS) (HR 0.46 [95% CI 0.31–0.68], p < 0.0001) benefit for the hypoxia-low cluster. Both LASSO and PAMR reduced the number of predictive genes to five, which were significantly associated with worse PFS (HR 0.39 [95% CI 0.26–0.59] p < 0.0001) and OS (HR 0.59 [95% CI 0.44–0.78], p < 0.001) for the hypoxia cluster. In multivariable analysis, the hypoxia gene signature was independently associated with worse PFS and OS and this association could be improved by combining it with ISS stage and TP53 mutations. The signature was validated in the COMMPASS, GSE57317, and GSE4452 datasets. Using whole bone marrow RNA data from GSE136324, the signature revealed genes associated with a more immune-suppressive TME, characterized by decreased neutrophil and NK cell infiltration and upregulation of immune checkpoints). **Conclusions:** We developed a hypoxia-based gene signature for MM, predictive of survival and associated with an immune-suppressive TME.

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Machine Learning–Based Unsupervised Molecular Subtyping of Malignant Plasma Single-Cell RNA Data Reveals Tumor-Immune Features Linked to Poor Outcomes in Multiple Myeloma

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Introduction: Multiple myeloma (MM) patients exhibit diverse clinical progression and therapeutic response, driven by tumor intrinsic features such as somatic alterations impacting the genetic and epigenetic landscape of a patient as well immune dysfunction in the tumor microenvironment (TME). We hypothesized that identifying molecular subtypes using unsupervised machine learning on gene expression profiles of malignant plasmas cells would uncover clinically actionable subtypes. In the previous pilot study, (Hamidi et al., 2023) we applied this approach to samples from 95 patients. In this study, we expanded our cohort to 521 samples and performed clustering on malignant plasma cells and not total plasma cells to better capture the heterogeneity in the tumors. **Methods:** Baseline samples from 521 MM patients from the MMRF CoMMpass study (NCT01454297), with more than four malignant plasma cells were pseudobulked and expression profiles were subjected to unsupervised learning based on consensus non-negative matrix factorization (cNMF) to identify molecular subtypes. **Results:** 2,921,589 cells passed through quality control and doublet detection, 13.00% of which were plasma cells (n = 379,882). Five distinct molecular subsets were discovered using cNMF. These subtypes were significantly associated with both T2T (p = 0.042) and overall survival (OS; P = 0.001). Subtype pNMF5.1 was associated with the worst clinical outcomes, including the shortest median T2T and OS. A multivariable Cox proportional hazards model incorporating clinical covariates such as age, gender, race, ISS stage and treatment regimen confirmed that the molecular subtypes were independently associated with OS. Biologically, plasma cells in worst outcome subset, pNMF5.1, were enriched in inflammatory and stress-related pathways including TNFa signaling, IL2-STAT5

signaling, apoptosis, hypoxia and unfolded protein response. This subtype also exhibited transitional EMT markers, indicating a tumor state marked by inflammation and cellular stress. Analyzing the TME scRNA-seq data revealed that the worst patient subset, pNMF5.1, had reduction in several key regulatory and adaptive cell populations including naïve CD4+ T, Tregs, naïve B, Memory B, and NK CD56 bright cells. Conversely, there was an expansion of pro-inflammatory and myeloid populations including inflammatory monocytes, granulocytes, CD8+ T effector and NK CD56 dim cells. This immune environment imbalance, characterized by chronic inflammation, loss of regulatory control and a diminished adaptive immune presence, likely contributes to disease progression and poor clinical outcomes. **Conclusions:** Applying innovative unsupervised machine learning on the scRNA-seq data of malignant plasma cells improves our ability to more accurately identify molecular subtypes of MM. This approach offers the potential for accurate prediction of therapeutic response as well as capturing biologically and clinically informative features beyond traditional risk factors.

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Exploration of Tumor Immune Gene Expression to Stratify Progression Risk in Newly Diagnosed Multiple Myeloma Patients from CoMMpass with 1q Cytogenetic Abnormality

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Introduction: Chromosome 1q copy number variations (+1q) are recognized as high-risk cytogenetic abnormalities by the International Myeloma Working Group. Present in 40% of newly diagnosed multiple myeloma (NDMM) patients, both 1q gain (3 copies) and 1q amplification (4+ copies) are linked to poorer survival outcomes. While previous studies investigated the clinical impact and timing of +1q, ongoing research aims to establish whether +1q is an independent marker of poor prognosis and to enhance patient stratification for individualized therapy. This study examines how gene expression from immune cells in the tumor microenvironment can be utilized to better assess disease risk in patients with +1q. **Methods:** We analyzed NDMM patients' tumor microenvironments along with their tumors to characterize gene expression patterns associated with +1q and survival outcomes. Immune data were generated using scRNA on CD138- bone marrow (BM) samples from the Multiple Myeloma Research Foundation (MMRF) Immune Atlas Network. Tumor data, including whole genome sequencing and bulk RNA-seq from CD138+ bone marrow (BM) samples, came from the MMRF CoMMpass Study. We used ssGSEA and custom R scripts to score pseudobulk immune samples using immune signatures (Azizi, et al. Cell 2018) and bulk tumor samples using MSigDB oncogenic signatures (Liberzon, et al. Cell Syst 2015). We then clustered immune and oncogenic signature scores simultaneously using k-means and associated clusters with survival. **Results:** From our cohort of 190 subjects with overlapping bulk and immune data, 125 (65.8%) were copy number neutral (2 copies), 54 (28.4%) had +1q gain (3 copies), and 11 (5.8%) had +1q amplification (4+ copies). Clustering of +1q patients yielded five clusters distinguished by patterns of immune and oncogenic gene signature scores. One cluster with significantly better progression free survival (median PFS 2355 days; HR 0.39, 95% CI [0.17, 0.88]; p = 0.0236) showed both low immune and low oncogenic signature scores (low-low group). This low-low group was associated with significantly lower monocyte proportions (6.9% vs. 15.9%; adj p = 0.00014) as well as significantly lower immune signature scores for anti-inflammatory, G1/S, G2/M, lipid mediators, and macrophage polarization. The low-low group also showed significantly higher scores for CD8+ T cell activation and the cytolytic effector pathway. Clustering based solely on oncogenic gene signatures resulted in a poor survival cluster dominated by high expression of four canonical MM pathways, including MTORC1 signaling, MYC targets, G2M checkpoint, and E2F targets. However, simultaneous clustering of immune signatures with oncogenic signatures modified this risk structure, resulting in clusters driven by other oncogenic and immune signatures. **Conclusions:** These results provide preliminary evidence that incorporation of tumor microenvironment immune signatures into cytogenetic risk stratification of NDMM patients can refine prognoses.

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Elevated Levels of Circulating Tumor Cells (CTCs) in Newly-Diagnosed Multiple Myeloma (NDMM) Patients Reflect a Highly Proliferative and Genomically Complex Profile

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Introduction: CTCs have emerged as a key prognostic factor in NDMM. However, it is unclear if high CTC counts only represent a surrogate of tumor burden or might also be driven by distinct genomic drivers. We aimed to define genomic and transcriptomic features associated with CTC burden. **Methods:** We interrogated 540 baseline patients from CoMMpass (IA22) with CTC information available, studied by the CellSearch System. Whole-exome/genome (WGS/WES) and RNA-seq data of bone marrow (BM) plasma cells (PC) were available for 85% and 51%. An external dataset (n = 135) with CTCs assessed by next-generation flow was used for validation, with RNA-seq and WGS of BM PCs available for 52% and 9.6%. **Results:** Elevated CTCs at baseline showed shorter progression-free survival (PFS) in both datasets. Notably, patients with ≤10 CTCs or ≤0.001% exhibited outstanding overall survival (OS). High CTCs were significantly associated with ISS, R-ISS, R2-ISS, and IMS risk classifications ($p \leq .003$). Moreover, gain/amp1q and del13q were enriched in high CTCs ($p \leq .005$), as well as MAF and NSD2 translocations ($p \leq .03$) in both datasets. Considering the genomic classification in [Maura, JCO 2024], complex genomic subgroups (ie, NSD2_Gain/Amp1q_Del13q, CCND1_Complex, and MAF_HyperAPOBEC; $p \leq .02$) were associated with high CTCs. Thus, we also observed a strong correlation between elevated CTCs and high-risk genomic features such as chromothripsis, gain/amp1q, APOBEC mutagenesis, MAF translocations, and RB1 ($p \leq .007$). External validation also revealed an association between high CTC counts and complex genomics. As to clinical outcomes, a cutoff of 1000 CTCs showed an independent association with PFS when combined, for instance, with chromothripsis, APOBEC, gain/amp1q, or RB1 ($p < .001$). Only APOBEC plus CTCs retained prognostic value for OS ($p = 0.01$). We analyzed RNA-seq data using a linear model adjusted for BM infiltration, identifying 210 genes positively correlated with CTCs (eg, CENPF or TAGLN2) and enriched in proliferation and cell cycle functions. The validation set confirmed this enrichment. Other 452 genes negatively associated with CTCs (eg, CXCL12 or CCL25) were linked to immune activation and cell adhesion. Hence, CTCs correlated with published PR indexes (ie, Zhan, Blood 2006, or Skerget, Nat Gen 2024; $p < .0001$) or the PC leukemia-like signature (Bruinink, JCO 2022; $p < .0001$). Combining CTC levels with PR showed important prognostic value. Low or high values of both markers identified two groups with favorable and shorter outcomes, respectively ($p < .0001$), and, importantly, high CTCs and low PR also separated a third group of patients with poor PFS. **Conclusions:** Overall, the addition of CTC enumeration to genomic classification may further improve the risk stratification of MM patients. Moreover, they retain prognostic significance independently of the latest high-risk genomic or stratifying systems and could serve as a surrogate for established markers of high-risk disease and tumor proliferation.

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Investigating Ribosome-Targeting Therapies for the Treatment of Relapsed/Refractory Multiple Myeloma

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Introduction: Resistance to targeting protein degradation by the standard-of-care proteasome inhibitors (PI) in multiple myeloma (MM) remains a challenge. Recent studies implicate altered ribosome synthesis and mRNA translation activity in driving MM disease progression and therapy resistance. The selective inhibitor of nuclear export selinexor, which represses mRNA export and translation, exhibited therapeutic benefit as a single agent and in combination with PIs in several clinical studies. Our group developed a selective inhibitor of RNA polymerase (Pol I) transcription CX-5461, which inhibits ribosome synthesis. We showed that CX-5461 is effective in preclinical MM models and provided a signal of therapeutic benefit in 3/6 patients with relapsed/refractory MM (RRMM) in a phase I trial. We thereby propose that targeting ribosome biogenesis and mRNA translation is a promising therapeutic strategy for RRMM. **Methods:** We examined the effects of selinexor and CX-5461 on ribosomal assembly and the association of mRNAs with ribosomes in PI-resistant MM models using polysome profiling experiments. To define biomarkers of response to selinexor and CX-5461, genome-wide CRISPR-Cas9 knockout screens of PI-resistant MM cells were performed and novel mediators of sensitivity and resistance to these treatments were identified. In parallel, we characterised the bone marrow (BM) microenvironment in response to CX-5461 in MM mouse models and RRMM patient samples through immunophenotyping and spatial proteomic studies. **Results:** Both selinexor and CX-5461 reduce the formation of functional ribosomes and alter mRNA translation activity in PI-resistant MM cells, confirming their action in targeting the ribosome. The screen revealed antigen presentation and processing, adaptive immune response, and activation of NF-κB promote resistance to selinexor. In particular, we found 3 candidate genes encoding subunits of a phosphatase complex, whose deletion contributes to selinexor resistance via NF-κB signalling. We also discover defects in DNA damage response and repair processes confer sensitivity to CX-5461, which is consistent with its dual role in inhibiting Pol I and topoisomerase II activity. In addition, we noted a decrease in CD8+ T cell population expressing exhaustion markers CTLA4, PD-1, LAG3, and TIGIT in mice treated with CX-5461. In agreement with this finding, analyses of BM trephines indicated immune activation in patients with stable disease after CX-5461 treatment. We are currently conducting single-cell RNA sequencing to examine the interaction between immune and MM cells induced by selinexor and CX-5461 in vivo, and performing spatial transcriptomics on patient BM trephines from the

phase III SeaLAND study which assesses the combination of selinexor and lenalidomide in NDMM. **Conclusions:** Our findings provide insights into molecular mechanisms underlying the disruption in protein homeostasis in MM, and strong evidence to promote the clinical development of therapies targeting the ribosome for RRMM.

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An Integrated Spatial and Single-Cell Multiomics Platform for Translational Research in Multiple Myeloma

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Introduction: Multiple Myeloma (MM) is a genomically heterogeneous cancer of malignant plasma cells (PC) residing in the bone marrow. Despite recent therapeutic advances, it is incompletely understood why some patient populations remain largely therapy-refractory or relapse, even with targeted immunotherapies. Whilst MM classification based on genomic features and gene expression profiling (GEP) is well-described, the role of spatial interactions between tumour cells and the bone marrow tumour microenvironment (TME) in dictating treatment responses is insufficiently defined. Although spatial heterogeneity in MM has been demonstrated, it is unknown whether spatially and genomically distant clones interact differently within their immune and stromal compartments. Isolated in situ 'omics' assays provide limited information due to biased selection of marker panels or discordance between transcriptional and proteomic profiles. We hypothesize that a combined, systematic approach to integrate multiple layers of information (multiplexed imaging, unbiased LC/MS and targeted proteomics, transcriptomics, genomics) within their spatial bone marrow and single-cell context represents a technology platform to advance our understanding of the interactions between tumour and microenvironment activation or exhaustion phenotypes and how they shape responses to therapy. **Methods:** In this proof of concept, technology development platform, matched bone marrow trephines and aspirates from newly diagnosed patients (n = 4) were subjected to a workflow that encompassed: 1. On formalin fixed, paraffin-embedded sections: a) Xenium spatial transcriptomics (10X Genomics, custom panel), b) multiplexed immunofluorescence or imaging mass cytometry panels to deep phenotype tumour and immune cells, c) laser capture microdissection of regions of interest (ROIs) followed by both liquid chromatography/mass spectrometry (LC/MS) proteomics and d) targeted-region genome panel and shallow whole-genome sequencing. 2. On aspirate samples: single-cell a) LC/MS proteomics, b) multiplexed mass cytometry, c) long-read transcriptomics for transcript isoform identification, and d) bulk CD138+ targeted genomic sequencing. A data analysis pipeline utilising machine-learning to integrate data is being implemented. **Results:** In this proof of concept study we successfully developed an experimental pipeline that allows disease phenotyping in unprecedented detail, and correlation of in situ tumour clonal heterogeneity with the immune and stromal tumour microenvironment. **Conclusions:** Our next translational step is the deployment of this workflow to longitudinal clinical trial in situ samples with correlation to single cell data from bone marrow aspirates. Taken together, application of this translational platform will provide new insights into MM pathobiology and both tumour and microenvironment-mediated therapeutic response and resistance mechanisms.

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Integrating Microenvironment with Tumor Multi-Omic using Unsupervised Machine Learning to Model Heterogeneity Refines Multiple Myeloma Subtypes and Reveals Immune-Based Clusters with Prognostic Impact

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Introduction: A major limitation of current molecular subtyping of Multiple Myeloma (MM) is the omission of bone marrow microenvironment influences. Interactions between malignant plasma cells and their immune/stromal niche critically shape MM progression and therapy response. We hypothesized that integrating TME data with tumor multi-omics would refine patient stratification and uncover novel, clinically relevant subgroups beyond those identified by tumor-only models. **Methods:** We analyzed 389 newly diagnosed MM patients from the MMRF CoMMpass study for whom matched whole-exome, RNA-seq, baseline clinical data and CyTOF immune-profiling data was available. Using an unbiased, unsupervised machnile learning based clustering method based on similarity network fusion (SNF) the different modalities were integrated into a single similarity model, and spectral clustering

defined patient groups. The resulting clusters were compared with the twelve tumor-only MM-PSN subgroups from our previous work (Bhalla et al., Sci Adv 2021). Clinical outcome measurements like time to second line and overall survival (OS) differences were evaluated with multivariate Cox regression adjusted for International Staging System (ISS) stage and conventional cytogenetic risk. **Results:** SNF resolved six biologically coherent clusters whose composition and outcomes could not be explained by genetics alone. The best-surviving group, designated Cluster 6, combined standard-risk hyperdiploidy with a microenvironment dominated by Th1-skewed immunity: abundant Th1 cells, CXCR3-positive T-cell subsets, $CD4^+$ effector-memory lymphocytes and supportive fibroblasts. At the opposite extreme, Cluster 4 united classic high-risk lesions, t(4;14) or t(14;16) together with 1q gain, in SLAMF7-positive myeloma cells with an immunosuppressive niche rich in TIGIT-expressing granzyme-B-positive NK. This cluster exhibited the poorest prognosis, with a hazard ratio for death of 4.46 relative to Cluster 6 ($p < 0.001$). Cluster 2, an intermediate-to-poor prognostic group (HR = 2.14, $p = 0.07$), was characterized by a proliferative transcriptomic program, frequent t(4;14) and a subset of t(11;14) cases carrying co-occurring 11q gain, accompanied by neutrophil enrichment, naïve $CD8^+$ and $CD4^+$ T cells, and CD28 expression on tumor cells. In multivariate analysis cluster membership remained an independent predictor of OS after adjustment for ISS and cytogenetics, outperforming individual high-risk genomic markers. **Conclusions:** By integrating immune-stromal profiling with genomic and transcriptomic data, we uncovered immune-active ("hot") and immune-suppressed ("cold") myeloma phenotypes that explain outcome variability more effectively than conventional tumor-centric classifications. This integrative approach underscores the prognostic impact of the microenvironment and reveals actionable immune states for potential therapeutic targeting.

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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. 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 PGK1/PKM 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 PGK1 and PKM. Knockdown PGK1/PKM leads to a decrease in osteoclast differentiation. The level of PGK1 and PKM were significantly increased in MM patients with osteolytic destruction. The above results suggests that the interaction of PGK1/PKM 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 glycolysis-related proteins PGK1 and PKM.

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Longitudinal Analysis of Clonal Hematopoietic Mutations (CHIP) in Transplant Eligible Multiple Myeloma (MM) Patients: Trends From Pre-Transplant to 1 Year

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Introduction: CHIP mutations (mtns) are common in MM patients (pts) at time of diagnosis (dx), and may impact survival, but there is limited data around clonal evolution trends. We are expanding on previous results (ASH 2024) of prospective analysis of CHIP mtns in a uniformly treated cohort of 173 IMID naïve MM pts at therapy-related time-points (TPs), including pre-transplant (tx) after non immunodulatory agent (IMID)-containing induction (TP1, 173 pts), 3 months (mos) post-tx using high-dose melphalan (prior to IMID start, TP2, 103 pts), and 1 year post-tx, TP3 (56 pts). **Methods:** CHIP was identified using single-molecule molecular inversion probes (SmMIP) next generation sequencing to a minimum depth of 4000x, with threshold variant allele frequency (VAF) of 1% (for previously unidentified mtns); calls were subjected to filters to reduce false positives. **Results:** Baseline characteristics of the 173 pts were as expected, with median age at dx of 66 years, 59% male, 58.4% IgG sub-type, 24% ISS stage 3 and 24% high risk cytogenetics. 94% of pts received proteasome-inhibitor based induction. 92% of those starting maintenance (60% of overall cohort) received IMID. At TP1, 63/173 (36%) pts had at least 1 CHIP for a total of 83 mtns, with 14/63 (22%) having co-mtns. DNMT3 accounted for 37/83 (44.5%) mtns, followed by TET2 (15/83, 18%) and PPM1D (8/83, 10%). At TP2, 36/103 pts (35%) had 54 mtns, with co-mtns in 12 (33%). As in TP1, most common mtns were DNMT3a (29/54, 53%), TET2 (10/54, 18%) and PPM1D (4/54, 7%). At TP3, 26/56 pts (46%) had 43 mtns, with co-mtns in 7/26 (27%). DNMT3a accounted for 18/43 (42%). Prevalence of TP 53 mtns increased, at 7/43 (16%) at TP3, compared to 5/83 (6%) at TP1, and 4/54 (7%) at TP2. Next we tracked the fate of 83 mtns in 63 pts seen at TP1. Of these, at least 1 further time-point data (TP2 or 3 or both) was available for 56 mtns (40 pts) of which 3 TP data was available for 25 mtns (18 pts). Of the 56 TP1 mtns, 15 (26%) were non-recurring at any TP, and 41 were recurring. Of 41 recurring mtns, 8/41 (20%) were only detected on lookback analysis after being identified at later TPs, initially being below cut-off VAF. DNMT3a comprised a minority (2/15, 13%) on non-recurring mtns, despite higher prevalence (25/56, 45%) at TP1. Tet2 accounted for 6/15 (40%) of non-recurring mtns (baseline prevalence (12/56, 21%)). The mean VAF at TP1 was 6.6, and remained stable from TP1 to TP2, and TP2 to TP3. A few mtns (DNMT3a, PPM1D, ASXL1) in individual pts showed greater VAF variations than expected. **Conclusions:** In this longitudinal study, the overall incidence of CHIP mutations is stable from non-IMID induction through high dose melphalan and 1 year of IMID maintenance. However, individual mutations can expand (TP53) or be lost (TET2), though many new mutations can be found at baseline at very low VAF. Clinical correlates and longer follow-up for evolution patterns is ongoing.

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Integrative Genomic and Transcriptomic Profiling Reveals Distinct Characteristics of Immunoglobulin D Multiple Myeloma

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Introduction: Immunoglobulin D multiple myeloma (IgD MM) is a rare form of the disease, accounting for less than 2% of all cases. Although a precise IgD MM diagnosis is sometimes overlooked, this MM subtype is clinically known to be associated with rapid disease progression at diagnosis, an aggressive clinical course, and a poor prognosis compared with other MM subtypes. However, the pathogenesis and disease properties, including molecular characteristics, are not well studied. **Methods:** We collected 37 bone marrow samples from patients diagnosed with MM and isolated the myeloma cells using the CD138 marker. Serum IgD levels were measured in IgD MM candidates to confirm the subtype diagnosis. To identify the genomic and transcriptomic features of IgD MM compared to non-IgD MM, we performed whole-genome and bulk RNA sequencing on the myeloma cells. We analyzed whole-exome and RNA sequencing data from the CD138-positive fraction of bone marrow mononuclear cell (BMMC) samples provided by the Multiple Myeloma Research Foundation (MMRF) CoMMpass study (NCT01454297) to validate our findings. **Results:** Whole-genome sequencing (WGS) data revealed an average of 8,872 somatic single nucleotide variants (SNVs) and 934 insertions and deletions (indels) in 37 multiple myeloma (MM) patients. Mutational signature analysis showed that SBS9 varied widely among patients. Notably, all four IgD MM patients had significantly high SBS9 signatures. Analyzing RNA-seq data, we found that IgD MM patients with high SBS9 signatures exhibited distinct gene expression patterns. Analysis of differentially expressed genes (DEGs) and pathway gene expression revealed higher expression of genes associated with the DNA repair system and somatic hypermutation in IgD MM patients. Based on the B-cell lineage and plasma cell differentiation process, these patterns of gene expression might suggest that IgD MM develops early in B-cell differentiation. A computational analysis using in-house MM single-cell RNA sequencing data supports this hypothesis by revealing higher pre-B and pro-B cell populations in IgD MM than in non-IgD MM. We performed an identical analysis on whole-exome and RNA sequencing data from the MMRF database. Of the 30 patients for whom sufficient somatic mutations could be obtained, three patients had a high SBS9 signature and high IGHD gene expression, and were classified as IgD MM candidates. These three patients also showed an upregulation pattern of genes associated with DNA repair systems and

somatic hypermutations. **Conclusions:** Our research revealed that IgD MM has unique characteristics, such as high SBS9 mutational signatures and increased expression of genes related to the DNA repair system and somatic hypermutation. Further research into IgD MM may identify its specific characteristics and underlying pathogenesis, leading to tailored treatments.

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Immunomodulatory Drugs (IMiDs) Induce the Expression of Long Non-Coding RNAs NEAT1 and NEAT1_2 in Myeloma Cells

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Introduction: NEAT1 is a long non-coding RNA with its gene locus on chromosome 11q13, and has two isoforms designated NEAT1_1 and NEAT1_2. It has been demonstrated that NEAT1_2 plays a central role in the formation of the nuclear structure paraspeckle, and that it serves a significant function in responses to stress such as viral infection. Furthermore, its expression is upregulated in numerous cancer cells, and p53 induces its expression. We previously confirmed that NEAT1 is highly expressed in multiple myeloma (MM) cells, and that its expression is induced by p53, as previously reported, in a Tet-on wild-p53 expression MM cell line. Moreover, we discovered that it is induced by anti-MM drugs such as Bortezomib, and that this induction is mediated by HSF1 in the heat shock pathway. In this study, we investigated the effects of IMiDs on the expression of NEAT1 and NEAT1_2 and the regulatory mechanisms governing their expression. **Methods:** Lenalidomide, pomalidomide and iberdomide were administered to the MM cell lines, and after 72 hours, the expression of NEAT1, NEAT1_2, p53, p21, HSF1 and HSP were quantified by RT-qPCR. To elucidate the involvement of HSF1 in NEAT1, we additionally employed MM cell line that had been transfected with Tet-on shHSF1. **Results:** Lenalidomide (10 μM) increased NEAT1 expression 3.63-fold in MM.1S, 2.78-fold in MM.1S-Shp53, 0.65-fold in KMS11, 0.96-fold in KMS12PE, and NEAT1_2 was 4.93-fold in MM.1S, 4.22-fold in MM.1S-Shp53, 0.49-fold in KMS11, and 1.29-fold in KMS12PE. Administration of 10 μM pomalidomide resulted in a 5.73-fold increase in NEAT1 in MM.1S, an 8.50-fold increase in MM.1S-Shp53, a 6.80-fold increase in KMS11, and a 1.71-fold increase in KMS12PE. Furthermore, NEAT1_2 expression was 12.01-fold in MM.1S, 15.08-fold in MM.1S-Shp53, 15.48-fold in KMS11, and 1.89-fold in KMS12PE. When 10 μM iberdomide was added, the expression level of NEAT1 was 4.21-fold in MM.1S, 4.84-fold in MM.1S-Shp53, 2.13-fold in KMS11, and 2.14-fold in KMS12PE. The expression level of NEAT1_2 was 7.83-fold in MM.1S, 10.72-fold in MM.1S-Shp53, 4.72-fold in KMS11, and 2.69-fold in KMS12PE. However, the addition of lenalidomide, pomalidomide, or iberdmide did not increase the expression levels of p53, p21, HSF1, or HSP in any of the MM cell lines. Unlike NEAT1 induced by PI and cytotoxic drugs, NEAT1 expression induced by IMiDs was not suppressed even when HSF1 was knocked down in the MM cell line with Tet-on shHSF1. **Conclusions:** These findings demonstrate that pomalidomide and iberdomide, the members of the IMiD class, exhibit significantly higher efficacy in inducing NEAT1 expression compared to lenalidomide. Furthermore, the results indicate that the well-established p53 and heat shock pathways are not implicated in this mechanism. It is imperative to investigate the unidentified expression control mechanisms and elucidate the significance of NEAT1 expression induction by IMiDs.

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Onco-miR-148a Expression and Its Function in Multiple Myeloma

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Introduction: MicroRNAs (miRNAs) are a class of short non-coding RNAs that are 19 to 25 nucleotides in length. They play a critical role in the post-transcriptional regulation of gene expression by promoting mRNA degradation and suppressing translation of target mRNAs. Abnormal expressions of miRNAs have been reported in a variety of cancers. Our laboratory has previously studied tumor suppressor miRNAs that are downregulated in multiple myeloma (MM). In this study, we examined the expression and function of oncogenic miRNAs that are upregulated in MM. **Methods:** Small RNA sequencing was used to analyze miRNA expression in 10 consenting MM, 5 MGUS, and 3 controls. We measured selected miRNAs' expression in CD138-positive plasma cells obtained from 105 MM, 69 MGUS, and 14 controls by RT-qPCR and evaluated changes in cell proliferation upon transfection of the inhibitor or the mimic of the miRNAs in MM cell lines. Altered expression of the miRNAs by transfection of either their inhibitor or mimic was confirmed by RT-qPCR. The mRNA and protein expression levels of target genes were evaluated in MM cell lines transfected with miRNA inhibitor or mimic. **Results:** Among the top 10 differentially expressed miRNAs identified by small RNA sequencing in the comparison of MM and control groups, we selected miR-148a, which was found to be significantly overexpressed in the MM group

compared to the control group (p = 0.000391). RT-qPCR confirmed that expression levels of both miR-148a-5p and miR-148a-3p were found to be significantly higher in the MM. In vitro, cell proliferation was found to be inhibited by the transfection of a miR-148a-3p inhibitor and promoted by the transfection of its mimic in KMS28BM and KMS27, but not in KMS11 and KMS26. The transfection of the miR-148a-5p inhibitor or mimic did not result in any alterations in cell proliferation. The expression levels of the genes selected as potential targets of the by in silico prediction and the significantly decreased expression in the MM group compared to that in the control group by RNA sequencing and related to tumor suppression were measured using RT-qPCR. A correlation analysis revealed a negative association between the expression of miR-148a-3p and four specific genes (SH2B3, PREX1, PTEN, and CCDC6) in MM cell lines. No substantial alterations in the expression levels of target genes' mRNA and proteins were observed in cell lines that had been transfected with a miR-148a-3p inhibitor or a miR-148a-3p mimic. However, a downward trend in CCDC6 expression was noted in the presence of a miR-148a-3p mimic. **Conclusions:** The expression levels of both miR-148a-3p and miR-148a-5p have been observed to be elevated in MM. The findings of this study suggest that high expression of miR-148a-3p in patients with MM may promote cell proliferation and a tumor suppressor gene CCDC6 is regarded as one of the target genes.

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Integrative Genetic Profiling of Circulating Tumour DNA and Bone Marrow for Multiple Myeloma Prognostication

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Introduction: Increased availability of next-generation sequencing (NGS) has expanded our knowledge on the spectrum of genetic alterations in multiple myeloma (MM). Bone marrow (BM) analysis is the standard of care for assessing disease status and is used for routine prognostic assays in MM. Circulating tumour DNA (ctDNA) has emerged as a minimally invasive assay for genomic characterization of cancers and may more completely reflect the MM genomic landscape in patients with extramedullary disease. In this study, we used targeted NGS gene panels to characterize genomic alterations in tumour and ctDNA of MM patients. **Methods:** The two-part study was designed to capture genetic variants in patients with plasma cell dyscrasia. A 34 gene amplicon-based NGS panel was used to assess genetic variants in stored buffy coat of archived bone marrow (BM). A separate 376 gene hybrid-capture panel was used to investigate the mutational profile in ctDNA from patients. Tumour (BM) and ctDNA from each sample were used for library generation using standard protocols, sequenced (Miseq and NextSeq), and analysed using Archer and SeqOne analysis platforms respectively. Variants were curated using Franklin and literature search to identify likely clinically significant (LCS) and clinically significant (CS) variants. **Results:** Thirty-one ctDNA and 22 bone marrow samples were analysed. Advanced stages of disease were associated with greater likelihood of detecting LCS or CS variants in the BM. Panel sequencing of BM identified biallelic TP53 inactivation in a patient, which was not otherwise detected by routine laboratory testing. ctDNA analysis showed a high concordance with BM mutations among patients with secondary myeloid malignancies. **Conclusions:** ctDNA analysis, in a similar pattern to BM analysis, identifies clinically significant variants in patients with plasmas cell dyscrasias, with increased detection of significant variants in advanced disease, and may have utility in the detection of myeloid variants in the evaluation of second malignancy.

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Clinical Impact of Cytogenetic Abnormalities and Detection Discordance between Conventional Karyotyping and FISH in Multiple Myeloma

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Introduction: HCytogenetic abnormalities at diagnosis are key prognostic factors in multiple myeloma (MM). This study aimed to evaluate the frequency of chromosomal aberrations in MM patients and their association with overall survival (OS), and to analyze discrepancies between conventional cytogenetic analysis (CCA) and fluorescence in situ hybridization (FISH). **Methods:** In this retrospective cohort study, 98 newly diagnosed MM patients at Dong-A University Hospital were included. All had results available from both CCA (G-banding) and FISH analysis, which targeted the following abnormalities: del(1p32), dup(1q21), t(4;14), t(6;14), t (11;14), CEP12, del(13q), IGH rearrangement, t(14;16), t(14;20), and TP53 deletion. Clinical variables including hemoglobin, platelet count, calcium, albumin, creatinine, β2-microglobulin, ISS stage, M-protein subtype, chemotherapy regimen, and stem cell transplantation status were reviewed. The normal karyotype group served as the comparator. **Results:** The median age was 66 years, and the median follow-up duration was 24.7 months. Cytogenetic abnormalities were identified in 82.6% of patients. Anemia was significantly more common in the abnormal karyotype group (P = 0.01). Among clinical variables, only age >65 years was significantly associated with inferior OS (P = 0.02). The most common abnormalities were del(13q) (17.9%), dup(1q21) (13.8%), hyperdiploidy (11.9%), and t(11;14) (9.2%). Among these, del(13q) (P = 0.03), hypodiploidy (P = 0.008),

and dup(1q21) (P = 0.01) were significantly associated with worse OS. Notably, 33.7% of cases showed discordant results between CCA and FISH. In particular, patients with dup(1q21) detected by CCA had significantly poorer survival outcomes (P = 0.002). **Conclusions:** This study confirms that specific cytogenetic abnormalities, especially del(13q), hypodiploidy, and dup(1q21), are associated with inferior survival in MM. Moreover, discrepancies between CCA and FISH were common, and in the case of dup(1q21), detection by CCA provided more prognostic relevance. These findings highlight the complementary roles of both cytogenetic techniques and suggest the need for integrated interpretation in MM prognostication.

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Stromal Cell Dysfunction and Chronic Inflammation Characterize the Multiple Myeloma Induced Vertebral Fracture

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Introduction: Vertebral fractures are common complications in benign osteoporosis (OP) and multiple myeloma (MM). Following fracture and tissue injury, there is an orchestrated balance of initial inflammation, followed by resolution of inflammation and secondary bone healing. In MM, malignant plasma cells induce chronic bone marrow inflammation and deregulation of immune and bone remodeling cell interactions. However, there is a lack of knowledge regarding the abnormal microenvironment's response to fracture. Thus, we explored the immune response, stromal cell function, and bone-forming capacity directly at the fracture site in MM-induced vertebral fractures. **Methods:** Bone marrow aspirates and bone biopsies were collected from the fracture site of 38 MM and 12 OP patients undergoing vertebroplasty. Explant cultures of osteoblastic cells were established from fresh bone biopsies and characterized by their proliferation capacity, and ability to form mineralized matrix. Formalin-fixed, decalcified, paraffin-embedded, sectioned bone biopsies were Masson's Trichrome stained, and analyzed for signs of sclerotic bone formation. RNA was extracted from CD138+ depleted bone marrow cells, and whole mRNA transcripts sequenced. Bone marrow cells from 3 MM and 3 OP patients underwent single-cell sequencing using the 10X Chromium Next GEM 3′ protocol. **Results:** Cultured osteoblastic cells from MM patients had reduced proliferation capacity ($p = 0.013$), and ability to form mineralized matrix ($p = 0.044$) in comparison to OP. Histomorphometric analysis revealed high variation in sclerotic bone formation in the fracture between patients (range 0–92% of total bone area), but with no significant difference between MM and OP. Gene set enrichment analysis of CD138-depleted bulk transcriptomic data revealed enriched pathways of innate immunity and cytokine signaling such as Interferon Gamma Response ([STRING], $p < 10^{-21}$), TNFα signaling via NF-κB ($p < 10^{-18}$), Interferon Alpha Response ($p < 10^{-17}$), and Complement System ($p < 10^{-15}$) in MM. Single-cell data supported differential expression of inflammatory cytokines, with a two to threefold increase in CD14+ and CD16+ monocytes, and upregulation of complement components 1q A, B, and C ($10^{-9} < p < 10^{-4}$). Likewise, TNFα and IFN-inducible response genes were particularly enriched in cytotoxic CD8+ T-cells, e.g, TNF, NFKB1, IFIT1–3, and IFIH1 (Hallmark_TNFα_Signaling_via_NFKB [MSigDB], $p < 10^{-11}$, Hallmark Interferon Gamma Response [MSigDB], $p < 10^{-16}$, Interferon Signaling [Reactome Pathways, STRING], $p < 10^{-9}$). **Conclusions:** Our findings reveal a dysregulated bone marrow microenvironment in MM vertebral fractures, characterized by chronic inflammatory activity and reduced osteoblast function. Despite this, new bone formation is present in the majority of patients, indicating preserved bone formation capacity. Ongoing studies and in-depth analysis will further explore regulators of immune and bone activity in MM-induced fractures.

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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.

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Targeting PIM-2 and PARP1 Induces MICA Expression on Multiple Myeloma Cells to Activate NK Cells Through NKG2D Binding

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Introduction: The ability to induce immunogenic death in tumor cells has been shown to activate specific anti-tumor T cells; however, the potential of non-specific natural killer (NK) cells to be activated through interaction with tumor cells remains under-researched. This study aims to investigate how inducing DNA damage in multiple myeloma (MM) cells leads to overexpression of MICA, facilitating the binding of NKG2D on NK cells and enhancing their anti-tumor activities. **Methods:** The relationship between PIM-2, PARP1, and prognostic outcomes in MM was analyzed using publicly available data alongside clinical samples. An in vitro co-culture system composed of MM cells and NK cells was employed to assess the effects of SMI-16a (PIM-2 inhibitor) and ABT888 (PARP1 inhibitor) on tumor proliferation and apoptosis. Key metrics included DNA damage assessment, evaluation of MICA protein expression, the NKG2D/MICA signaling axis, and NK cell functionality. Subsequently, an NSG mouse model was established using RPMI-8266 cells to assess the combined effect of SMI-16a and ABT888 on tumor growth, apoptosis, and NK cell activity. **Results:** The combination of SMI-16a and ABT888 resulted in a marked increase in DNA damage, indicated by elevated levels of the marker pH2AX in MM cells, relative to single-agent treatments. This combination also significantly boosted functional markers in NK cells, including perforin, granzyme B, and NKG2D. The increase in DNA damage was correlated with heightened MICA expression, which activated NK cells via the NKG2D/MICA signaling pathway. Both in vitro and in vivo studies validated the efficacy of this combination in inhibiting tumor growth and promoting apoptosis. **Conclusions:** Our findings suggest that the concurrent application of PIM-2 and PARP1 inhibitors can significantly induce MICA expression on MM cells, thereby enhancing NK cell activation through NKG2D binding. This novel mechanism may restore NK cell function and represents a promising therapeutic strategy for multiple myeloma patients. Further investigations are warranted to elucidate the detailed mechanisms underpinning how SMI-16a and ABT888 induce DNA damage and subsequently enhance MICA expression in MM cells.

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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:** 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. **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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LILRB4 Drives Myeloid Immunosuppressive Microenvironment in Multiple Myeloma and Facilitates the Inferior Outcome of Patients

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Introduction: Recent advancements in the treatment of multiple myeloma (MM), including immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, and T cell-redirecting therapies such as chimeric antigen receptor (CAR) T cells and bispecific antibodies (BsAbs), have significantly improved patient outcomes. Nevertheless, MM remains incurable. Our previous work demonstrated that expanded myeloid-derived suppressor cells (MDSCs), impaired dendritic cells, and protumoral osteoclasts in the bone marrow of MM patients play a major role in establishing a protumoral tumor immune microenvironment (TiME). However, the origins of tumor-associated myeloid cells in myeloma remain unclear. **Methods:** Single-cell RNA sequencing was performed to investigate the biological characteristics of MM cells and the TiME of MM patients. Survival-associated immune regulatory molecules were identified. LILRB4-overexpressing MM cell lines and mouse models were constructed. Flow cytometric analysis was performed on myeloid suppressive cells, megakaryocyte–erythroid progenitors, $CD45^+$ erythroid progenitor cells (EPCs), and erythroid-derived myeloid cells (EDMCs) in the bone marrow. Co-culture assays evaluated the immunosuppressive function of EDMCs/MDSCs. Cytokine arrays, RNA-seq, Western blotting, and functional analyses were conducted to elucidate the direct and indirect interactions between MDSCs and tumor cells that drive immune evasion and cancer progression. **Results:** Our prior studies identified LILRB4 as a high-risk gene in MM, with its overexpression correlating with poor prognosis and promoting monocyte-to-MDSC differentiation, thereby contributing to the TiME-induced immunosuppressive phenotype in MM patients (Haematologica 2024 & 2025). This study further revealed that the proportion of cells with myeloid features within the erythroid differentiation lineage is increased in patients with high LILRB4 expression. Through in vivo and in vitro studies, we show that CD45+ EPCs in the myeloma microenvironment lose their erythroid maturation potential and instead undergo trans-differentiation into EDMCs, driven by high levels of CCL3 secreted by LILRB4+ MM cells. Our findings propose a novel hematopoietic pathway in which MM "hijacks" erythroid-committed CD45+ EPCs, diverting them toward a myeloid fate to facilitate tumor immune escape. EDMCs, as key immunosuppressive components, potently inhibit CD8+ T-cell responses and accelerate tumor progression. Anemia, a common complication in myeloma, is associated with poor prognosis. While rhEPO and ESAs alleviate anemia, they fail to improve survival in cancer patients—possibly because they induce CD45+ erythroid progenitors that tumors exploit to expand immunosuppressive myeloid cells. **Conclusions:** Targeting LILRB4-mediated erythroid-to-myeloid diversion (EDMCs) may overcome immunotherapy resistance in MM and tumor-associated anemia.

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Multiple Myeloma Patients with Admixture-Defined African Ancestry Have Equal Clinical Outcomes to Those with European Ancestry When Receiving Highly Effective Therapies

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Introduction: Clinical outcomes in multiple myeloma (MM) patients according to race have been variably reported, with shorter progression-free survival (PFS) in Black patients in some cohorts, but equitable outcomes in other cohorts, particularly clinical trials. We recently participated in the Polyethnic-1000 initiative: using whole genome sequencing (WGS) to investigate cancers having a higher prevalence in Black populations. Here, we expand to a large cohort of clinically-available targeted sequencing data, considering topical regimens for newly-diagnosed and relapsed MM. **Methods:** Data was assessed for all patients treated at MSKCC with daratumumab-based induction regimens (dara-quads), with a minimum of 3-month follow-up available. Genetic admixture was calculated from germline samples using the MSK-IMPACT-Heme targeted sequencing panel. Ancestry group was assigned by dominant contribution (>50%) from 5 geographically-based populations (European; EUR, African; AFR, South Asian; SAS, East Asian; EAS, and Native American; NAM). Key somatic features and PFS were considered according to self-declared race and computed genetic admixture, using Fisher tests and Kaplan Meier respectively. As validation, PFS was also considered for patients receiving commercially-available CAR-T cells and bispecific antibodies (BsAb). **Results:** Clinical data was available from 506 patients treated with dara-quads, with self-declared data defining 74 Black, 349 White, 30 Asian and 53 Other/Unknown. Median age of

diagnosis did not differ by race, being 63.7 years (y) for Black, 65.0y White, 64.2y Asian and 64.0y for Other. None of t(11;14), del17p/TP53mut or ISS III had a significantly different incidence by race. In addition, race did not predict for MRD-status after 4-6 cycles of induction, nor for PFS. Admixture data from MSK-IMPACT-Heme was available for 286 patients treated with dara-quads, defining 215 EUR, 47 AFR, 11 SAS, 6 EAS, 1 NAM and 6 highly-admixed. 28 patients had self-declared "Other" or "Unknown" race, but with MSK-IMPACT-Heme data were able to be assigned to an ancestry group. 38 patients had admixture data available from both WGS and MSK-IMPACT-Heme and demonstrated 97% concordance. Restricting analysis to EUR and AFR due to available numbers, again, none of median age, incidence of t(11;14), del17p/TP53mut, ISS III, MRD-negativity nor PFS varied by ancestry group. This data was confirmed in relapsed patients receiving CART (n = 165) and BsAb (n = 178), where again neither race nor genetic ancestry predicted for PFS. **Conclusions:** Clinical response to highly effective MM therapies in both induction and relapsed settings are equivalent when considering either self-declared race or computed genetic ancestry. Computed data allows inclusion of patients for whom race is unknown. Overall, this data suggests that any reported variance in clinical outcomes by race may largely indicate unequal healthcare access rather than biological difference in therapy-responsiveness.

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Charting Spatial Heterogeneity in Multiple Myeloma by Using a Minimally Invasive Cell-free DNA Profiling

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Introduction: Multiple myeloma (MM) is a malignancy of plasma cells characterized by complex genetic alterations and interactions with the bone marrow microenvironment. Despite therapeutic progress, disease progression and treatment resistance remain major challenges. Spatial heterogeneity—referring to genetic and phenotypic variation across different disease sites—contributes to these issues and is often missed by single-site biopsies. Liquid biopsy, particularly the analysis of cell-free DNA (cfDNA), offers a non-invasive approach to detect tumor-derived signals from multiple locations. This study aims to investigate whether cell-free DNA (cfDNA) can reflect the genomic complexity of multiple myeloma (MM) by capturing tumor-derived fragments from multiple disease sites. **Methods:** Sixty-two newly diagnosed MM patients underwent 18F-FDG PET/CT and were profiled using low-pass whole genome sequencing (LP-WGS) on cfDNA from peripheral blood (PB) and genomic DNA from CD138+ plasma cells from bone marrow (BM). Copy number alterations (CNAs) were identified using the ichorCNA algorithm with a normal sample panel as reference. Concordance between PB and BM was evaluated by comparing arm-level CNA calls and calculating a weighted average copy number across genomic segments. **Results:** CNA profiles from PB and BM were filtered for tumor fraction ≥3% and a mean absolute deviation (MAD) <0.20, enabling the selection of high-quality, low-noise profiles for accurate analysis. Comparison of the two compartments revealed a median concordance of 83.3% (range: 26.6–100%), resulting in the identification of two patient groups: those with predominantly unmatched profiles (33/62; 53%) and those with predominantly matched profiles (29/62; 47%). Concordance between cfDNA and gDNA profiles was directly correlated with tumor fraction (median ctDNA in unmatched vs. matched groups: vs. 3.99% vs. 12.06%; $r = 0.60$; $p = 3.63 \times 10^{-7}$). Previously, we found that high ctDNA levels were linked to diffuse disease, including EM, PS, and FL lesions. In this study, patients with spatially distinct lesions—especially PS and FL with Deauville score 5—showed greater discordance between cfDNA and BM profiles (PS: 67 vs. 85%, $p = 0.0268$; FL: 72 vs. 90%, $p = 0.0210$). PET-positive patients (EM, PS, or FL with DS = 5) had larger, more active lesions, with higher SUV values correlating with greater BM–PB genomic mismatch ($p = 0.04$). **Conclusions:** cfDNA profiling provides a non-invasive way to capture multiple myeloma's genomic complexity and may reflect spatial heterogeneity. Lower concordance with bone marrow profiles is associated with high tumor burden and active lesions. cfDNA can complement biopsies and aid personalized monitoring and treatment. **Acknowledgements:** AIRC – Associazione Italiana Ricerca sul Cancro, AIL – Associazione Italiana Leucemia, Linfomi e Mieloma, Bologna.

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Contribution of ARID1A Mutations in the Development of Extramedullary Plasmacytoma

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Introduction: n/a. **Methods:** n/a. **Results:** n/a. **Conclusions:** The prognosis of multiple myeloma (MM) has improved dramatically with the advent of novel therapeutic agents, including immunotherapies. Extramedullary disease (EMD) is predominantly observed at the time of relapse and remains a challenge due to its refractoriness to treatment. We recently performed mutational profiling on samples from 24 cases of EMD samples and identified RAS/BRAF mutations in 23 cases (95.8%), suggesting that these mutations are essential in the pathogenesis of EMD development. However, the molecular mechanism underlying the development of EMD remains unclear. In addition to RAS/BRAF and TP53 mutations, our data demonstrated ARID1A mutations at a relatively high frequency (four of 24 EMD samples). Although the overall prevalence of ARID1A mutations in our cohort was low, 75% (Six out of eight) of patients harboring ARID1A mutations developed EMD. ARID1A mutations have been widely reported across various malignancies and are generally considered loss-of-function mutations. Recent studies have reported that ARID1A plays a critical role in the differentiation of plasma cells from the germinal center stage, and it has emerged as a potential therapeutic target. However, in our in vitro studies using multiple myeloma cell lines, we observed that both low ARID1A-expressing clones and ARID1A knockdown were associated with a less differentiated immature cellular phenotype by qPCR and flowcytometry. These findings suggest that ARID1A mutations may contribute to the development of undifferentiated myeloma clones and the consequent emergence of EMD. Ongoing studies are focused on determining therapeutic targets with the goal of preventing progression to the development and/or the treatment of EMD.

PA-250

Systematic Assessment of MYC by Fluorescence in situ Hybridization in Multiple Myeloma Identifies a High-Risk Population Independent of Other Risk Factors

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Introduction: MYC testing is not routinely performed in multiple myeloma (MM) despite being recognized as a prognostic biomarker. We present the impact of systematic MYC testing for alterations on outcomes in patients (pts) with MM and its relation to clinical features and cytogenetics. **Methods:** A total 133 pts who underwent bone marrow biopsy and had a diagnosis of MM (147 total samples) were systematically assessed for MYC alterations using fluorescence in situ hybridization (FISH) testing over a 24-month period. 126 were assessable for progression-free survival (PFS), and 92 were newly diagnosed with MM (NDMM). MYC alterations were classified as rearrangements (MYC-R) or gains. Clinical characteristics, cytogenetic alterations, and outcomes were compared across MYC status. PFS was defined as time from diagnosis to death or progression/relapse of disease as defined by the International Myeloma Working Group criteria. **Results:** MYC alterations were present in 44 of 133 MM pts (33%). MYC-R was present in 35 pts (26%), while MYC gain was present in 13 pts (9.8%). Most MYC-R partners were not identified on standard of care FISH, with MYC::IGH being present in 7/35 cases. Compared to non-altered MYC (MYC-negative) cases, those with MYC-R were older (median 75 vs. 67 years, $p = 0.005$), and more likely to present with international staging system III (56% vs. 29%, $p = 0.008$) and hypoalbuminemia (68% vs. 42%, $p = 0.01$). MYC-R cases had higher rates of del(17p): 23% vs. 6.7% ($p = 0.02$), t(4;14): 23% vs. 9% ($p = 0.07$), and lower rates of t(11;14): 17% vs 37%, $p = 0.03$). MYC-R was associated with higher rates of high-risk cytogenetics (HR-CG - del(17p), t(4:14), t(14;16)); 46% vs 19%, $p = 0.003$), HR-CG plus gain(1q) (74% vs 55%, $p = 0.04$), and HR-CG plus gain(1q) or del(1p), 80% vs 56%, $p = 0.01$). Pts with MYC-R had significantly shorter PFS compared to MYC-negative (15.6 vs. 35.7 months, $p = 0.017$). Other variables associated with PFS included ISS, R-ISS, LDH, albumin, del(17p), and HR-CG. In multivariable model, only MYC-R was associated with inferior PFS (HR 2.82, 95% CI 1.12–7.06, $p = 0.027$). Additionally, when patients were stratified by MYC-R and HR-CG status, patients with MYC-R and no HR-CG had inferior PFS compared to MYC-negative/no HR-CG patients ($p = 0.001$) and similar to when there was the presence of HR-CG. **Conclusions:** MYC-R is a common (27% of cases) alteration that is associated with co-occurrence of other HR-CG alterations, advanced clinical presentation, and significantly inferior PFS, even in the absence of other HR-CG features. Importantly, the presence of MYC-R was associated with inferior PFS regardless of HR-CG status, ECOG, or R-ISS at diagnosis, suggesting it is an independent predictor. These findings highlight the prognostic relevance of MYC rearrangement and support its utility as a risk stratification biomarker that can be widely incorporated into current FISH panels.

PA-251

A Single-Cell Coding and Noncoding Transcriptomic Atlas Reveals ncRNA-Driven Remodeling of the Bone Marrow Microenvironment in Multiple Myeloma

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Introduction: Interactions between myeloma cells and the immune microenvironment are a critical target for developing next-generation immunotherapies for multiple myeloma (MM). To investigate these interactions, single-cell transcriptomics enables comprehensive profiling of the MM bone marrow microenvironment (BMME); however, current analyses primarily focus on coding genes, neglecting the substantial noncoding transcriptome due to challenges in genomic overlap. To address this, we have developed a novel integrated coding-noncoding RNA profiling approach to elucidate the noncoding landscape of the MM-BMME. We hypothesize that specific cytogenetic mutations give rise to distinct genomic profiles regulated by the noncoding transcriptome, thereby altering MM phenotypes and, consequently, the BMME. **Methods:** To accomplish this, we generated an expanded human reference genome integrating mRNA and ncRNA annotations (>175k genes, 80% noncoding) from LncBook2.1 and GENCODEv47, maximizing noncoding gene capture while preserving coding gene detection from single-cell or bulk sequencing data. Benchmarking this approach, we demonstrate that alignment with the integrated genome annotation increases noncoding gene capture by over threefold (to 133,846 genes) in a single-cell dataset. Harnessing our integrated annotation, we generated and aligned single-cell RNA-seq data (N = 481) from CD138- immune cells, as well as bulk RNA-seq data from CD138+ myeloma cells, from patients enrolled in the MMRF CoMMpass trial. This resulted in the first integrated coding-noncoding single-cell atlas of MM-BMME comprising >1.9 million cells, spanning plasma, stromal, and immune compartments, including 45 immune subclusters with ncRNAs representing 24–38% of significantly differentially expressed genes. **Results:** To investigate the impact of ncRNAs driven by cytogenetic mutations, we first identified ncRNAs differentially expressed ($P < 0.05$) in myeloma cells between patients harboring specific mutations versus those without. Subsequent survival analyses revealed 29 cytogenetic-specific ncRNAs associated with patient outcomes ($P < 0.01$), including tumor suppressors (N = 16, HR< 0.4) and oncogenes (N = 13, HR >1.4). Network and pathway analyses indicated these ncRNAs may modulate critical cancer pathways, including proliferation and intercellular signaling. Differential abundance testing revealed that expression of 20 of these ncRNAs is associated with altered immune composition in 22 subpopulations ($P < 0.05$); for example, increased expression of amp (1q21)-associated oncogenic ncRNA HSALNG0008530 resulted in an increased proportion of mature neutrophils linked to poor survival. Lastly, to validate the clinical relevance of these ncRNAs, we are investigating their identities and functions in vitro. **Conclusions:** Collectively, our study presents a comprehensive coding-noncoding MM-BMME atlas, highlighting ncRNAs as regulators of MM phenotypes and immune microenvironment interactions, offering promising biomarkers and therapeutic targets.

PA-253

Immunosuppressive Bone Marrow Microenvironment Promotes Multiple Myeloma Proliferation in Adult Mice with Induced Osteoblast and Osteocyte Deficiency

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Introduction: Most multiple myeloma (MM) patients relapse and become refractory to treatment. This may be because MM cells are protected in the tumor microenvironment (TME) and reactivate only under permissive conditions. Osteoblasts are versatile regulators of hematopoietic cells. We previously showed that inhibition of Activin A in SCID mice transplanted with human MM.1S increased osteoblast numbers and inhibited MM growth (Vallet et al., PNAS). Here, we hypothesize that losing mature osteoblasts promotes MM progression. **Methods:** We generated immunocompetent mice with inducible deletion of mature osteoblasts by mating mice carrying floxed diphtheria toxin receptor (DTR) alleles with mice expressing Cre-recombinase driven by the osteocalcin promoter (OC-Cre). This led to the expression of DTR in mature osteoblasts (OC-Cre/iDTR) only. Littermates lacking the OC-Cre allele (iDTR) were used as controls. Until diphtheria toxin (DT) treatment, the OC-Cre/iDTR mice were immunocompetent and indistinguishable from iDTR control mice as shown by flow cytometry and micro-computed CT (micro-CT). Mice reach skeletal maturity by 8 weeks of age. Beginning at 8 weeks of age, the OC-Cre/iDTR and iDTR control mice were treated with 25 µg/kg DT once a week to induce mature osteoblast deficiency. At 9 weeks of age, 1 × 106 5TGM1 luciferase tdTomato positive (5TGM1-Luc-Tom) MM cells were injected into the tibia. MM expansion, immune profiling, and molecular mechanisms were assessed by bioluminescence imaging (BLI), flow cytometry, cytokine array, ELISA, micro-CT, and immunohistochemistry up to 8 weeks post MM cell inoculation. **Results:** DT injections induced more than 80% loss of mature osteoblasts and osteocytes beginning after 1 week as assessed by micro-CT, histomorphometry, immunohistochemistry for osteocalcin, and ELISA for serum osteocalcin and sclerostin. Notably, the number of osteoclasts per trabecular area and serum CTX levels were unchanged, indicating normal osteoclast numbers and activity. One

week after the 5TGM1-Luc-Tom MM intratibial inoculation, both OC-Cre/iDTR and iDTR control mice showed similar BLI flux; however, it was rapidly lost in the iDTR control mice and multiplied 30–50-fold in OC-Cre/iDTR mice, indicating proliferation of the MM cells. Assessing 200 cytokines and growth factors in the BM of these mice showed altered levels of immune regulatory cytokines such as IL-4, IL-13, and CCL2. Flow cytometric analysis of the bone marrow (BM) constituents from the MM-cell-injected tibia revealed immunosuppressive BM TME characterized by increased Tregs and MDSCs in OC-Cre/iDTR mice compared to the iDTR controls. **Conclusions:** These data show that MM cells expand rapidly within BM in the absence of mature osteoblasts and osteocytes in adult mice, at least in part, due to the immunosuppressive BM TME. Expanding the mature osteoblast niche may provide novel therapeutic avenues and reduce disease burden, creating an environment for long-term tumor control.

PA-254

Ancestry-Associated Dysregulation of the Bone Marrow T Cell Compartment in Multiple Myeloma Revealed via scRNA-seq and CyTOF Profiling

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Introduction: Multiple Myeloma (MM) disproportionately affects Black individuals in the U.S., with an incidence nearly double that of other groups. Although differences in the frequencies of cytogenetic events and age of onset have been observed, the immune microenvironment (IME) in Black patients with MM has not yet been investigated. Given the critical role of the IME in response toward current MM therapies, we examined ancestry associated differences in IME and outcomes. **Methods:** ScRNA-seq data of 337 newly diagnosed MM (NDMM) patients with >1.4 million cells from the MMRF Immune Atlas (IA) was used for this analysis. Ancestry was estimated from blood whole exome sequencing data. Ancestry associated alterations in immune composition or expression were assessed adjusting for sex, age, ISS stage, and BMI. To validate our findings, we generated an independent cohort (Mayo Clinic) of 94 BM aspirates using CyTOF. Of these, 41 patients had a precursor condition, 28 had NDMM, 37 had treated MM (TrMM) and 39 were Black, and 55 were White. **Results:** In the 337 NDMM patients of the Immune Atlas, 63 self-reported as 'Black', while 257 self-reported as 'White'. Fewer high risk cytogenetic events, such as del(17p13), were observed with high African ancestry (AA), though triplet therapy and ASCT were significantly underutilized. PFS and OS were similar across race when matched for therapy.T, NK, and Myeloid compartments showed significant alterations with ancestry. In T cells, AA significantly correlated with higher cytotoxicity (PRF1, FGFBP2, GNLY, $p < 0.05$), and enrichment of cytotoxic CD4+ and CD8+ cells ($p < 0.001$). Naive CD8+ T cells showed significant enrichment with high AA, while Naïve CD4+ T cells showed significant reduction ($p < 0.04$). High AA showed depletion of MAITs ($p < 0.05$, SLC4A10, ZBTB16, KLRB1), an MR1 responsive effector population with innate-like properties. In NK cells, higher AA was associated with adaptive NK markers (KLRC2+, FCER1G-, $p < 0.001$), a memory-like, cytotoxic NK population which has been associated with chronic viral infections. Lastly, AA ancestry showed significant enrichment of CD16+ non-classical monocytes (nCM, $p < 0.05$). Differential expression across cellular clusters showed significant upregulation of RPS26 with AA. Differences in expression were associated with the C allele for the rs1131017 germline variant, which strongly associated with AA ($p < 0.001$). In the independent CyTOF cohort, NDMM AA patients displayed similar enrichment of terminal effector T cell populations ($p < 0.05$). T cells alterations across race were specific to NDMM and TrMM groups. In the healthy cohort, AA patients were enriched in CD57+, Adaptive NK cells. **Conclusions:** High African ancestry MM patients exhibit significant dysregulation in T and NK cell compartments, which are strongly associated with outcomes. Given the central role of the immune landscape in determining therapeutic response, it is imperative to ensure adequate representation of underrepresented minorities in clinical trials.

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Multi-hit Cytogenetics Risk Events Associated with IFN-I Suppression across TME of NDMM Patients and Poor Outcomes

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Introduction: Multiple myeloma (MM) is a heterogeneous malignancy, with patients often exhibiting high-risk cytogenetic abnormalities linked to poor outcomes. While alterations such as t(4;14) and gain of 1q are well studied, emerging evidence suggests that the cumulative presence of multiple cytogenetic hits has a greater negative prognostic impact than single events. The mechanisms by which these co-occurring alterations affect the bone marrow microenvironment and drive progression remain unclear. We hypothesize that multiple high-risk events remodel the immune microenvironment, promoting disease progression and adverse outcomes. **Methods:** To investigate the impact of multi-hit cytogenetic events on the immune microenvironment, we analyzed scRNA-seq data from 337 newly diagnosed MM patients generated as part of the Immune Atlas initiative. Cytogenetic alterations of these patients were derived from whole-genome and whole-exome sequencing of CD138$^+$ bone marrow aspirates from the CoMMpass cohort. Patients were classified as having multi-hit high-risk disease if they exhibited either (i) two high-risk cytogenetic events—such as NSD2 t(4;14), MAF t(14;16), or del(17p13)—or (ii) one high-risk event in combination with gain of 1q21. **Results:** Based on cytogenetics information, we stratified 33 as 'multi-hit' high-risk and 34 as single-hit high-risk. Multi-hit high-risk status was significantly associated with worse progression-free survival (PFS) compared to standard-risk patients, even after adjusting for age, treatment regimen, and autologous stem cell transplant (ASCT) status (HR = 2.34, $p < 7.2e-5$). In contrast, single-hit high-risk patients showed a non-significant trend toward inferior PFS (HR = 1.51, $p = 0.071$). The most frequent multi-hit combination involved NSD2 translocation [t(4;14)] and gain of 1q21, observed in 23 patients. ScRNA-seq Immune clusters analysis revealed that multi-hit patients exhibited marked reductions in several IFN-I-stimulated CD4$^+$ and CD8$^+$ T cell subsets, accompanied by decreased expression of antiviral response markers such as ISG15, XAF1, and IFI44L. These patients also displayed a significant enrichment of inflammatory CD16$^+$ non-classical monocytes. These immune alterations were significantly different from both single-hit high-risk and standard-risk cohorts. Further stratification of patients harboring both NSD2 and 1q21 revealed a distinct enrichment of late-activated, cytotoxic CD8$^+$ and CD4$^+$ T cells, not seen in patients with NSD2 or 1q21 alone. Enrichment of these populations correlated with rapid MM progression. Secondary analyses suggested that suppression of IFN-I signaling is primarily driven by the presence of 1q21 in combination with another high-risk lesion. Suppression was observed across multiple immune and malignant populations in the scRNA-seq and paired bulk RNA tumor datasets. **Conclusions:** Patients with multiple multi-hit high risk myeloma display distinct immunologic traits from patients with standard risk or single-hit high risk myelomas.

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Next-Generation Molecular Techniques as an Alternative to Conventional FISH in Newly Diagnosed Multiple Myeloma: A Pilot Study

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Introduction: Risk stratification in newly diagnosed multiple myeloma (NDMM) has traditionally relied on conventional fluorescence in situ hybridization (FISH). However, novel next-generation sequencing (NGS) technologies offer a more precise and comprehensive molecular characterization of the disease. Incorporating these advanced approaches is critical for improving risk stratification and enabling measurable residual disease (MRD) tracking. **Methods:** NDMM patients (2023–2024) were evaluated using conventional FISH and NGS to detect somatic mutations, chromosomal translocations, and copy number variations (CNVs). Genomic DNA (~20 ng) was extracted from purified CD138+ plasma cells. NGS was performed using the EuroClonality-NDC assay on the AVITI sequencing system (Element Biosciences), enabling simultaneous detection of clonal IG/TR gene rearrangements, SNPs, and chromosomal translocations. CNVs were assessed by DigitalMLPA (SALSA® digitalMLPA™ Probemix D006), which combines traditional MLPA with NGS to analyze up to 644 genomic targets simultaneously. Sequencing was performed on an Illumina MiniSeq, and data were analyzed with Coffalyser software. FISH, NGS and digitalMLPA results were compared, focusing on high-risk features: 1q21 gain/amplification, del(1p32), t(4;14), and del(17p). **Results:** FISH and NGS data were available for 34 NDMM patients. FISH failed in one case, and two samples lacked sufficient material for MLPA (though mutation analysis was successful). For 1q21 gain/amplification, FISH detected 13 positives versus 17 by NGS (81% concordance, 25/31 pairs). Del(1p32) was found in 3/33 cases by FISH and 6/32 by NGS (77% concordance, 24/31). Translocation t(4;14) was identified in 4/33 by FISH and 3/33 by NGS (97% concordance, 30/31), and del(17p) in 3/33 by FISH and 4/32 by NGS (97% concordance, 30/31). NGS identified HR features in 10 patients missed by FISH, while FISH detected 4 HR features not captured by NGS. Additionally, NGS revealed TP53 mutations in 3/

32 cases, further upgrading patient risk. Beyond structural abnormalities, somatic mutations were frequently identified (e.g., KRAS in 15/33, NRAS in 4/33, BRAF in 3/33). Clonotypic CDR3 sequences were identified in 33/34 patients (97%), supporting potential MRD monitoring. **Conclusions:** NGS combined with DigitalMLPA offers a robust and comprehensive molecular assessment of NDMM, often outperforming conventional FISH. These techniques enable enhanced risk stratification by incorporating key somatic mutations such as TP53 and offer the additional advantage of identifying CDR3 sequences for MRD tracking. Where available, molecular approaches should be preferred over FISH for initial evaluation of NDMM. Supported by Ministry of Health of the Czech Republic, grant nr. NW24-03-00062.

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Mapping Cell-Cell Communication Dynamics Across the Spectrum of Multiple Myeloma Evolution Using Single-Cell Transcriptomics

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Introduction: Multiple myeloma (MM) is a malignancy marked by clonal proliferation of plasma cells (PCs) in the bone marrow (BM), progressing through MGUS, SMM, and symptomatic MM. While tumor-intrinsic features are well-studied, less is known about how BM cell–cell communication evolves during disease. Intercellular signaling plays a critical role in tumor progression and immune evasion. We used MultiNicheNet, a computational tool integrating ligand-receptor expression with downstream transcriptional responses, to investigate how communication between immune and stromal cells is remodeled across disease stages compared to healthy donors (HD). **Methods:** We analyzed scRNA-seq data from 12 GEO datasets comprising HD (n = 54), MGUS (n = 25), SMM (n = 14), and MM (n = 85), totaling over 434,000 BM cells after downsampling to a maximum of 1,000 cells per patient. Cell types were annotated and MultiNicheNet was used to infer differential communication (up- and down-regulated ligand-receptor pairs) between each disease stage and HD. For each comparison, the 50 most significant upregulated and downregulated interactions were identified and categorized by sender and receiver cytotypes, recurrence, and disease stage specificity. **Results:** We observed distinct alterations in cell–cell communication across stages. Among the most recurrent downregulated interactions were S100A8–CD69 and ANXA1–FPR1 (shared in MGUS/SMM), and TYROBP–TREM1, suppressed in all stages and primarily involving monocytes. Stage-specific losses included ADAM17–ITGB1 (MGUS), S100A9–ITGB2 and ICAM1–ITGB2 (SMM), and CLEC2D–KLRB1 and TNFSF13B–TNFRSF13B (MM), affecting NK, T cells, PCs and myeloid lineages. Among upregulated interactions, PTPRC–CD247 emerged as a consistent feature across all stages in NK-related circuits (e.g., NK–NK, CD8–NK). MGUS showed early NK activation signals (e.g., TGFB1–TGFBR3, ICAM3–ITGAL), while, in SMM stage, PCs showed increased inhibitory interactions such as BST2–LILRB3/LILRA5 with CD16+ cells. MM was marked by classical monocyte-driven inflammatory signals such as S100A8/A9/A12–TLR4, IFNG–IFNGR2, and ANXA1–FPR1. Abundance analysis showed enrichment of NK cells in MGUS, while plasma cells were increased in SMM and MM. Monocyte levels remained stable. **Conclusions:** This study maps dynamic shifts in BM intercellular signaling during MM evolution, highlighting conserved (e.g., PTPRC–CD247) and stage-specific ligand-receptor axes. MGUS features NK-centered signaling, SMM shows rising inhibition and plasmacytoid involvement, and MM exhibits myeloid-driven inflammation. While functional implications remain to be fully defined, these findings point to novel therapeutic avenues and biomarkers tailored to disease stage.

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High Expression of NSD2 in Non t(4;14) Newly-Diagnosed Multiple Myeloma Patients May Mimic t(4;14) Biology

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Introduction: In newly diagnosed multiple myeloma (ndMM) t(4;14) causes overexpression of the histone methyltransferase NSD2 (MMSET) which adds dimethyl groups on histone 3 lysine 36 residues leading to a gene expression program associated with poor prognosis. Interestingly, some patients without the translocation can have high NSD2 expression. Here, we compared genomic and prognostic features between t(4;14) vs non-t(4;14) patients with high vs low NSD2 expression. **Methods:** We analyzed multi-omics (DNA- & RNA-seq) data from three independent cohorts (CoMMpass,

IFM2009, GAMER) with 1703 ndMM patients total. **Results:** In two datasets, most non-t(4;14) showed downregulated NSD2 vs normal PCs. However, ~25% of these non-t(4;14) had higher expression of NSD2 transcripts vs normal PCs. We compared clinical outcomes in t(4;14) patients, non-t(4;14) with high NSD2 (H-NSD2), and non-t(4;14) with low NSD2 (L-NSD2). H-NSD2 patients had similarly poor PFS and OS to the t(4;14) and significantly worse outcomes compared to L-NSD2 (H-NSD2: mPFS 22mo, mOS 63.5mo; t(4;14): mPFS 27.8mo, mOS 72.2mo; L-NSD2: mPFS 42.3mo, mOS NR). These findings were replicated on all datasets, confirming a prognostic role for high NSD2 on outcomes, independent of t(4;14). H-NSD2 patients in CoMMpass had significantly higher prevalence of high risk features eg, P53 mutations (OR = 3.42 [1.58–7.43]), del17p (OR = 2.69 [1.48–4.83]), and t(14;16) (OR = 2.50 [1.04–5.86]) and significantly lower prevenance of hyperdiploidy (OR = 0.26 [0.17–0.39]) vs L-NSD2 patients. This enriched pattern of high risk features was replicated in IFM2009 and GAMER datasets. Transcriptomic analyses revealed that H-NSD2 patients exhibited significantly higher FGFR3 expression (log2FC = 3.2, adj. $p < 2.2e-16$), resembling t(4;14) tumors. We found 367 genes with significant expression changes between L- and H-NSD2 groups (adj. $p < 0.01$ & abs (log2FC) > 1) after adjusting for cytogenetic imbalances. Increased genomic instability processes, including G2M checkpoint and mitotic spindle, were significantly upregulated (q-value< 0.0001) in H-NSD2 patients, while DNA repair and oxidative phosphorylation were downregulated (q-value< 0.001). Key upregulated genes in both H-NSD2 and t(4;14) groups included JAM3, CDC42BPA, FGFR3, and others. Analysis of master regulators in the H-NSD2 group using RNA expression, ChIPseq, and single-cell ATAC-seq data identified E2F1/2/7/8, PHF19, and FOXM1 among the top transcriptional regulators. **Conclusions:** A subset of ndMM may have high expression of NSD2 independent of t(4;14) with poor clinical outcomes. The H-NSD2 group had significantly more high-risk genomic alterations with biology similar to t(4;14) group correlated with high NSD2 levels. Further ongoing analysis would elucidate the biology of high NSD2 and associated tumor genomic features and may support clinical investigation of NSD2 inhibition in the H-NSD2 MM patients.

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Independent and Complementary Value of RNA Expression Signatures in High-Risk Multiple Myeloma

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Introduction: Gene expression signatures are valuable for capturing the biological heterogeneity of multiple myeloma (MM), revealing disease mechanisms, progression, and treatment vulnerabilities. However, frequent somatic changes in MM, such as copy number alterations and translocations, impact the transcriptome. To evaluate the added value of RNA-based information, we developed an ensemble of RNA signatures and compared them to DNA-based models like the IMS/IMWG Consensus Genomic Staging for high-risk MM. **Methods:** We analyzed RNA sequencing data from 1,620 newly diagnosed MM patients and added 690 with array-based profiles, totaling 2,310 patients across five independent datasets. Seven established gene expression risk models were harmonized for RNAseq platforms, and their combined risk scores were stratified into four categories based on data type. **Results:** We compared both continuous and stratified gene expression (GEX) risk scores—GEX-negative, GEX high-risk (≥4 positive signatures), GPI-positive, and Others (1–3 signatures, GPI-negative)—against a DNA-based risk model. Across all datasets, GEX high-risk and GPI-positive patients showed significantly worse progression-free survival (PFS; HR 3.6 and 2.6) and overall survival (OS; HR 4.45 and 3.97), with p-values < 1.0e-6. We then compared the RNA ensemble to the IMS/IMWG risk model. In our multivariate analysis, we discovered that both the DNA-based (HR = 1.4, $p < 0.001$) and RNA-based (HR = 3.6, $p < 0.001$) risk models serve as independent risk factors. The RNA-based models identified an additional 7% of patients within the IMS/IMWG risk stratification who had significantly poorer outcomes, while there were no corresponding DNA markers evident. To explore mechanisms driving risk in GEX high-risk patients without GPI, we compared their DNA profiles to other groups. While GEX high-risk and GPI groups had similar frequencies of key DNA risk features, patients negative for all signatures—who had better outcomes—showed significantly fewer classical DNA risk markers, including TP53 mutations, 1q gains, and CDKN2C deletions (FDR <0.01). We further analyzed transcriptomic features unique to the GEX high-risk group lacking GPI and found significant differences from the other groups. A total of 482 genes were dysregulated (adj $p < 0.01$), with strong enrichment in cell adhesion pathways (FDR <0.01). This enrichment was validated across all datasets using gene set variation analysis, confirming cell adhesion as a hallmark of this subgroup (Kruskal-Wallis $p < 1e-5$). **Conclusions:** Our analysis of a large patient cohort across multiple datasets demonstrates the potential to establish a standardized workflow for combining gene expression signatures. It also highlights that some patients cannot be accurately identified using current DNA risk markers but still have poor prognoses. Therefore, RNA expression retains independent information that should be considered in future studies.

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Comparison of NGS-Based PlasmaSeq and FISH for Routine Genomic Testing in Multiple Myeloma

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Introduction: Fluorescence in situ hybridization (FISH) is widely used for cytogenetic risk stratification in multiple myeloma (MM) but has limitations due to restricted probe panels and high sample input requirements. Moreover, recent IMS/IMWG guidelines suggest the need to move over to sequencing based methodologies. PlasmaSeq is a next-generation sequencing (NGS)-based assay that detects copy number changes, structural variants, and relevant somatic mutations for risk-stratification and immunotherapy targets. This study compares FISH and PlasmaSeq in bone marrow (BM) samples from routine real world clinical testing. **Methods:** Fifty-nine BM samples from MM patients at various stages were analyzed by PlasmaSeq (NCGM, Raleigh NC) and standard FISH per institutional protocols. PlasmaSeq identified clonal plasma cell–associated genomic alterations including aneuploidy, deletions, amplifications, translocations, and mutations. Concordance was assessed in cases where both tests were performed; discordances were reviewed and categorized. **Results:** DNA input ranged from 1 ng/ul to 90.6 ng/ul with a bone marrow plasma cell content ranging from < 5% to ~80% across all samples. PlasmaSeq detected clonal plasma cells in 43/59 (73%) samples based on an integrated mutational profile based clonal determination tool. Of the remaining 16 where PlasmaSeq indicated no clonal profile, FISH failed in 14 and was negative in 2. Of the 43 patients, PlasmaSeq identified 18 (42%) Hyperdiploid (HMM) cases. In 14 of 43 PlasmaSeq-positive cases (32.6%), FISH was either not performed or unsuccessful; all 14 had clinically significant findings on PlasmaSeq. Twenty-nine cases had results from both tests: 21 (72%) were concordant. Eight cases (28%) were discordant, with 7 abnormalities unique to PlasmaSeq while 2 were detected with FISH. However, the events specific to FISH were ruled out by sequencing (1p32 deletion mapped outside CDKN2C and gain1q located downstream of CKS1B outside of the chr1q21 cytoband). Of the 7 events detected by PlasmaSeq alone, 4 cases were HMM and not tested by FISH, a narrow gain1q event below FISH resolution, t (14;20) translocation and narrow del1p32 missed by FISH. Furthermore, PlasmaSeq was able to identify mutations in MM-relevant genes in 65% of patients. RAS pathway genes were involved in 18 patients (42%) and TP53 mutations in 6 (14%) patients with clonal plasma cells. **Conclusions:** PlasmaSeq achieved a 100% diagnostic discovery rate in all 43 clonal-positive cases. In 32.6% (14/43), PlasmaSeq refined or reinterpreted FISH-reported abnormalities. These results support PlasmaSeq, a sequencing-based method, as an important tool for comprehensive genomic profiling in MM.

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Single-Cell Transcriptomic Profiling Reveals Immune Aging and Tumor Microenvironment Imprinting in Smoldering Multiple Myeloma

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Introduction: The tumor microenvironment (TME) is a key regulator of disease progression in Smoldering Multiple Myeloma (SMM). The interplay between malignant plasma cells and various immune components, such as myeloid cells and T cells, can affect tumor growth via cross-talk between these populations. Therefore, dissecting TME imprinting in SMM is crucial to better risk stratification based on the evolving paradigm of treating SMM patients. Here, we explore the intricate mechanisms of immune and SMM cell interactions and compare markers in peripheral blood that may be reflective of bone marrow status. **Methods:** We have sequenced 26 PBMC and 21 BM samples from 14 SMM patients using single-cell RNA sequencing. These include 21 paired BM and PB samples at the time of diagnosis and at later time points for disease monitoring. We have also sequenced 32 normal BM samples from healthy donors and 30 BM and 21 PB samples from MM patients. **Results:** We first looked at major cell populations (T, B, NK, monocytes, dendritic cells) representation in BM and PB and found that only CD4+ ($R = 0.46$, $p = 0.1$), CD8+ ($R = 49$, $p = 0.1$) and rare T ($R = 0.64$, $p = 0.02$) cell populations correlate between BM and PB. We did not observe any correlation between PB and BM for other populations (B, NK cells and monocytes). Cell signaling analysis in the BM showed that SMM cells release strong macrophage inhibitory factors (MIF) (CD74 and CXCR4) towards monocytes and T cells (p-value < 0.01). In contrast, higher TACI-BCMA interaction between monocytes and SMM cells was observed and was aberrant compared to normal plasma cells (p-value < 0.01). The SMM microenvironment was overall more similar to the MM microenvironment when compared to normal bone marrow. Accelerated immune aging significantly differed from healthy donors for B, NK, CD4+ T, and CD8+ T cells compared to SMM and MM (p-

value = 0.00057). **Conclusions:** By combining large datasets processed very similarly, we observed that T cells in PB may reflect BM, and future studies on immune function may be restricted to PB. This correlation, however, is much weaker for other cell types such as B cells, monocytes, and macrophages. This may be consequent to these cells requiring further MIF signaling within the BM. MIF signal can stimulate BM stromal cells to produce IL-6, a pro-inflammatory cytokine that is important for myeloma cell survival and growth. MIF may also contribute to creating a pro-tumor microenvironment by influencing the polarization of macrophages. Accelerated immune aging in tumor samples, especially compared to normal donors, may be explained due to overstimulation of these cells. Our findings highlight the role of MIF-driven dysregulation in promoting immune aging as well as the potential of PB T cells as non-invasive biomarkers for immune monitoring in SMM. Further association studies with clinical features are ongoing and will be presented.

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Temporal and Spatial Determinants of CAR-T Cell Therapy Efficacy in Multiple Myeloma

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Introduction: While chimeric antigen receptor (CAR) T therapy offers promise for relapsed/refractory multiple myeloma (MM) patients, disease recurrence remains problematic. Delineating the mechanisms behind CAR T cell failure is essential for enhancing therapeutic efficacy and achieving durable remissions. To this end, we evaluated the spatial transcriptomes of longitudinal MM cases to understand the immune and tumor landscape during CART treatment and uncover fundamental mechanisms and spatial biomarkers that may guide the development of more effective CAR T cell therapies. **Methods:** We utilized Xenium spatial transcriptomics on pre and post CAR T bone marrow biopsies treated with BCMA CART. All samples were run using the Human Multi-Tissue and Cancer panel (377 genes) with a custom 100 genes added. To reduce batch effects, paired specimens were run on the same slide and processed using the Xenium Multi Tissue Stain protocol to aid cell segmentation followed by H&E staining. Samples were all processed using Xenium instrument software for cell segmentation and probe deconvolution followed by downstream analysis in R utilizing Seurat and custom scripts. To annotate the cell types, we first performed label transfer (via Seurat functions FindTransferAnchors and MapQuery) using both internal and external MM single-cell datasets. We then manually evaluated cell type annotation based on marker gene expression. Image-based analysis of Xenium samples following cell type assignment was performed using the Xenium Explorer desktop application (10x Genomics). **Results:** We assayed over one million cells across 20 samples, including 7 paired pre/post CART, 5 pre-CART and 1 post-CAR T singletons using the Xenium platform. Treatment response for paired samples included 1 complete response (CR), 3 partial response (PR), 3 progressive disease (PD). All singletons had PD. Cells spanned the following lineages: lymphoid, megakaryocyte/erythroid, myeloid and stromal compartments with more granular cell annotation encompassing adipocytes, osteoblasts, and mesenchymal stem cells, among others. The myeloid lineage represented the largest proportion of cells (range: 25%-50%). CAR T treatment in the PR patients led to a notable decrease in B and plasma cells while patients with PD exhibited an increase in the same compartments post-CAR T and plasma cells continued to express TNFRSF17 (i.e. BCMA). Additionally, a majority of post-CAR T samples showed a modest increase in stromal cells, although specific stromal subtypes varied across patients. We observe megakaryocyte dense regions and plasma cells located in two spatial orientations, spatially diffuse and spatially dense and do not observe differences in the two spatial stratification patterns associated with treatment response. **Conclusions:** Longitudinal spatial profiling of MM during treatment can identify microenvironmental structures that may either hinder or support disease responses to CAR T therapy. Additional data is needed for detailed clinical correlation.

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Treatment of Plasma Cell Disorders Post Solid Organ Transplant – A Positive Single Center Experience using Immunomodulatory Drugs

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Introduction: Immunomodulatory drugs (IMiDs) have significantly improved prognosis in the treatment of plasma cell disorders. There is reticence to prescribe IMiDs to solid organ transplant (SOT) recipients as the limited literature to date suggests that IMiDs carry a significant risk of solid organ transplant rejection (SOTr). We aim to review the outcomes of SOT recipients with plasma cell disorders treated with IMIDs at a single center. **Methods:** We conducted a retrospective chart review of all SOT recipients at our center, from 2016 to 2025, who were treated for plasma cell disorders. Data collected included transplant type, treatment details & patient & allograft outcomes. **Results:** 7 patients met the inclusion criteria: 4 received IMiD, lenalidomide 5 mg, 1 patient also received pomalidomide & 3 patients received no IMiDs, serving as a comparison group. Clinical indications for IMiD included treatment of de novo disease, relapsed disease & maintenance therapy. Median time post-transplant to IMiD therapy initiation was 6 years (range 5–14 years). Median duration of follow-up after initiation of IMiD was 3 years (range 0.5–4 years). Most patients were maintained on triple IS. Of

Table 1 (abstract PA-264) Patient characteristics, hematologic response & allograft outcomes (MMF: mycophenolate mofetil, MPA: mycophenolic acid, Pred: prednisone, SM: Smouldering myeloma, Tac: Tacrolimus (target level), VGPR: Very Good Partial Response)

Case	Age	Sex	HLA Mismatch (DSA)	Haematological Diagnosis	Transplant to IMiD (Years)	Time on IMiD (Years)	Haematological response to IMiD	Is
1	61	F	3	LCDD	–	–	VGPR	Pred 5, Tac (6–8), MPA 360 mg BD
2	64	M	3	AL Amyloidosis	–	–	VGPR	Pred 5, Tac (6–7), MMF 1 g BD
3	72	F	Unknown	MM	–	–	VGPR	Tac (5–6), MMF 500 mg BD
4	67	M	0	SM	5	4	VGPR	Tac (1–3)
5	69	M	6 (A2)	MM	5	3	VGPR	Pred 5, Tac (6–7), MMF 1 g BD
6	82	M	1	MM	15	3	VGPR	Pred 5, Tac (4–6), MMF 250 mg BD
7	57	F	6 (Moderate A2, A24)	MM	7	0.5	No response	Pred 5/25, Tac

note, all 4 patients were concurrently treated with daratumumab, a monoclonal antibody targeting CD38. There was no rejection documented in all patients. **Conclusions:** In this case series, IMiD use in SOT recipients was not associated with SOTr & resulted in hematologic VGPR in 3 out of 4 patients. This contrasts with the majority of existing literature, which suggests a risk of SOTr as IMIDs induce T-cell proliferation, IL-2 & IFN-γ production & inhibit regulatory T-cell function. As all of our patients were concurrently on an anti-CD38 antibody, it raises a hypothesis about daratumumab potentially mitigating the risk of rejection. A recent study demonstrated that anti-CD38 Felzartamab was effective in the treatment of antibody mediated rejection, & while T-cell mediated rejection (TCMR) has been primarily associated with IMiD use, in this study, the anti-CD38 did not induce TCMR. Additional studies exploring optimal IS strategies & the potential role of daratumumab in mitigating rejection risk for SOT patients on IMiD therapy are needed.

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Unravelling the Effect of Subclonal Copy Number Variants on Immune Microenvironment and Survival

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Introduction: In multiple myeloma, subclones—distinct populations of myeloma cells within a patient's tumor—are crucial for understanding disease progression, treatment response, and potential relapse. Analyzing subclone-level changes in transcriptomic data, copy number variation, and their interactions with immune cells is essential for unraveling tumor heterogeneity and identifying potential targets to enhance myeloma treatment. We investigated the genomic characteristics of these subclones and their interactions with immune cells in newly diagnosed multiple myeloma (NDMM) samples. **Methods:** CD138+ scRNA-seq and scATAC-seq multiomic data from NDMM patients (n = 21) were obtained from the published study dbGAP phs003220 (Johnson et al., IMS 2022, PMC11099140). Matched CD138− scRNA-seq data of immune cells were sourced from Sudha et al., IMS 2023. Subclones for each tumor sample were identified using inferCNV (v1.8.1) and a custom-built integration pipeline that utilized both scRNA-seq and scATAC-seq data. Interactions between subclones and immune cell types were identified using CellChat (v1.6.0). Copy Number Abnormality (CNA) profiles between subclones from single-cell and whole genome sequencing (WGS) data (phs003220) were compared, and similarity scores were calculated. Due to differing technologies (RNA-seq vs WGS) and sequencing depth (single cell vs. bulk), this score reflects how well single-cell multiomics captures major chromosomal changes seen in WGS. Subclone-to-immune cell interactions were quantified, and statistical significance of chromosomal abnormalities was analyzed. Survival analysis was performed on the most common myeloma abnormalities. **Results:** On average 45% of copy number variants overlap between WGS and scATAC-seq. Samples with low Jaccard index tend to have more subclones and more complex CNAs. Patients with 1q gain and 13q loss cooccurring in the same clone showed significantly shorter progression-free survival (PFS) ($P = 0.03$) compared to patients with both 1q gain and 13q loss but in separate subclones. In the bone marrow microenvironment, subclones showed the highest interactions with CD8 T cells. Overall, 70% of the patients showed high MIF-CD74/CXCR4 interactions between tumor subclones and immune clusters. Subclones with 13q loss showed significant interactions with all immune cell types ($P < 0.05$) compared to those with normal 13q. In contrast, subclones with 1q gain showed significant interactions with myeloid and myeloid dendritic cells in comparison to those with normal 1q. **Conclusions:** These findings position subclonal CNA profiling as both a prognostic tool and

therapeutic roadmap. Interaction networks—especially myeloid recruitment in 1q+ clones—offer actionable targets to disrupt tumor-immune crosstalk in high-risk MM. Co-occurring 1q gain and 13q loss mark aggressive disease and poor survival, often missed by bulk sequencing. Future work should validate these findings and explore therapies targeting both malignant subclones and immune niches.

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Monosomy 13 and Deletion of 13q Predict Inferior Outcomes in Multiple Myeloma Patients Undergoing Upfront Autologous Transplant

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Introduction: Monosomy 13/deletion(13q) is a common cytogenetic abnormality in multiple myeloma (MM). Although often associated with other high-risk cytogenetic abnormalities (HRCA), its independent prognostic significance remains unclear. **Methods:** We conducted a retrospective, single-center chart review of MM patients who underwent autologous hematopoietic stem cell transplantation (autoHCT) between 2010 and 2021 at our institution with available fluorescence in situ hybridization (FISH) results. HRCA were defined as del(17p), t(4;14), t(14;16), t(14;20), gain/amplification of 1q and del(1p). **Results:** A total of 1,680 patients were included, with monosomy 13/del(13q) identified in 591 cases (35.1%). Monosomy 13 was more common (428, 25.5%) than del(13q) (162, 9.6%). Compared to patients without HRCA or monosomy 13/del(13q) (reference group), those with isolated monosomy 13/del(13q) (n = 77) had significantly shorter progression-free survival (PFS; median 37.3 months vs. 64.6 months, p = 0.0002) and overall survival (OS; median 105.4 months vs. 131.0 months, p = 0.0171). A similar adverse prognostic effect was observed in patients with monosomy 13/del(13q) co-occurring with non-HRCA (n = 162) (median PFS 39.4 months, p < 0.0001; median OS 91.1 months, p = 0.0003). Co-occurrence of HRCA with monosomy 13/del(13q) (n = 352) was associated with shorter PFS (33.9 vs. 48.9 months, p = 0.0020) and OS (81.6 vs. 98.3 months, p = 0.0005) compared to HRCA alone. In subgroup analyses, monosomy 13/del(13q) was associated with inferior PFS in patients with specific HRCAs, including t(4;14), del(17p), and del(1p), but not with gain/amplification of 1q. Finally, multivariate Cox regression analyses confirmed that monosomy 13/del(13q), whether isolated or co-occurring with non-HRCA, was independently associated with inferior PFS (HR 1.36, 95%CI: 1.17–1.58, p = 0.0001) and OS (HR 1.49, 95%CI: 1.21–1.84, p = 0.0002). **Conclusions:** In this large cohort of MM patients who received upfront autoHCT, monosomy 13/del(13q) was an independent adverse prognostic factor, associated with inferior PFS and OS. Its negative impact was evident both in isolation and with concomitant non-HRCA, and was further exacerbated when co-occurring with HRCA, indicating an additive detrimental effect.

PA-267

Tumor-Immune Microenvironment Interaction Drives the Co-Evolution of Multiple Myeloma and Immune Cells in a Novel Mouse Model Engineered with Human Immune System

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Introduction: A variety of pre-clinical mouse models have been established to recapitulate different biological features of multiple myeloma(MM). Depending on the need of the studies, the mice that were used are either immunocompromised (NSG/SCID) or immunocompetent (syngenic/transgenic) with the immune system of the mice. Both models, however, do not truly mimic the immunological feature in MM patients and thus, may not be translationally relevant for the interrogation of MM-immune-microenvironment interaction. We aim to address this deficiency by generating an immunocompetent mouse model, i.e. mice that are humanized with human immune system (humice). We have previously shown its efficacy for MM engraftment and that MM cells grown in humice possess different molecular profile compared to them in non-humice NSG. Here, we decipher how tumor-immune interaction in humice affects the integrity of the immune system and MM responsiveness to immunotherapies. **Methods:** U266-Luc-GFP cells were inoculated into the humice, via teil vein and tumor growth was monitored with bioluminescence imaging. Upon reaching desired tumor burden, we randomized the xenografts into three treatment arms (n = 6); (a)vehicle (b)teclistamab (c)lenalidomide. Serial withdrawal of PBMCs was performed on MM-engrafted (MM-humice) and -non-engrafted humice (non-MM-humice) once every fortnightly for immune profiling via flow cytometry. **Results:** In tumor-free condition, the non-MM humice demonstrated a stable profile for all the principle immune components, namely the CD3+ T cells, CD19+ B cells, CD56+ NK cells and CD14+ monocytes, suggesting an unperturbed immune system without tumor stimulation or immune-tumor interaction. CD138 expression in the PBMC showed a gradual increase in the MM-humice, whereas its expression remains low in the non-MM-humice, suggesting the presence of circulating

malignant plasma cells in the humice and how human immune microenvironment in vivo could support MM growth. This was accompanied by a complex mixture of other immune phenotypes; CD3+ T cells showed a gradual increase in cell population, in tandem with the immune checkpoint PD1 protein. CD19+ B cell population was declining, whereas CD56+ NK cells and CD14+ monocytes displayed a delayed surge in its abundance. While the T helper cell (CD4+,Th) population remain stable, its cytotoxic counterpart (CD8+,Tc) experienced a progressive increase. There was also a fluctuation of naïve (CD45RO+) and memory (CD45RA+) Th and Tc. Teclistamab showed greater efficacy than lenalidomide, associated with enriched Tc and NK cells. **Conclusions:** We showed that, in our humice, immune cells undergo physiological alterations when exposed to MM cells, suggesting that immune integrity may be affected by immune-tumor interaction. The complex immune profile also replicates the immune heterogeneity observed in the patients. Our data therefore supports the use of these humice as a translationally relevant model for studying immune-tumor interactions and testing immunotherapies.

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A Vicious Cycle Between Sensory Nerve Outgrowth and Myeloma Tumor Progression in the Bone Marrow

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Introduction: Bone pain is a common complication in patients with multiple myeloma (MM). Sensory nerve (SN) fibers have been reported to increase and intermingle with MM cells in bone marrow in MM models. However, interactions between MM cells and SNs have not been studied. In the present study, we aimed to explore SN spreading in the bone marrow and clarify the underlying mechanisms of SN neurite outgrowth in MM and the role of SNs in MM progression. **Methods:** Mouse and human MM cell lines were inoculated into the bone marrow of femurs or tibiae in SCID mice to generate in vivo MM models. Femurs or tibiae were resected, and immunostained after optical clearing with CUBIC method. CGRP+ SNs in bone were then visualized by a light sheet microscope. Neurite extension was analyzed with an axon investigation system. MM cell-specific secreted proteins were selected by a comprehensive proteome analysis for culture supernatants. **Results:** The distribution and density of CGRP+ SN fibers were substantially increased in the bone marrow of femurs or tibiae with MM lesions. MM cell supernatants enhanced neurite sprouting and outgrowth of SNs. Among MM cell-specific secreted proteins, neogenin1 (NEO1) stimulated neurite sprouting and outgrowth SNs derived from DRG cells as well as SN cell lines. NEO1 was constitutively overexpressed in MM cells in all 30 patients' bone marrow samples tested. NEO1-knockout (KO) RPMI8226 cells mitigated their neurite outgrowth in vitro and reduced the density of SN fibers in MM bone marrow lesions in vivo, suggesting soluble NEO1 as an MM cell-derived SN elongation factor. Membrane-bound NEO1 is a receptor for repulsive guidance molecule-a (RGM-a) which is abundantly contained in sera. rRGM-a inhibited SN neurite outgrowth and acutely retracted elongated neurites in the presence of NGF. However, addition of rNEO1 almost completely abolished the RGM-a's action. Indeed, rNEO1 and rRGMa formed a complex in a liquid phase as judged by immunoprecipitation. Therefore, soluble NEO1 from MM cells is suggested to induce neurite outgrowth at least in part through acting as a decoy receptor to inhibit RGMa. Intriguingly, the proliferation of MM cells was enhanced in cocultures with SNs. Extracellular vesicles (EVs) isolated from SN supernatants showed potent MM cell proliferation activity. In contrast, pharmacological denervation of SNs by repeated administration of high-dose capsaicin substantially suppressed MM growth in 5TGM1 and JJN3 MM-bearing mouse models. Moreover, NEO1-KO cell growth was attenuated in in vivo models, although rNEO1 did not affect MM growth in vitro. **Conclusions:** MM cells induce neurite hyperplasia in the bone marrow which may increase SN sensitivity to pain and promote MM progression, forming a vicious cycle between SN hyperplasia and MM progression. SNs are implicated as a new niche component in MM, as there has been no previous concept of MM progression being controlled by the peripheral nervous system.

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Combining FISH and CMA Improves the Yield of Detection of 17p Deletion in Myeloma

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Introduction: Recurrent cytogenetic abnormalities in multiple myeloma define disease biology, prognosis, and affect treatment responses. Fluorescence in situ hybridization (FISH) on a CD138 enriched sample is a gold standard for identification of prognostically significant abnormalities including copy number changes and translocation. FISH analysis is limited to the set of probes used, and variability in the breakpoint or size of the deleted/amplified chromosome fragment may affect the sensitivity. Lately single nucleotide polymorphism (SNP) or chromosomal microarray analysis (CMA) technique has been increasingly used for the detection of cytogenetic abnormalities in myeloma and other malignancies. This technique involves hybridization of fragmented DNA to a large nucleotide sequence probes microarray, thus allowing accurate and

sensitive detection of copy number changes of very small chromosomal segments, as well as copy neutral loss of heterozygosity (cnLOH), but is unable to detect balanced translocations. As both FISH and CMA are designed to accurately detect prognostically important copy number changes such as del 17p, gain 1q and del 1p, which are included in the standard FISH probe sets, using both FISH and CMA could be redundant for the detection of these abnormalities. To investigate this question, we compared the sensitivity of del 17p detection using concurrently performed CMA and FISH. **Methods:** Both FISH and CMA were performed on CD138-enriched myeloma samples. CMA was performed using ThermoFisher CytoScan HD microarrays for copy number and heterozygosity alterations. We identified myeloma bone marrow samples analyzed at our institution, for which both FISH with del17p probe and CMA were performed concurrently. **Results:** We identified 355 myeloma bone marrow samples with >5% plasma cells for which both CD138 enriched FISH for 17p deletion and CMA were performed. 17p deletion was identified by both FISH and CMA in 21 (5.9% samples). In additional 15 (4.2%) samples 17p deletion was detected by FISH but not CMA. In additional 11 (3.1%) samples FISH did not detect a 17p deletion, however CMA detected either a 17p deletion encompassing tp53 or monosomy 17. Overall, utilizing both techniques together, 17p deletion was detected in 47/355 (13.2%) samples; while using only FISH it was detected in 36/355 (10.1%) samples and using only CMA it was detected in 32/355 (9%) samples. Additionally, copy neutral loss of heterozygosity (cnLOH) of 17p or 17 was detected by CMA in 4 samples. **Conclusions:** Our results demonstrate that combining FISH and CMA performed on CD138 enriched bone marrow samples results in higher sensitivity of detection of 17p deletion in multiple myeloma, allowing for more accurate risk stratification.

PA-270

Spatial Transcriptomics Profiling Reveals Resistance Mechanisms in Extramedullary Myeloma Plasmacytomas Following CAR T-Cell Therapy

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Introduction: Extramedullary multiple myeloma (EMM) represents an aggressive disease manifestation frequently associated with poor prognosis and therapy resistance. Understanding the tumor clonal heterogeneity and tumor microenvironment of EMM lesions in the context of CAR T-cell therapy is paramount for identifying novel therapeutic targets and informing more effective treatment strategies. **Methods:** We performed comprehensive spatial transcriptomic analysis on 5 distinct EMM samples obtained from five heavily pre-treated multiple myeloma patients failing CAR T-cell therapy (1 Pre-CAR-T lesion, 4 Post-CAR-T lesions). The lesions originated from various anatomical locations (neck mass, liver mass, thigh mass, neck lymph node, epidural tumor). All samples underwent spatial profiling using the CosMx SMI 6k panel. Downstream analysis was performed on selected high quality FOVs from each EMM sample. **Results:** The total number of cells detected on each EMM sample ranged from 20,154 cells to 155,648 cells (mean 61042 cells, total cells 305211), which were largely subdivided into the following cell compartments: Plasma/ B cells, NK/ T cells, Myeloid cells, among others. The average number of genes detected ranged from 114 to 729 genes/cell. Differentially expressed genes derived from sample specific myeloma cell clusters were classified into 3 transcriptional groups and present across multiple samples. Two clusters were more transcriptionally active, one contained a proliferative signature (MKI67, HMGB2, STMN1) while the other upregulated a larger subset of genes (BRAF, BCL2), and a third transcriptionally quiescent cluster. Within the tumor microenvironment, we observed regional confinement of antigen-presenting cells (APCs) and T cells in all EMM samples. Notably, in the liver EMM sample, this confinement was particularly striking, with APCs and CD8 T cells restricted to a small region while over 80% of the tumor consisted of myeloma cells, indicating a generally poor immune infiltrate. Cell communication analysis revealed enrichment of immunosuppressive interactions of myeloid cells amongst themselves (S100A9/CD68 and S100A9/ITGB2) and with CD8 T cells (S100A9/ITGB2 and B2M/KLRD1). These interactions can potentially disturb Myeloid and T cell trafficking to other tumor regions, contributing to the formation of an immunosuppressive microenvironment in EMM. **Conclusions:** Spatial transcriptomics of EMM reveals pronounced inter- and intra-tumoral heterogeneity in both clonal architecture and immune microenvironments. The identification of highly proliferative tumor cells along with immune deserts, spatially restricted T cell/APC niches, and immunosuppressive signaling circuits highlights critical barriers to effective immune surveillance in EMM. These findings underscore the importance of tissue-specific microenvironmental contexts in shaping therapeutic response and provide a rationale for incorporating spatially informed biomarkers and combinatorial immune-modulating strategies in the treatment of EMM.

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Study on Loss of Sex Chromosomes in Peripheral Blood Cells of Patients with Multiple Myeloma: A Cross-Sectional Analysis in Indian Setup

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Introduction: Loss of sex chromosomes has been observed both as an age-related phenomenon in the elderly and in individuals with hematological malignancies. There is a clear gender disparity in multiple myeloma (MM) incidence, with approximately 57% occurring in males and 43% in females. The underlying cause of this disparity remains poorly understood. Differences between genders at the genomic level may contribute to variations in cancer susceptibility, and outcomes. We undertook this study to explore association between the loss of sex chromosomes and MM. **Methods:** An analytical cross-sectional study was conducted across three study populations; MM, non-MM malignancies and healthy control group. The patients were selected irrespective of the status of their disease or chemotherapy. Detailed clinical evaluation was performed followed by a CBC and interphase FISH using dual-color CEP XY probes (MetaSystems) on peripheral blood samples. Following DAPI (4,6-diamidine2-phenylindole) counterstaining, the slides were examined using a Zeiss microscope fitted with FITC-TRITC epifluorescence optics, and a digital camera with ISIS software (Metasystems, GmbH, Altlussheim, Germany). 1000 interphase nuclei were scored for every sample. Nuclei with presence of one or two X chromosomes was used to score the cells. The proportion of the total number counted is used to describe the X and Y loss rate. The relevant FISH findings, clinical data and other laboratory investigation values were cross analyzed and integrated. **Results:** A total of 80 samples (29 MM, 33 non-MM and 18 healthy controls) were analyzed with mean loss of sex chromosome being 0.46 ± 0.25%, 1.7 ± 0.22% and 0.25 ± 0.29% respectively, the difference being statistically significant ($p < 0.0001$). 55% of females had a mosaic loss X chromosome (mLOX) in more than 0.4% cells and 20% of male had a mosaic loss of Y chromosome (mLOY) in more than 0.3% cells. Significant correlation was observed between mLOX and age at menarche (r-0.460; p-0.0016) but not with age at menopause. There was no significant correlation of mLOX/ mLOY with age at onset, prevalence of hypercalcemia, renal dysfunction, anemia and bone lesions in both males and females. **Conclusions:** Loss of sex chromosome was not significantly higher in MM compared to healthy controls and was much less pronounced than non-MM malignancies. A significant correlation exists between sex chromosome loss and age at menarche suggests a possible link between early hormonal parameters and genomic instability. Lack of significant correlation with age at onset and CRAB parameters indicate that sex chromosome loss is not directly associated with disease severity or progression in myeloma. However chromosomal instability may lead to other non-MM malignancies.

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Dual Roles of IRE1α Inhibition in Reversing Mitochondrial ROS-Induced CD8+ T Cell Senescence and Exerting Direct Anti-Tumor Effects in Multiple Myeloma

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Introduction: Multiple myeloma (MM), a hematologic malignancy driven by clonal expansion of plasma cells within the bone marrow (BM) niche, induces profound CD8+ T cell dysfunction through immunosuppressive mechanisms. Our prior work revealed that dysregulation of the IRE1α-XBP1s-SLC38A2 axis impairs glutamine metabolism and drives T cell senescence in MM. However, the mitochondrial mechanisms linking this axis to T cell senescence remain undefined. **Methods:** We performed single-cell RNA sequencing to profile mitochondrial pathways in MM-derived and healthy CD8+ T cells. Genetic silencing of XBP1s/SLC38A2 was coupled with flow cytometric quantification of mitochondrial reactive oxygen species (mtROS). Pharmacological inhibition of IRE1α (compound 17#) was evaluated for its dual effects on T cell rejuvenation and MM suppression using nutrient-deprived primary T cells, patient-derived BM samples, and MM cell lines. RNA sequencing was employed to disclose pathway alterations in T cells treated with 17#. The therapeutic potential was validated in the genetically engineered Vk*MYC mouse model. **Results:** Single-cell RNA sequencing analysis uncovered marked downregulation of mitochondrial respiration components and SLC38A2-mediated glutamine transport in MM patient-derived BM CD8+ T cells, accompanied by elevated oxidative stress markers. Mechanistically, XBP1s knockdown in CD8+ T cells reduced mtROS accumulation, while SLC38A2 genetic ablation exacerbated mtROS production. Compound 17# significantly reduced senescence marker KLRG1 expression and increased perforin expression in nutrient-deprived BM CD8+ T cells from healthy donors and in BM CD8+ T cells from MM patients, while promoting T cell proliferation. Importantly, 17# did not impair the viability of peripheral blood mononuclear cells from healthy donors or alter the immune phenotypes of normal CD8 + T cells. Transcriptomic profiling revealed 17#-mediated activation of the NPR2-cGMP-PKG signaling axis, which correlated with enhanced T cell function. Notably, 17# exhibited direct anti-myeloma activity and reduced tumor burden in Vk*MYC mice,

paralleled by decreased mtROS in BM CD8+ T cells and reduced KLRG1+CD57+CD28− senescent T cell frequency. **Conclusions:** Targeting the IRE1α-XBP1s axis simultaneously reverses T cell senescence through mtROS modulation via the SLC38A2/NPR2-cGMP-PKG cascade and exerts direct anti-myeloma effects. This dual-action therapeutic strategy addresses both microenvironmental immunosuppression and malignant cell growth, demonstrating significant translational potential for MM treatment.

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Insights into Ubiquitination-Associated Genes in Multiple Myeloma: A Multi-Omics Mendelian Randomization Study

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Introduction: Multiple myeloma (MM), a malignant plasma cell disorder with age-related incidence, presents bone pain, anemia, and renal dysfunction. Current therapies (chemotherapy, proteasome inhibitors) face challenges like resistance, toxicity, and cost. Ubiquitination influences MM progression via protein degradation and DNA repair, yet its specific roles in drug resistance remain unclear. This Mendelian randomization study integrates multi-omics (eQTLs/mQTLs/pQTLs) and GWAS data to identify causal ubiquitination-related genes and methylation/expression regulators using SMR analysis. By uncovering pathogenic mechanisms and therapeutic targets, this framework aims to address treatment limitations and advance precision strategies for MM. **Methods:** This study used multi-omics Mendelian randomization (MR) approach to explore the causal associations between ubiquitination-related genes and MM. The analysis integrated genome-wide association study (GWAS) data from the UK Biobank (discovery dataset) and FinnGen R11(validation dataset), along with blood methylation quantitative trait loci (mQTLs), expression QTLs (eQTLs) and protein QTLs (pQTLs). The summary data-based MR (SMR) method and HEIDI test were employed to evaluate the associations and pleiotropy. Colocalization analysis identified shared genetic variants, and the integration of eQTLs, mQTLs, and pQTLs data explored the causal associations between DNA methylation, gene expression, and protein abundance. **Results:** This study integrated MM GWAS with ubiquitination-associated blood mQTLs, eQTLs, and pQTLs to identify causal genetic-epigenetic interactions. SMR analysis revealed 70 MM-associated methylation sites (48 genes), including SPOP with opposing effects: cg14245135 increased risk (OR = 1.37) and cg05551217 decreased it (OR = 0.53). Nine ubiquitination-related genes (e.g., EED, SPOP, UBAP1) showed divergent MM associations via eQTLs, while pQTLs implicated STC1 (protective) and TNFAIP3 (risk). Multi-omics integration highlighted LTN1, SPOP, and UBAP1, where methylation (e.g., SPOP's cg14245135/cg05551217) bidirectionally regulated gene expression and MM risk. Hypermethylation at LTN1 sites suppressed expression, elevating risk, whereas UBAP1 hypomethylation reduced expression, increasing susceptibility. Colocalization supported most methylation effects (except LTN1's cg24692254) and UBAP1 expression, though FinnGen validation failed for eQTL/pQTL findings. Epigenetic modulation of ubiquitination-related genes—particularly SPOP's dual methylation effects—underscores complex gene-environment interactions in MM pathogenesis. **Conclusions:** Our findings highlight the potential causal roles of ubiquitination-related genes, particularly LTN1, SPOP, and UBAP1, in MM pathogenesis. Future study should focus on validating these genes to develop targeted therapeutic strategies.

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Retrospective Analysis of Molecular Profile of Plasma Cell Myeloma at Diagnosis

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Introduction: Plasma cell myeloma is a malignant disorder characterized by clonal proliferation of bone marrow plasma cells. Somatic mutations frequently occur as secondary events in the development of plasma cell myeloma. Common recurrent mutations implicated in plasma cell myeloma include those involving KRAS, NRAS, BRAF and TP53 genes and they are potentially targetable with new therapeutics. The primary objective was to determine the prevalence of the NRAS, KRAS, BRAF and TP53 mutation in newly diagnosed plasma cell myeloma patients. The secondary objectives included (i) analysis of the progression free survival (PFS) and overall survival (OS) of the RAS/BRAF mutated group and the unmutated group and (ii) the baseline prognostic factors on PFS and OS in newly diagnosed plasma cell myeloma patients **Methods:** This is a retrospective cohort study of 33 patients aged between 18–65 year-old who were diagnosed with symptomatic plasma cell myeloma between January 2017 to December 2022 in Princess Margaret Hospital. DNA from bone marrow was extracted by standard procedures using QIAamp DNA Blood Mini Kit. Next generation sequencing was performed to detect mutations in four commonly mutated genes in plasma cell myeloma (KRAS, NRAS, BRAF and TP53) using a commercial TruSight Tumor 15 sequencing panel according to manufacturer's protocol. **Results:** 14 out of 33 subjects had either KRAS/NRAS or BRAF mutation. 1 patient had TP53 mutation. There was no significant difference in both PFS and OS in RAS/BRAF mutated and unmutated group. Univariate analysis showed receiving ASCT was a favourable factor for both OS and PFS, while the presence of deletion 17p was associated with poorer overall

survival. In multivariate analysis, RAS/BRAF mutation did not demonstrate negative impact both on overall survival and progression free survival. Presence of deletion of 17p remained an independent prognostic factor in both OS and PFS. ASCT had a positive impact both on progression free survival and overall survival. **Conclusions:** RAS/BRAF mutation did not show any prognostic effect in PFS and OS in newly diagnosed multiple myeloma patient in this study. Further study will be needed to evaluate its clinical utility in newly diagnosed multiple myeloma patients.

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Genomic Profiling of Multiple Myeloma via Optical Genome Mapping: An Exploratory Analysis of Response and Progression in Newly Diagnosed and Relapsed Disease

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Introduction: Multiple myeloma (MM) is characterized by genomic complexity and risk-stratified by cytogenetic abnormalities. Optical genome mapping (OGM) provides a high resolution genome wide platform capable of detecting both structural variants (SV) and copy number variants (CNV) beyond the scope of conventional cytogenetics. It may uncover novel cytogenomic complexity with potential prognostic and therapeutic relevance. **Methods:** Two cohorts of patients from two major cancer centers in the US underwent OGM detection. Clinical data was collected including clinical features such as Extramedullary disease (EMD), plasma cell leukemia (PCL), Line of therapy (LOT) and treatment regimens before/after OGM, response to therapy after OGM. CNV burden and SVs such as chromoanagenesis and MYC rearrangements were assessed from OGM data. Associations between genomic findings and clinical outcomes were performed using Fisher's exact test for response status and log-rank test for OS. **Results:** This study included a total of 83 patients, 46 newly diagnosed MM (NDMM) and 37 relapsed refractory MM (RRMM). In the NDMM cohort (median follow up from diagnosis was 15.2 mo [95% CI, 13.9–17.4]) induction regimens varied (78% D-VRd, 13% DRd, others D-CyBorD or KRd). 13.6% exhibited chromoanagenesis, 30.4% harbored MYC rearrangements. One-year OS rate in chromoanagenesis-positive patients is lower compared with patients without chromoanagenesis (0.8 [95% CI, 0.52, 1.0] vs. 0.94 [95% CI, 0.87, 1.0]), however, this difference in OS was not significant (p-value = 0.245). In the RRMM cohort (median follow up 81.2 mo [95% CI, 59.8–169]), patients had a median of 3 prior LOT (range 1–12) before OGM. Post-OGM 94.6% received additional therapy, including CAR-T (n = 6), bispecifics (n = 13), Dara-based triplet or quadruplet (n = 7), hypercytoxan (n = 3). Chromoanagenesis was identified in 31.4% of RRMM, and MYC rearrangements in 32.4%. Chromoanagenesis was significantly more common in patients with RRMM compared with NDMM (p = 0.08). It is also more common in patients with EMD /PCL, occurring in 7 of 15 cases (47%), compared to only 14 of 68 patients (21%) without (p = 0.05). Interestingly, high-risk cytogenetic features by conventional cytogenetics—were observed in 75% of EMD/PCL cases and 60% of non-EMD/PCL cases, a difference that was not statistically significant (p = 0.39). **Conclusions:** Cytogenomic aberrations, such as chromoanagenesis detected by OGM, may be associated with inferior survival, aggressive clinical features such as EMD and PCL, and clonal evolution acquired during disease progression from NDMM to RRMM. These findings suggest that cytogenomic profiling may enhance the current prognostic tools for risk stratification in NDMM. Prospective validation in larger cohorts is warranted to support the integration of cytogenomic data into clinical decision-making.

PA-276

Macrophages Promote Aberrant DNA Repair in Multiple Myeloma Via the CXCL5/CXCR2 Axis

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Introduction: Multiple myeloma (MM) is closely associated with abnormal DNA repair and genome instability. The bone marrow (BM) microenvironment, particularly myeloma associated macrophages (MΦs) is critical to the progression of MM. However, there is limited understanding on the role of MΦs in DNA repair in MM. **Methods:** Western blot, RT-qPCR, flow cytometry, immunofluorescence and immunohistochemistry, comet assay, Single-cell RNA sequencing, transient siRNA transfection, Second-generation sequencing, HR and NHEJ reporter assays and MM xenograft model were conducted in the research. **Results:** Our study found that MΦs promoted DNA repair in MM cells by the CXCL5/8-CXCR2 axis

both in vitro and in vivo, and protected MM cells progression after DNA damage. However, Other non-tumor cells, like T, NK, neutrophils from peripheral blood and stromal cells in bone marrow, had no such effect of significantly enhancing DNA repair of MM cells. MΦs mainly promoted to the repair of DNA double-strand breaks (DSBs) in MM cells through the non-homologous end joining (NHEJ) pathway both in vitro and in vivo, rather than the homologous repair (HR) pathway to reduce the accuracy of DNA repair. In addition, MΦs increased the probability of chromosomal translocations in MM cells. Furthermore, clinical data confirmed that MΦs are closely associated to the genetic complexity of MM patients' primary cells. MΦs from high cytogenetic risk MM patients had more significant effect of enhancing MM cells DNA repair. **Conclusions:** We demonstrate that cocultured MΦs protected MM cells by promoting DSB repair via CXCL5/8-CXCR2 axis. MΦs enhanced the NHEJ pathway, but reduced repair accuracy and promoted chromosomal translocations in MM cells. The study elucidates a mechanism by which MΦs regulates DNA repair in MM in the microenvironment and provides a potentially new target to counter MM progression.

PA-277

Crosstalk Between m6A and H3K27ac via the YTHDC1-EP300 Feedback Loop Promotes Myelomagenesis

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Introduction: Multiple myeloma (MM) is an incurable hematological malignancy characterized by clonal plasma cell infiltration of the bone marrow and secretion of monoclonal immunoglobulins. In addition to genetic abnormalities and tumor-microenvironment interactions, epigenetic dysregulation has emerged as a key player in MM pathogenesis. Among these, N6-methyladenosine (m6A), the most abundant internal RNA modification, regulates RNA metabolism through the dynamic interplay of writer, eraser, and reader proteins. Aberrant expression of m6A modifiers is frequently observed in cancer and exerts either oncogenic or tumor-suppressive effects in a cancer type-dependent manner. However, the precise roles and mechanisms of m6A modifiers in myelomagenesis remain unclear. **Methods:** We conducted a series of in vitro and in vivo experiments, including cell culture, primary MM cell isolation, lentiviral transfection, CCK-8 assays, colony formation assays, flow cytometry, xenograft models, RT-qPCR, Western blotting, and RNA decay assays. Multi-omics analyses, including RNA-seq, RIP-seq, MeRIP-seq, ChIP-seq, and ATAC-seq, were also performed. **Results:** We identified that the m6A reader protein YTHDC1 plays a critical role in myelomagenesis. YTHDC1 is significantly overexpressed in MM cells compared to normal cells from healthy donors, and its elevated expression correlates with poor prognosis. Functional experiments in vitro and in vivo demonstrated that YTHDC1 promotes MM cell proliferation, regulates cell cycle progression, and modulates DNA damage repair in an m6A-dependent manner. Through integrative analyses of transcriptomic profiling, YTHDC1 RIP-seq, m6A MeRIP-seq, and MM patient cohort data, we identified EP300, which encodes the histone acetyltransferase p300, as a direct downstream target of YTHDC1. Mechanistically, YTHDC1 recognizes and binds to m6A-modified EP300 mRNA, enhancing its stability and promoting its overexpression in MM cells. Furthermore, p300 functions as a histone acetyltransferase and transcriptional coactivator, enhancing YTHDC1 transcription by mediating H3K27ac and recruiting TFs of IRF3 and IRF4 to the YTHDC1 promoter. These findings suggest a positive feedback loop between YTHDC1 and EP300, in which epitranscriptomic and epigenetic mechanisms cooperate to drive MM development. **Conclusions:** This study explored the crosstalk between RNA m6A and histone H3K27ac in MM, proposing a novel positive feedback loop between YTHDC1 and EP300 that promotes myelomagenesis, highlighting the YTHDC1-EP300 axis as a promising target for therapeutic intervention.

PA-278

NAMPT in Myeloma-Associated Macrophages Drives Drug Resistance through Mitochondrial Metabolic Reprogramming and Immune Evasion via the SIRT1/STAT3/SPP1 Axis

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Introduction: The immunosuppressive microenvironment remains a major challenge in multiple myeloma (MM) treatment. As key participants, the role of myeloma-associated macrophages (mMΦs) is still unclear. Nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the NAD+ salvage pathway, is overexpressed in various cancers and immune cells. Through sc-RNA seq analysis, we identified a subset of macrophages with high NAMPT expression associated with MM progression and contributed to drug resistance and immune evasion. This study further investigated the regulatory role of NAMPT in mMΦs. **Methods:** n/a **Results:** NAMPT knockdown (KD) or inhibition with FK866 reprogrammed mMΦs toward an M1-like phenotype, characterized by decreased M2 markers (CD163, CD206) and increased M1 markers (CD80, CD86) and pro-inflammatory cytokines (IL-1β, IL-6). In co-culture experiments, NAMPT-deficient mMΦs significantly enhanced bortezomib (Bor)-induced apoptosis of H929 and JJN3 cells compared to controls. Intratumoral injection of NAMPT-KD or FK866-inhibited mMΦs attenuated tumor growth and restored Bor

sensitivity in xenograft NCG mice. Supplement of NAMPT catalytic product NMN reversed these effects in vitro and in vivo, confirming the essential role of NAMPT in macrophage-mediated drug resistance. Mechanistically, NAMPT maintained mitochondrial homeostasis by preserving NAD+ pools and redox balance (NAD+/NADH ratio). NAMPT depletion triggered mitochondrial dysfunction, evidenced by (1) reduced ATP production and oxygen consumption rate (OCR); (2) collapsed membrane potential measured by JC-1 staining; and (3) abnormal mitochondrial morphology, such as lost and whorled cristae by TEM. Beyond cell-intrinsic effects, NAMPT-hi mMΦs suppressed T cell function. NAMPT-deficient mMΦs reinvigorated CD8+ T cell function, boosting IFN-γ and granzyme B expression while reducing exhaustion markers (TIM-3, LAG-3). Transcriptomics and functional validation identified SPP1 as NAMPT downstream target of NAMPT. SPP1-deficient mMΦs similarly enhanced T cell cytotoxicity, but these effects were insensitive to NMN supplementation. Further mechanistic studies revealed that NAMPT sustains SIRT1 activity through NAD+ maintenance. Using Co-IP and ChIP assays, we demonstrated that SIRT1-mediated deacetylation enhanced STAT3 binding to the SPP1 promoter, driving its transcriptional activation. This NAMPT-NAD+-SIRT1-STAT3-SPP1 axis ultimately enabled mMΦs to suppress T cells and promote MM progression. **Conclusions:** Our study identified NAMPT-hi mMΦs as key drivers of multiple myeloma progression, orchestrating both drug resistance and immune evasion. Targeting NAMPT reprogrammed macrophages toward a M1-like phenotype, enhanced bortezomib sensitivity by disrupting mitochondrial homeostasis, and restored CD8+ T cell function through the NAD+-SIRT1-STAT3-SPP1 axis.

PA-279

NEDD4-1-Mediated Ubiquitination of CCR7 Reprograms Macrophage Function and Enhances theraputic Sensitivity in Multiple Myeloma

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Introduction: Drug resistance in multiple myeloma (MM) is associated with MM-associated macrophages (mMΦs). Although the E3 ubiquitin ligase NEDD4-1 has been shown to enhance MM cell sensitivity to Bortezomib (Bor), its role in modulating mMΦs functional properties to improve drug efficacy remains unclear. **Methods:** Immunofluorescence and Western blot were assessed to detect the expression level of NEDD4-1 in mMΦs differentiated from bone marrow of MM patients and peripheral blood mononuclear cells of healthy donors. Transfection of mMΦs with small interfering RNA and overexpressed plasmids was carried out to construct a knockdown and overexpression model of the NEDD4-1 gene. Expression of pro-inflammatory factor in mMΦs and mMΦs polarization phenotype were assessed by cytokine array, qPCR, and ELISA. The expression of CD206 in mMΦs and apoptosis of MM cells were detected by flow cytometry. The NEDD4-1 substrate protein CCR7 was screened and validated using mass spectrometry-based proteomic analysis and Co-IP. The mutant plasmid of Lys 342 site of CCR7 was transfected into mMΦs, and the degree of its ubiquitination was detected by ubiquitination co-precipitation assay. **Results:** We observed that as M-CSF induced the differentiation of healthy donor PBMCs into macrophages, the expression of NEDD4-1 gradually increased, accompanied by a progressive elevation in the expression of the M2 marker CD206. Then, we established NEDD4-1 knockdown (KD) and overexpression (OE) models using adenovirus vectors in mMΦs, detection revealed that the NEDD4-1-KD group exhibited decreased expression of iNOS, IL-6, CCL5 and CXCL10 along with increased expression of ARG-1, CD206, and IL-10. Additionally, its protective effect on primary MM cells and cell lines was attenuated in co-culture conditions. In contrast, the NEDD4-1-OE group showed the opposite trends. The above evidence suggested that macrophages with low NEDD4-1 expression tend to exhibit M2 polarization phenotype. In vivo, NEDD4-1KD or OE mMΦs in xenograft NCG mice revealed that high NEDD4-1 mediated M1 macrophage polarization to decrease tumor burden. Mechanistically, further analysis revealed that NEDD4-1 bound to CCR7, and mediated K63-linked ubiquitination at the Lys 342 site of CCR7, impairing CCR7 membrane function and suppressing mMΦs transition to the M2 phenotype. **Conclusions:** This study demonstrates that NEDD4-1 hindered MΦ polarization toward the M2 type by facilitating K63-linked ubiquitination of CCR7 at Lys342, ultimately enhancing Bor sensitivity in MM cells. These findings provide novel insights into MM drug resistance mechanisms and highlight potential therapeutic targets.

PA-280

The m5C-Binding Protein YB-1 Modulates Proteasome Inhibitors Resistance in Multiple Myeloma Via Epigenetic Modification

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Introduction: Multiple myeloma (MM) is a malignant proliferative disorder of plasma cells, and resistance to proteasome inhibitors (PIs) represents a major obstacle in MM treatment. Emerging evidence suggests that 5-methylcytosine (m5C) plays a pivotal role in driving MM drug resistance, although the underlying mechanisms remain unclear. Notably, previous studies have established that Y-box binding protein 1(YB-1) functions as a cytoplasmic m5C reader, regulating RNA metabolism through diverse mechanisms. **Methods:** Bone marrow samples from MM patients and peripheral blood

mononuclear cells from healthy donors were collected after obtaining informed consent. CD138+ cells were isolated via positive selection using CD138-conjugated microbeads. The human myeloma cell lines were transfected with short hairpin RNA lentiviral particles in order to obtain stable cell lines with different YB-1 expression levels. Cell viability was evaluated using flow cytometry and cell counting kit-8 assays. **Results:** Here, we found that YB-1 is highly expressed in CD138+ cells isolated from MM patients compared to healthy donors and is associated with poor prognosis. In vitro experiments suggested that YB-1 knockdown could greatly trigger the apoptosis of MM cells and induce G2 phase arrest under the treatment of PIs. We restored YB-1 expression by overexpressing wild-type (WT) YB-1 or the binding deficient mutant YB-1-Mut(W65F) on the basis of YB-1 knockdown. Subsequently, we observed that the restoration of WT-YB1, but not YB-1-Mut(W65F), substantially rescued the survival of MM cells under PIs treatment, indicating that YB-1 regulates PIs resistance in MM in a m5C-dependent manner. To identify YB-1-mediated downstream effectors modulating MM PIs resistance, we conducted multiple high-throughput sequencing analyses (Bis-seq, RIP-seq, and RNA-seq) and obtained three potential downstream targets (SESN2, ZFP36, TTYH3). Further analysis of MM patient gene expression profiles suggested a stronger correlation between YB-1 and SESN2. We conducted an RNA decay assay in MM cells and our data showed that YB-1 maintains SESN2 mRNA stability by binding to its m5C methylation sites. SESN2 is a highly conserved stress-induced protein that protects cells from external factors such as stress and autophagy. Based on survival analysis, we found that high expression of SESN2 is associated with poor prognosis of MM patients. Furthermore, in vitro phenotypic assays showed that the depletion of SESN2 significantly enhanced the killing effect of PIs on MM cells, while the supplementation of SESN2 substantially rescued the PIs sensitivity of MM cells resulting from YB-1 deficiency. **Conclusions:** In summary, our study reveals that YB-1 confers PIs resistance by stabilizing SESN2 mRNA via m5C modification in multiple myeloma. This discovery unveils a novel epigenetic mechanism underlying drug resistance and identifies YB-1 as a potential therapeutic target for overcoming chemoresistance in MM treatment.

PA-281

LILRB4 Drives Daratumumab Resistance in Multiple Myeloma via STAT3/PIM1 Activation and Lipid Metabolic Reprogramming of the Immune Microenvironment

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Introduction: Multiple myeloma (MM), characterized by malignant proliferation of plasma cells, remains an incurable hematologic malignancy despite therapeutic advancements. The introduction of anti-CD38 mABs like daratumumab (Dara) has significantly improved clinical outcomes. However, drug resistance and relapse remain major clinical challenges, with the underlying mechanisms being not fully understood. Exploring resistance mechanisms and identifying sensitization strategies are critical priorities in current research. **Methods:** Single-cell RNA sequencing (ScRNA-seq) was performed on CD138$^+$ tumor cells from Dara-resistant MM patients. Lentiviral transduction generated isogenic MM cell lines with leukocyte immunoglobulin-like receptor B4 (LILRB4) overexpression (OE) or CRISPR/Cas9-mediated knockout (KO). **Results:** ScRNA-seq data derived from Dara resistant patients to revealed a significantly elevated expression of LILRB4 in the residual resistant tumor cells. However, Flow cytometry analysis indicated that alterations in LILRB4 expression did not significantly affect the expression of CD38. This finding suggests that LILRB4 mediates resistance is independent of target antigen regulation. Subsequent Transcriptomics demonstrated that LILRB4 upregulates the STAT3/ proviral integration site for PIM1 pathway at the transcriptional level. High PIM1 expression not only promotes the proliferation of MM cells but also enhances the resistance of tumor cells to natural killer (NK) cell-mediated cytotoxicity by suppressing pro-apoptotic signals. In clinical cohorts, patients with high PIM1 expression exhibited significantly shorter overall survive. Mechanistically, gene set enrichment analysis (GSEA) indicated that LILRB4 OE activates the cholesterol synthesis pathway. Moreover, we observed that LILRB4 significantly regulates intracellular protein acetylation. These findings indicate that LILRB4 might modulate lipid metabolism to exert an impact on acetyl-CoA supply. Consequently, this activates the STAT3 pathway and upregulates the expression of downstream PIM1. Further investigations have demonstrated that LILRB4 is capable of reshaping the immune microenvironment through the regulation of tumor cell lipid metabolism. Specifically, overexpression of LILRB4 in MM cells leads to an increase in lipid secretion. This, in turn, suppresses the activity and cytokine release of NK cells within the microenvironment. This immunosuppressive effect synergizes with the upregulation of PIM1 to establish a dual "metabolic-immune" resistance barrier. PIM1 directly promotes tumor survival, while abnormal lipid metabolism impairs the function of immune cells, indirectly reducing Dara Antibody-dependent cellular cytotoxicity (ADCC). **Conclusions:** Our findings show LILRB4 is a master regulator of Dara resistance via STAT3/PIM-mediated proliferation and lipid-driven NK cell dysfunction. Co-targeting this axis with PIM inhibitors and lipid metabolism modulators may overcome resistance, guiding precision immunotherapy in MM.

PA-282

Pan-RAS Inhibitor RMC-6236 Suppresses Myeloma Growth and Shows Enhanced Efficacy with SWI/SNF Inhibition

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Introduction: Oncogenic RAS signaling is a central driver of multiple myeloma (MM), with alterations in KRAS, NRAS, or FGFR3 present in nearly half of all cases. The development of tri-complex pan-RAS inhibitors offers a promising strategy to address this critical therapeutic gap in MM. **Methods:** We evaluated the anti-myeloma activity of novel pan-RAS inhibitors, RMC-6236 and RMC-7977, across a broad panel of over 50 MM cell lines. Drug effects and mechanisms were assessed using viability assay, phospho-proteomics, Western blotting, and proximity ligation assays (PLA). In vivo anti-tumor activity and toxicity were tested using MM xenograft models. High throughput drug combination screens explored synergy effect with several agents targeting cell cycle, mTORC1/2, and SWI/SNF complex. **Results:** RMC-6236 and RMC-7977 induced potent and selective cytotoxicity in KRAS-, NRAS-, and FGFR3-dependent MM lines, with IC50 values in the low nanomolar range. In vivo, daily oral administration of RMC-6236 (10 mg/kg) significantly suppressed tumor growth without observable toxicity. Phosphoproteomic analysis showed decreased phosphorylation of MAPK1/3 and mTORC1 substrates (EIF4EBP1, RPS6KA3, RPS6). Western blots confirmed reduced phosphorylation of MEK (S217/221), S6K (T389), and RPS6 (S235/236), indicating suppression of MAPK and mTORC1 signaling following RMC-6236 treatment. PLA demonstrated that RMC-6236 disrupted interactions between RAS and its downstream effectors MEK, MTOR, and SLC3A2. High throughput combinatorial drug screens discovered that RMC-6236 was highly synergistically toxic in combination with SWI/SNF inhibitor FHD-286. Combined treatment with RMC-6236 and FHD-286 induced potent apoptosis and robust tumor growth suppression in xenograft models. **Conclusions:** Our findings demonstrate that RMC-6236 shows broad and potent anti-tumor activity in RAS- and FGFR3-driven MM by suppressing MAPK and mTORC1 signaling. Its therapeutic efficacy is significantly enhanced in combination with SWI/SNF inhibitor FHD-286. These findings represent a promising therapeutic strategy that supports further clinical investigation in RAS-dependent MM.

PA-283

Fueling the Fighters: Cytokine-Driven Optimization of Allogeneic NK Cells for Multiple Myeloma Immunotherapy

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Introduction: Allogeneic NK cells are promising candidates for cell-based immunotherapy against multiple myeloma (MM), readily obtainable from peripheral blood. Their therapeutic application is further enhanced by the low risk of GvHD. However, clinical applications are hampered by donor heterogeneity and a lack of standardized ex vivo expansion protocols. This study aimed to develop an optimized ex vivo expansion protocol suitable for NK cells obtained from the majority of donors. **Methods:** Isolated primary NK cells from healthy donors were expanded over five weeks in Miltenyi NK MACS medium supplemented with three combinations of interleukins (ILs) IL-2, IL-15, and IL-21. We established a comprehensive pipeline to assess NK cell fitness, phenotype, and functionality against MM cell lines. First, we evaluated proliferation and viability, followed by analysis of key surface receptor expression related to NK cell activation, inhibition, and exhaustion. Lastly, we assessed pivotal NK metabolic fitness, degranulation, and cytotoxicity. **Results:** The continuous NK cell profiling during ex vivo culture revealed donor-specific responses to IL combinations. Based on their expansion and viability profiles in different IL conditions, NK cells were classified into three functional groups. Group 1 exhibited enhanced proliferation and viability in IL-15 + IL-21, with increased expression of activation markers during culture. However, when cultured in IL-2 + IL-15, the same cells demonstrated moderate proliferation but higher degranulation and cytotoxicity (e.g., 74% vs. 47% on day 7). Group 2 maintained robust growth in both IL-15 + IL-21 and IL-2 + IL-15 conditions, showing no significant differences in key marker expression, but cytotoxicity was significantly higher in IL-15 + IL-21 (e.g., 86% vs. 26% on day 14), alongside increased degranulation. Group 3 showed superior expansion and viability in IL-2 + IL-15 conditions. This group demonstrated downregulation of inhibitory CD161, with upregulation of activation markers CD69 and NKG2D. Although degranulation did not vary significantly across conditions, cytotoxicity was markedly higher in IL-2 + IL-15 (e.g., 64% vs. 12% on day 7). Moreover, a combination of IL-2 and IL-21 did not sustain NK cells beyond two weeks, whereas IL-15 proved to be crucial for NK cell proliferation and maintenance. **Conclusions:** Robust NK cell expansion while preserving cytotoxic function is critical for developing reliable "off-the-shelf" immunotherapies, particularly in the context of CAR-NK cell therapies against

MM and other hematological malignancies. Our findings emphasize substantial primary NK cell donor-to-donor variability and distinct functional responses to different IL combinations during long-term ex vivo expansion. Our findings warrant further analysis in a larger donor cohort to refine and validate expansion protocols that ensure consistent potency and clinical applicability of primary NK cell-based therapies for MM.

PA-284

Quadruplet Therapy and ASCT in Multiple Myeloma: Does It Increase Toxicity?

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Introduction: El tratamiento de los pacientes con mieloma múltiple (NDMM) recién diagnosticados elegibles para trasplante autólogo de células madre (ASCT) en la práctica clínica real se basa en la combinación de inhibidores del proteasoma, fármacos inmunomoduladores y esteroides, con la posible adición de un anticuerpo monoclonal anti-CD38. **Methods:** OBJECTIVES: To assess whether quadruplet therapy (QT) increases the risk compared to triplet therapy (TT) in terms of peripheral blood hematopoietic stem cell (PBHSC) mobilization difficulties, hematological toxicity, need for blood products, and other complications related to myelotoxicity. MATERIALS AND METHODS: Análisis retrospectivo unicéntrico de una cohorte de pacientes tratados con TT o QT entre 2013 y 2025, a los que posteriormente se les realizó un TCMA. Se recogieron datos de 73 pacientes y 83 procedimientos de TCAS. **Results:** Clinical and biological characteristics (age and sex distribution) were similar in both groups. Forty patients received TT and 33 received QT. Ten patients underwent tandem ASCT (6 from the TT group and 4 from the QT group). Conditioning regimens consisted of MEL200 in 59 patients, BuMel in 12, and MEL140 in another 12. The use of plerixafor was similar between groups. Although there was a percentage difference, it was not statistically significant ($p = 0.183$). Statistically significant differences were found in the number of procedures required for PBHSC collection in the QT group ($p = 0.02$). Regarding procedure-related toxicity: the median recovery time for neutrophils and platelets was 10.5 and 13 days in the TT group, and 11 and 14 days in the QT group, respectively. Platelet recovery was significantly delayed in the QT group ($p = 0.046$). The median red blood cell transfusion requirement was 2 units in both groups; platelet transfusions were 2 in the TT group and 3 in the QT group. No significant differences were found in febrile neutropenia or mucositis incidence or grade. La mediana de estancia hospitalaria fue de 15 días en el grupo TT y de 18 días en el grupo QT, con diferencias estadísticamente significativas ($p = 0,044$). La mortalidad relacionada con el tratamiento fue 0 en ambos grupos. **Conclusions:** Los anticuerpos monoclonales representan un avance clínico significativo, demostrando un perfil de seguridad favorable. En nuestra experiencia, su uso no aumenta la toxicidad de ASCT. Aunque se observaron más procedimientos de recolección de PBHSC, estancias hospitalarias prolongadas y recuperación tardía de plaquetas, estos no resultaron en un aumento de los requisitos de transfusión.

PA-285

Secondary Clones Identified by Mass Spectrometry in Baseline Samples Remain Stable or Disappear Early During Monitoring in Multiple Myeloma Patients

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[1]The Binding Site (part of Thermo Fisher Scientific)

Introduction: Mass spectrometry offers improved sensitivity over electrophoretic methods for identifying and quantifying monoclonal proteins. Besides the main M-protein, it can identify secondary, low-level M-proteins not previously reported by standard methods, with unknown clinical significance. We report on dynamic changes of secondary M-proteins identified by mass spectrometry and their clinical relevance in patients with active disease. **Methods:** The study included 62 intact immunoglobulin multiple myeloma patients, with at least one follow-up sample taken within 6(±3) months from baseline. Serum samples were analyzed with the Immunoglobulin Isotypes (GAM) for the EXENT® Analyzer (The Binding Site, part of Thermo Fisher Scientific). M-proteins were identified and quantified in baseline samples by the EXENT System and compared to immunofixation and serum protein electrophoresis (SPE) results. Secondary M-proteins were defined as monoclonal intact immunoglobulins (IgG, IgA, IgM) < 0.200 g/L and ≥0.015 g/L, or kappa and lambda only peaks with no associated heavy chain. Persistent M-proteins were defined by their presence during follow-up, based on the same m/z value (±4). **Results:** The EXENT System correctly identified the main M-protein in baseline samples from all patients (28 IgGκ, 16 IgGλ, 7 IgAκ, 8 IgAλ, 2 IgMκ, 1 IgMλ). Median M-protein levels were 19.3 g/L (0.2–76.6) by EXENT and 21.2 g/L (6.0–69.4) by SPE. The EXENT System identified at least one secondary M-protein < 0.200 g/L in 29 (47%) patients. Secondary M-proteins were IgM in 33% of cases, IgA in 5%, IgG in 9%, κ in 28%, and λ in 23%. All primary M-proteins ≥0.200 g/L reported in baseline samples by the EXENT System were still present after 6 (±3) months of follow-up, whereas only 10 out of 43 (23%) secondary M-proteins (from 9 patients) persisted during this period. Most persistent secondary M-proteins were IgM (60%), and none had

increased relative to baseline levels during follow-up. 52% of patients with secondary M-proteins at baseline experienced progressive disease, compared to 39% of those with no secondary clones; however, time-to-progression was not significantly different (1009 vs. 869 days; log-rank = 0.50). Persistence of secondary clones over the first 6 months of follow-up did not seem to be associated with an increased risk of progression (1282 vs. 1009 days for patients with vs. without persistent clones; log-rank = 0.82). **Conclusions:** The EXENT System offers detailed characterization of the clonal landscape in myeloma patients and allows discrimination between primary and secondary clones based on unique M protein characterization and baseline levels. The presence of secondary baseline clones or their persistence during follow-up does not seem to increase the risk of progression. Most secondary M proteins are IgM and disappear early following treatment, suggesting they represent transient B-cell clonal expansion unrelated to the disease, or small myeloma clones particularly sensitive to therapy.

PA-286

High-Throughput Chemical Biology Screens Unravel Precision Medicine Strategies for Multiple Myeloma

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Introduction: The emergence of therapy resistant tumor clones remains a significant challenge in myeloma, which is often driven by the substantial genetic heterogeneity of MM. Strategic targeting of core MM vulnerabilities, however, might minimize the risk of resistance development and maximize therapeutic benefit. Integrating our whole-genome CRISPR profiling database with high-throughput combinatorial drug screens we aim to develop novel, multi-agent therapeutic strategies designed to benefit relapsed/refractory MM patients. **Methods:** Drug combinations were identified and prioritized based on 1) Gene essentiality mapping by CRISPR screening to identify druggable dependencies, 2) High-throughput screening of 2803 clinically relevant compounds (MIPE Library 6.0), and 3) Synergy screening to systematically evaluate tens of thousands of drug combinations. **Results:** To identify effective drug combinations for myeloma we performed whole-genome CRISPR screens in 30 human MM cell lines and chemogenomic screens in 6 MM cell lines, leading to the selection of 70 drugs targeting core MM dependencies (like IRF4) and mutations common at relapse (like RAS). A proof of concept combinatorial "all-vs-all" drug screen of 39 targeted agents (741 drug pairs in 10 × 10 matrix blocks), chosen for synergy with the SMARCA2/4 inhibitor FHD286, validated our approach by showing that on-target co-dependencies drive synergistic interactions. Unsupervised hierarchical clustering based on synergy scores revealed sub-clusters of drugs with similar drug-interaction landscapes and enabled us to identify hotspots of strong synergy, particularly around SMARCA2/4, CDK8, PI3K/MTOR, and MAPK pathways. We then integrated clinical-grade pan-RAS inhibitors into our drug library to refine therapeutic strategies for RAS dependent MM. Combinatorial screens of RMC6236 against the MIPE library demonstrated strong synergy with established and experimental anti-MM agents, including FHD286. Validation studies in our preclinical model systems confirmed that combining RAS inhibition with agents targeting core MM transcriptional circuits lowers the apoptotic threshold, demonstrating exceptional synergy and offering a new precision-medicine strategy for MM. **Conclusions:** Our combined chemogenetic approach unlocked novel precision medicine regimens for treatment resistant MM, which will serve as a crucial foundation for rapid clinical translation.

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A New PIKfyve Inhibitor Shows Subnanomolar Potency in Multiple Myeloma

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Introduction: Autophagy is a catabolic process that recycles unwanted cellular components in response to stress, critical for plasma cell homeostasis and sustainable immunoglobulin synthesis. Multiple myeloma (MM) cells are highly dependent on this cellular process for survival, underscoring the potential of targeting autophagy in MM. In this context, our group has focused on the inhibition of the PIKfyve kinase, a crucial regulator of autophagy, to selectively target autophagy-dependent MM cells. **Methods:** Following the synthesis of over 200 new chemical entities with clinical potential, derived from the novel PIKfyve inhibitor PIK001, we identified PIK085 as a remarkably potent new compound. We performed PK and ADME studies on PIK085 and evaluated its efficacy against human myeloma cell lines (HMCLs) compared to PIK001 and apilimod, the first-in-class PIKfyve kinase inhibitor. **Results:** The anti-MM activity of PIKfyve inhibitors was evaluated in the two most sensitive HMCLs, KMS26 and JJN3. Both HMCLs exhibited comparable IC50 values for Apilimod and PIK001 in the low nanomolar range (62 nM and 40 nM for KMS26, and 18 nM and 20 nM for JJN3, respectively). In contrast, our new compound, PIK085, demonstrated a 20- to 40-fold increase in potency, with IC50 values of 1.4 nM in KMS26 and 0.8 nM in JJN3. PIK085 also displayed an improved metabolic stability, with increased plasma concentrations following oral and IV administrations in mice when compared to PIK001 and apilimod.

PIKfyve inhibitors displayed synergistic activity with relevant anti-MM therapeutics, including selinexor, venetoclax, and iberdomide. Clinical potential of PIKfyve inhibition in the refractory setting was also shown by potent activity in IMiD-resistant isogenic HMCL models. Confirmation of autophagy disruption via PIKfyve inhibition was shown by the cellular vacuolation phenotype, a known phenotypic biomarker of PIKfyve inhibition, and increased levels of Sequestosome-1 protein expression. **Conclusions:** We present PIK085 as a promising preclinical candidate with subnanomolar potency in MM. Validation of PIKfyve inhibition as a single agent and in combination with other disease relevant therapeutics in in vivo models are n ongoing. Collectively, our work encourages further exploration of autophagy disruption in MM via PIKfyve inhibition, highlighting the potential of targeting plasma cell biology when investigating innovative treatment strategies.

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Phase 2 Registrational Study of Anitocabtagene Autoleucel for Relapsed and/or Refractory Multiple Myeloma (RRMM): Updated Results from iMMagine-1

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Introduction: Anitocabtagene autoleucel (anito-cel) is an autologous anti–BCMA chimeric antigen receptor (CAR) T-cell therapy with a novel D-domain binder under development for patients (pts) with RRMM. Updated results from the ongoing iMMagine-1 registrational trial are presented. **Methods:** Details of iMMagine-1 (NCT05396885) have been previously reported (Freeman et al., ASH 2024). Eligible pts were triple-class exposed, had progressed after ≥3 LoT, and were refractory to last LoT. Following leukapheresis, optional bridging, and anito-cel manufacturing, pts received lymphodepletion chemotherapy and a single infusion of anito-cel. The primary endpoint is overall response rate (ORR) by Independent Review Committee and assessed using 2016 IMWG criteria. MRD is assessed by next-generation sequencing, toxicity is graded per CTCAE version 5.0, and CRS and ICANS are graded by the ASTCT consensus criteria. This analysis reports investigator-assessed safety and efficacy outcomes. **Results:** As of October 31, 2024, 86 pts received anito-cel under the final manufacturing process with ≥2 months of follow-up and comprised the efficacy evaluable population; median follow-up was 9.5 months (range, 2–23). Pts had received a median of 4 prior LoT (range, 3–8) with 37 pts (43%) having received only 3 prior LoT. Seventy-four pts (86%) were triple-class refractory and 37 (43%) were penta-drug refractory. Investigator-assessed ORR was 97% (83/86) with a CR/sCR rate of 62% (53/86). Of those evaluable for MRD testing (n = 58), 54 (93.1%) achieved MRD negativity at least to the level of 10–5 and median time to MRD negativity was 1 month (range, 1 to 6 months). Using Kaplan-Meier methods, the duration of response (DoR), PFS, and OS rates at 12-month milestone timepoints are 75.6%, 78.5%, and 96.5%, respectively. Median DOR, PFS and OS have not been reached. The safety evaluable population (N = 98) had ≥1 month of follow-up by the data cut-off. The most common grade ≥3 treatment emergent adverse events (AEs) were cytopenias. Eighty-four pts (86%) had CRS Gr1 or less, including 17 (17%) with no CRS, and 96 (98%) had either no CRS or CRS resolution ≤14 days of anito-cel infusion. Any grade CRS was observed in 81 pts (83%) with 67 (68%) Gr1, 13 (13%) Gr2, and 1 (1%) Gr5. Median onset was 4 days (range, 1–17) with a median duration of 3 days (range, 1–9). Any grade ICANS was observed in 9 pts (9%) with 4 (4%) Gr1, 4 (4%) Gr2, and 1 (1%) Gr3. No delayed or non-ICANS neurotoxicities including no Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome have been observed. **Conclusions:** Ongoing results from iMMagine-1 demonstrate deep and durable efficacy and manageable safety in a 4L+ RRMM population. No delayed or non-ICANS neurotoxicities including no Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome have been observed across the Phase 1 or Phase 2 iMMagine-1 studies to date. Data including efficacy and safety in all treated pts will be presented.

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Enhanced Expression of TAGLN2 Predicts Negative Prognosis in Multiple Myeloma

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Introduction: Transgelin-2 (TAGLN2), a cytoskeletal actin-binding protein involved in promoting tumorigenesis of human cancers. The association of TAGLN2 with multiple myeloma (MM)

prognosis is unclear. Here, the clinical significance and potential function of TAGLN2 in MM were investigated. **Methods:** RNA-Seq data were downloaded from MMRF CoMMpass dataset. Microarray and single cell RNA-seq datasets were downloaded from the Gene Expression Omnibus (GEO) database. We analyzed the differences in TAGLN2 expression between healthy donors and MM patients and between samples with different clinical information. The association of TAGLN2 with MM prognosis and immune infiltration were also analyzed. **Results:** The expression of TAGLN2 showed an increasing trend with the progression of myeloma, and particularly showed higher levels in aggressive form of MM including plasma cell leukemia (PCL) and extramedullary MM. In addition, increased TAGLN2 expression was observed in the tumor cells from relapse MM compared to newly diagnosed MM (NDMM) or those without relapse. Survival analysis showed that high TAGLN2 expression level contributed to poor prognosis of MM patients. Functional enrichment analysis indicated that TAGLN2 may associated with cell cycle progression, cell adhesion and immune response in myeloma. Finally, we observed that TAGLN2 was distinctly correlated with tumor immunity in MM, evident by both increased immune cell infiltration and expressions of immune suppressive genes in myeloma cells, T cells, NK cells and monocytes. **Conclusions:** TAGLN2 might be used as reliable diagnostic and prognostic biomarker in MM.

PA-290

Optimal Treatment Strategy of Bisphosphonate Therapy in Multiple Myeloma: A Target Trial Emulation Study of Fracture Prevention versus Osteonecrosis of the Jaw Risk Using Nationwide Data

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Introduction: To identify the optimal bisphosphonate (BP) treatment duration in multiple myeloma (MM) patients by balancing the risks of osteonecrosis of the jaw (ONJ) and the benefits of fracture prevention. **Methods:** This retrospective study utilized a nationally representative Korean healthcare database (2007–2022) and emulated a target trial using the clone-censor-weight method. The cohort included 4,494 MM patients initiating BP therapy. BP exposure was categorized into five cumulative defined daily dose (cDDD) durations: ≤6, 7–12, 13–18, 19–24, and ≥25 DDD-months. Outcomes included 5-year cumulative risks of ONJ and fractures, with net clinical benefit calculated by integrating fracture prevention against ONJ risk. **Results:** BP durations of 13–18 DDD-months achieved the optimal balance, reducing fracture risk (−5.66%; 95% CI: −8.72, −2.53) while limiting ONJ risk (1.91%; 95% CI: 0.55, 3.50). Durations >19 DDD-months increased ONJ risk (8.85%; 95% CI: 4.37, 12.74) without additional fracture prevention. Durations of 7–12 DDD-months minimized ONJ risk (1.68%; 95% CI: 0.35, 3.77) but provided less fracture protection. **Conclusions:** Intermediate BP therapy (13–18 DDD-months) optimizes fracture prevention and ONJ risk in MM patients, supporting individualized strategies. These findings provide evidence for refining BP treatment guidelines and emphasize the need for further research in diverse populations.

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Comparative Analysis of Motixafortide versus Plerixafor for Stem Cell Mobilization and Collection in Multiple Myeloma: A Single Center Real-World Experience

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Introduction: Stem cell collection after 4–8 cycles of induction therapy remains the standard for multiple myeloma (MM) patients prior to autologous stem cell transplant (ASCT). Increasing demand for apheresis services, especially with the rise of CAR-T and other cell therapies, highlights the need for efficient mobilization strategies. Motixafortide, a CXCR4 antagonist with prolonged receptor occupancy (≥72 hours vs. plerixafor's ~6–12 hours), may enhance stem cell mobilization kinetics. **Methods:** This quality initiative compared a prospective cohort of 30 MM patients mobilized with motixafortide + G-CSF to 30 retrospective MM patients mobilized with plerixafor + G-CSF. The goal was to evaluate feasibility, mobilization efficacy, and safety of motixafortide in a real-world single-center setting. Cohorts were matched by age, gender, race, and prior exposure to daratumumab and IMiDs (lenalidomide/pomalidomide). Plerixafor (0.16–0.24 mg/kg SC) was administered if peripheral CD34 (pCD34) count was < 30 cells/μL on the evening before collection (Day 4 of 5 of G-CSF). Motixafortide (1.25 mg/kg SC) was given regardless of pCD34, based on clinical logistics. Premedication for motixafortide included cetirizine, famotidine, montelukast, acetaminophen, prednisone, and lidocaine cream with ice during a 1-hour monitoring period. Target collection was $\geq 4.0 \times 10^6$ CD34+ cells/kg, with minimum 12 L processed for pCD34 >50 cells/μL and 4 total blood volumes for pCD34 < 50 cells/μL. **Results:** Twenty-nine of 30 motixafortide patients completed mobilization. Fold-increase in pCD34 was similar between groups, though three "super-responders" were noted in the motixafortide cohort. A trend toward superior pCD34 increase with motixafortide was observed in patients with very low Day 4 pCD34 (< 5 cells/μL), but sample size limited conclusions. CD34 cell yield and collection

efficiency did not differ significantly. Twenty-seven patients in each group completed collection in a single day. Time on apheresis, blood volume processed, and CD34 product percentages were comparable. Adverse events requiring intervention occurred in 48% of motixafortide recipients, primarily pruritus (45%), tingling/burning (34%), pain (31%), erythema/rash (24%), and facial flushing (24%). No interventions were needed after plerixafor. One motixafortide patient experienced painful injection-site nodules lasting up to 3 months. **Conclusions:** In this real-world evaluation, motixafortide did not demonstrate superiority over plerixafor in pCD34 mobilization, stem cell yield, or collection efficiency in MM patients. Higher rates of adverse reactions with motixafortide influenced continued institutional preference for plerixafor in initial ASCT mobilization. Further studies will focus on motixafortide's role in poor mobilizers and post-transplant engraftment.

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Development of Novel CREB1-PROTACs for Enhanced Targeting of CREB1 in Multiple Myeloma

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Introduction: Multiple myeloma (MM) cells originate from antibody-producing plasma cells and endure chronic oxidative and proteotoxic stress due to the excessive immunoglobulin and free light chain production. We previously demonstrated that CD56 (neuronal cell adhesion molecule 1) promotes CREB1 (cAMP responsive element binding) activation in MM cells to support survival, though its precise mechanism of action remains unclear (Cottini et al, 2022). **Methods:** A panel of MM cell lines were treated with DMSO, CREB1 inhibitor (666-15), CREB1-PROTACs (Proteolysis-targeting chimeras), and proteasome inhibitors at variable concentrations. CREB1 loss-of- and gain-of-function models were also established. **Results:** Patients with high CREB1 expression had increased activation of gene sets associated with immune escape, leading to elevated expression of HLA-E (Ismael et al, 2024), as well as gene sets linked to oxidative stress endurance and modulation of the unfolded protein response (UPR). Silencing CREB1 with shRNAs in OPM-2 and H929 cells increased total and mitochondrial reactive oxygen species levels. CHIP-sequencing analysis revealed that CREB1 directly binds to the promoters of NFE2L2 (NRF2) and EIF2AK3 (PERK). Overexpression of CREB1 in U266 cells upregulated these factors, inducing the expression of genes involved in oxidative and protein stress adaptation. In contrast, CREB1 silencing in OPM-2 and H929 cells led to the downregulation of PERK, MCL1, BCL2, and TXNIP, while increasing apoptotic markers such as DDIT3 (CHOP), and PPP1R15A (GADD34). We then confirmed that the CREB1 inhibitor 666-15 downregulated CREB1 targets, including PERK, BCL2, MCL1, and TXNIP. Building on 666-15 backbone, four distinct CREB1-PROTACs were synthetized by the Medicinal Chemistry Core at the Ohio State University. PROTACs are a novel class of drugs which directly eliminate target proteins via the ubiquitin-proteasome system. Unlike conventional inhibitors that bind to an active site, PROTACs require only an anchoring point on the protein, enabling the targeting of previously "undruggable" proteins. We tested these four compounds for their ability to degrade CREB1 and induce cell death. All compounds successfully induce CREB1 degradation at various time points and concentrations, with compound #28 proving the most potent. Treatment of MM cell lines with 50–500 nM of compound #28 reduced viability and induced apoptosis while decreasing CREB1 downstream targets, including TXNIP, HLA-E, MCL1, and BCL2. Since PROTACs require active proteasomes, they cannot be combined with bortezomib or carfilzomib. Instead, we explored combination strategies with immunomodulatory drugs, observing synergy between compound #28 and lenalidomide, pomalidomide, and iberdomide. Further mechanistic studies, along with drug metabolism and pharmacokinetic analyses, are ongoing. **Conclusions:** In conclusion, CREB1-PROTACs represent a promising new class of compounds for the treatment of MM, warranting further development and investigation.

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Anti-Adhesion Properties of KTX-1001, a Selective NSD2/MMSET Inhibitor, Enhance Carfilzomib Sensitivity in Multiple Myeloma

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Introduction: In t(4;14) multiple myeloma (MM), the histone methyl transferase NSD2 gene is placed under the control of the IgH super-enhancer, leading to its overexpression and abnormally high levels of dimethylation of histone 3 at lysine 36 (H3K36me2). High NSD2 promotes MM cell growth, proliferation and cell-cell/cell-matrix adhesion in the bone marrow (BM) microenvironment. KTX1001 is an oral, small-molecule NSD2 inhibitor being evaluated in a Phase 1 trial in late stage MM (NCT05651932; Bories ASH 2024). We report initial characterization of KTX1001 in MM cell lines and biomarker analysis from patient derived BM samples. We find KTX1001's role in disrupting adhesion of MM cells by regulating CD44, CD56 and N-cadherin levels and driving synergy with carfilzomib (CFZ) in a bortezomib-resistant highly adherent cell line. **Methods:** KMS11 wildtype (WT) and bortezomib-resistant (BTZ) cells were treated with increasing doses of KTX1001, and proliferation and proportion of adherent cells were quantified. Matrigel assays assessed changes in suspension cells at days 7 and 11. Cell viability and synergy with CFZ were evaluated by CellTiterGlo. Adherent and suspension fractions of KMS11 WT

cells were cultured separately and subjected to CFZ dose-response assays. Colony formation assays evaluated KTX1001's effect on cell-cell interaction and colony formation. Gene and protein expression were quantified by RNASeq and Western. Patient samples were analyzed by mass cytometry. **Results:** KTX1001 monotherapy treatment of KMS11 WT/BTZ cells resulted in dose- and time-dependent reduction in cell adhesion, with a concomitant increase in suspension cells. While overall cell viability remained unaffected, colony formation was impaired. Transcriptomic profiling of non-adherent KMS11/BTZ cells after KTX1001 treatment revealed differentially reduced expression of adhesion-related genes including CD44, CD56 and TWIST1. Analysis of BM from KTX1001 treated patients demonstrated reduced expression of CD44, CD56, and H3K36me2 in MM cells at Cycle 2. KTX1001+CFZ combination treatment synergistically inhibited viability in WT and BTZ cells after four days. Transcriptomic analysis of KMS11/BTZ cells treated with KTX-1001+CFZ led to downregulation of adhesion-related genes, especially CD44 and N-cadherin. Additionally, KMS11 suspension cells were significantly more sensitive to CFZ than their adherent counterparts. Suspension cells pre-treated with KTX1001 exhibited enhanced sensitivity to CFZ versus untreated suspension cells. **Conclusions:** Inhibition of NSD2 by KTX1001 led to disruption of adhesive properties of MM cells that were mediated by CD44 and N-Cadherin in cell lines and patient samples. Further, the effects of KTX1001 on adhesion sensitized BTZ-resistant cells to combination treatment with CFZ. Analysis of patient samples from the ongoing trial that includes combination of KTX1001+CFZ would help ascertain synergy and the proposed molecular mechanism in the clinic.

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Safety Profile and Toxicity Comparison of Bispecific Antibodies in Relapse Refractory Multiple Myeloma: A Systematic Review of Clinical Trials

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Introduction: Bispecific antibodies (BsAbs) have emerged as a promising therapeutic strategy for patients with relapsed or refractory multiple myeloma (MM). However, their clinical use is often limited by a distinct and potentially severe toxicity profile, necessitating a deeper understanding of safety outcomes across BsAb targets. **Methods:** We performed a comprehensive pooled analysis of clinical trials evaluating BsAbs from both full-text publications and conference abstracts available up to April 2025. BsAbs were categorized based on their target antigens into two groups: B-cell maturation antigen (BCMA)-directed BsAbs and those targeting GPRC5D or FcRH5. To compare safety profiles across agents, Welch's t-test was applied. Principal component analysis (PCA) was also used to explore clustering patterns and identify similarities and differences in adverse events (AEs). **Results:** We analyzed 22 trials involving 2,374 patients with MM from early 2023 to April 2025. Among these, 1,276 patients received BCMA BsAbs, 841 patients were treated with GPRC5D/FcRH5 BsAbs, 157 received teclistamab + talquetamab (Tal), 65 patients received Tal+daratumumab (Dara), and 35 patients received Tal+pomalidomide (Pom). The overall response rate (ORR) was 60.57% in patients with a median follow-up of 11.83 months and a median of 5 prior lines of therapy. The Tal-based combinations (Tal+Dara/Pom) showed the highest efficacy, with an ORR of 81% and the highest rates of CR/sCR (19.62%) and VGPR (25%). Among all-grade hematologic AEs, neutropenia occurred in 40.4%, anemia in 39.2%, thrombocytopenia in 21.4%, lymphopenia in 19.2%, infections in 45.8%, and cytokine release syndrome (CRS) in 65%. For grade 3/4 AEs, infections occurred in 20.3%, CRS in 1.5%, neutropenia in 35.2%, anemia in 24.5%, thrombocytopenia in 13.5%, and lymphopenia in 17.7%. CRS and the need for tocilizumab were significantly more frequent with BCMA BsAbs vs GPRC5D/FcRH5 BsAbs, $P < 0.024$. Skillings Mack (Generalized Friedman's) findings emphasized substantial distinctions between BCMA and GPRC5D/FcRH5XCD3 in both overall and severe grade 3/4 AEs ($p < 0.0002$). PCA revealed agents with all grades and grade 3/4 showed similar clustering patterns except for three agents. Fatal AEs occurred in 12.55% of patients, primarily due to progressive disease (3.58%) or treatment-related toxicities (3.88%), with a higher rate of AE-related mortality observed in the BCMA-targeted BsAb group. **Conclusions:** The use of BsAbs in MM has demonstrated excellent efficacy; however, these agents have been linked to a unique AE profile. BCMA BsAbs were associated with less hematologic toxicity, 22.4% (grade 3/4: 17.4%) vs 30.6% (grade 3/4: 22%) for GPRC5D/FcRH5, and BCMA BsAbs were associated with lower CRS rates, 56.8% (grade 3/4: 1.3%) vs 73.1% (grad 3/4: 1.7%) for GPRC5D/FcRH5. This is important information for treatment selection and mitigation strategy development aiming to optimize patient outcomes.

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Tumor-reactive γδ T Cells Mediate Responses to the Antibody Drug Conjugate Belantamab Mafodotin in Multiple Myeloma

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Introduction: The BCMA-targeting antibody drug conjugate (ADC), belantamab mafodotin (belamaf) has been studied as monotherapy and has demonstrated clinically meaningful progression free survival (PFS) (DREAMM-7 and DREAMM-8 studies) and overall survival (DREAMM-7) benefits in combination regimens. Belamaf exerts its anti-tumor activity via direct cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and immunogenic cell death. It is proposed that the later accounts for the durability of responses observed across all DREAMM studies, however the role of T cells this process is unclear. To gain further insights into the mechanisms underlying the clinical activity of belamaf we preformed longitudinal profiling of the T cell receptor (TCR) repertoire in blood and bone marrow (BM) samples derived from patients receiving belamaf in combination with pomalidomide and dexamethasone (BPd) in the ALGONQUIN study (NCT03715478). **Methods:** Patients enrolled in Part 2 of the Algonquin study of BPd provided written informed consent for sample collection and correlative studies. Peripheral blood (PB) samples were collected at screening, at cycle 2 day 1 (C2D1) and every 6th cycle thereafter. BM specimens were obtained at screening, C2D1 and end of treatment (EoT). We conducted TCR capture and sequencing (CapTCR-seq) on DNA derived from PB mononuclear cells (PBMCs) and cell free DNA (cfDNA). To study the intratumoral T cell repertoires and phenotypes we used single-cell CITE-seq (cellular indexing of transcriptomes and epitopes sequencing) combined with single-cell αβ and γδ TCR sequencing applied to viably frozen BM cells from n = 11 myeloma patients. **Results:** BM CITE-seq analysis did not reveal upregulation of RNA and protein expression of T cell exhaustion markers TIGIT, PD-1, CD38, LAG3 or RNA expression of TOX across T or NK cell subsets at C2D1 or EoT. Consistent with the lack of T cell exhaustion, PB TCR diversity did not decline compared to baseline overtime including at EoT. Surprisingly, we observed that high γδ TCR diversity at C2D1 in the PB was significantly associated with improved PFS. In the BM, we observed an elevated proportion of intratumoral γδ T cells in responders compared to non-responders. Using a novel machine learning algorithm developed by our group we identified tumor-reactive γδ T cells from the CITE-seq data. Responders to BPd tended to exhibit expansion of baseline tumor-reactive γδ TCRs and influx of new tumor-reactive γδ TCRs at C2D1. Non-responders were comparatively devoid of tumor-reactive γδ T cells. **Conclusions:** γδ TCR diversity and the presence of tumor-reactive γδ T cell clones at C2D1 serve as a predictive biomarker for long-term responses to BPd. Immunogenic cell death caused by belamaf may result in the release of concealed tumor antigens or disruption of the tumor microenvironment prompting a γδ T cell response.

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Treatment Patterns and Outcomes in the Second and Third Lines and After Triple-class Exposure: Subanalysis of the Latin American Multiple Myeloma Registry Study (MYLACRE)

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Introduction: Patterns of care for multiple myeloma (MM) vary across countries. MYLACRE was a non-interventional registry of patients (pts) diagnosed with MM between Jan/2016 and Jun/2021 in Latin America. We analyzed MYLACRE pts treated in the 2nd and 3rd lines of therapy (LOT2 and LOT3), with the objective of characterizing treatment patterns. We also investigated treatment strategies and outcomes in the subset of triple-class exposed (TCE) pts. **Methods:** In MYLACRE, data were retrospectively collected, and treatment was left to investigators' discretion. The LOT2 Population comprised all pts who had an entry for the start date of LOT2. The LOT3 Population comprised all pts from the LOT2 Population who had an entry of the start date of LOT3. We defined TCE pts as those who had received ≥1 proteasome inhibitor (PI), ≥1 immunomodulatory drug (IMiD), and ≥1 anti-CD38 antibody, regardless of treatment duration. We only analyzed TCE pts with at least one subsequent LOT after becoming TCE. We analyzed time to next treatment (TTNT) and overall survival (OS) using the Kaplan-Meier method, with TTNT measured between Day 1 of the LOT of interest (LOT2, LOT3, or the first LOT after which a pt became TCE, according to the case) and Day 1 of the subsequent LOT. **Results:** Of the 1029 pts originally analyzed in MYLACRE, 405 and 167 entered the LOT2 and LOT3 Populations, respectively. In LOT2, the most frequently used PI, IMiD, and anti-CD38 were bortezomib (41.0%), lenalidomide (41.0%) and daratumumab (26.2%). Other agents used

in >10% were carfilzomib (17.0%) and thalidomide (19.3%). The median TTNT was 21.2 months (mo), and median OS was 26.1 mo. In LOT3, carfilzomib (26.9%), lenalidomide (34.7%), and daratumumab (18.6%) were, respectively, the most common PI, IMiD, and anti-CD38. Bortezomib (25.7%) and thalidomide (10.8%) were the next most frequent. The median TTNT was 12.2 mo, and median OS was 14.5 mo. A total of 166 (16.1%) pts had a record of treatment with ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 at some point. Of these pts, 48 (48/166 = 28.9%) initiated a subsequent LOT after TCE and entered the TCE Population. These pts became TCE after LOT1 (n = 5), LOT2 (n = 27), LOT3 (n = 8), or later (n = 8). Considering agents belonging to the PI, IMID, and anti-CD38 classes, carfilzomib was the agent most frequently used in the first LOT after TCE (52.1%), followed by lenalidomide (22.9%), pomalidomide (20.8%), daratumumab (18.8%), and thalidomide (10.4%). The median TTNT was 9.5 mo (95% CI, 5.9 to 19.4 mo). The median OS was 13.4 mo (95% CI, 10.6 to 17.7 mo). **Conclusions:** This snapshot of pts with MM treated in Latin America shows heterogeneity in treatments used in LOT2, LOT3, and after TCE status, suggesting a lack of standard of care in the real world. The difference between real-life drug use and international guidelines could also be determined by access barriers. The short OS, especially after TCE, highlights the importance of more effective treatment options to improve outcomes.

PA-297

Functional Evaluation of RHEB as a Lineage-Selective Dependency in Multiple Myeloma Using Integrated CRISPR, Epigenetic, and Expression Analyses

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Introduction: Multiple myeloma (MM) remains incurable and is driven by lineage-specific dependencies rather than consistent genomic mutations. RHEB, a GTPase activating mTORC1, was identified among 116 genes with MM-preferential essentiality in a genome-scale CRISPR screen by de Matos Simoes et al. (2023). Given its role in supporting proteostasis and managing ER stress, RHEB represents a plausible MM-selective therapeutic target. **Methods:** Candidate surface and plasma cell–specific genes were first curated via the Human Protein Atlas and cross-validated using RNA-seq data from the MMRF CoMMpass study. Functional prioritization was guided by CERES-based CRISPR screening data from DepMap. To independently assess RHEB dependency, we merged CRISPR gene-effect (Chronos and CERES), dependency probability, and OncoTree lineage data across 700+ cell lines. Mann–Whitney U tests were applied to compare MM versus non-MM dependency. Chromatin accessibility (ATAC-seq) and tissue expression (GTEx) were used to assess transcriptionalactivity and specificity. **Results:** RHEB was initially identified as an MM-preferential gene in CERES datasets, with elevated chromatin accessibility in MM models and low expression in most normal tissues. However, our independent validation using Chronos data revealed no statistically significantenrichment of RHEB dependency in MM versus non-MM lines (gene effect p = 0.228; dependency p = 0.111). Despite this, functional literature supports RHEB's critical role in managing MM cell survival via mTORC1 signaling, proteostasis, and ER stress buffering. **Conclusions:** Although our Chronos-based analysis did not confirm statistical enrichment of RHEB dependency in MM, converging evidence from CRISPR studies, epigenomic activation, and transcriptomic specificity suggests a lineage-selective vulnerability. Future work includesCRISPR knockout studies in MM vs. normal plasma cells and preclinical evaluation of RHEB- targeted inhibitors or combination regimens with proteasome inhibitors. Keywords: RHEB, multiple myeloma, CRISPR screening, DepMap, mTORC1, plasma cell, proteostasis, therapeutic target

PA-298

Uncovering Shared Cancer-Restricted Cryptic Antigens as T Cell Targets in Multiple Myeloma Patients Treated with Dendritic Cell/Myeloma Fusion Vaccine

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Introduction: Identifying novel tumor-specific antigens for T cell therapy is a critical step in developing next-generation immunotherapies for Multiple Myeloma (MM). Cryptic peptides from untranslated regions, tumor-specific splice variants, retroelements, and non-coding RNAs aberrantly translated in MM may represent a

potent yet underexplored class of neoantigens. Studying primary myeloma cells from patients in a cancer vaccine trial (CTN 1401), we discovered shared tumor antigens, including retroviral-derived epitopes, as potential targets for cellular immunotherapy. **Methods:** We developed a discovery framework integrating whole-exome sequencing, RNAseq, ribosome profiling, and single-cell immunoprofiling (gene expression + TCRseq) to identify (neo+cryptic) antigens that are transcribed, translated, and predicted to be antigenic. We applied this to 16 MM patient samples from the BMT CTN 1401 trial (NCT02728102). Detected peptides were prioritized using a machine learning algorithm trained on thousands of validated antigens. Prioritized antigens were confirmed for plasma cell specificity via single-cell RNAseq, and MHC-I presentation potential assessed using public immunopeptidomic datasets. Top antigens are being validated and matched with cognate TCRs using single-cell multiomics (gene expression, TCRs, and antigen binding) with DNA-barcoded dCODE MHC-I Dextramers. **Results:** Of the over 2,000 cryptic and mutation-derived peptides identified through our framework, 69 high-confidence, cancer-restricted cryptic antigens were prioritized. These antigens originated from 3′/5′ UTRs, retrotransposons, and endogenous retroviruses. Notably, six novel shared antigenic retroelements were identified, originating from the L1, L2, and ERV1 subfamilies, with the L2 element being consistently detected across 10 patients. Most remaining prioritized antigens arose from non-canonical ORFs in the 3′/5′ UTRs of plasma cell-associated genes, including BCMA, SLAMF7, and emerging candidates such as EGR1, TRIB1, and UBE2J1, likely generated through alternative splicing or aberrant transcription. Additionally, novel shared neoantigens were identified from UCHL1 and TPTE, two genes found to be aberrantly expressed in malignant plasma cells. Single-cell immunoprofiling revealed significant α/β TCR clonotypic expansion associated with high cryptic antigen abundance, suggesting active T cell engagement. We are currently conducting dCODE MHC-I Dextramer profiling to evaluate the intrinsic and vaccine-induced T cell responses against these tumor-specific targets. **Conclusions:** This study reveals a novel repertoire of shared, cancer-restricted cryptic antigens in MM, many arising from retroelements and previously annotated non-coding regions. These peptides are immunogenic and tumor-specific. Integration with dCODE profiling and TCR tracking provides a roadmap for identifying clinically relevant T cell targets and optimizing vaccine-based immunotherapies in MM.

PA-299

A35, a Novel Small Molecule Kinase Inhibitor, Shows High Efficacy in Multiple Myeloma and Overcomes IMiDs Resistance

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Introduction: RAS mutations activate multiple kinase pathways and occur in 50% of multiple myeloma (MM) patients. The mutation frequency increases as the disease progresses and is associated with a poorer prognosis. Furthermore, despite significant advances in immunotherapy, patients eventually develop resistance, highlighting the need for novel treatment strategies, particularly those that target kinase pathways beyond immunotherapies. In an effort to develop small-molecule kinase inhibitors, we developed A35, a novel kinase inhibitor for the treatment of MM. **Methods:** The anti-MM efficacy of A35 was evaluated on a panel of human MM cell lines using proliferation, apoptosis, and cell cycle assays. The impact on kinase signaling pathways was assessed by western blot assays in MM.1S and LP1 cells following 24 hours of A35 treatment. Kinase activity profiling of A35 was investigated using scanMAX KINOMEscan Lead Hunter Panel (Eurofins). In vivo anti-MM effects were tested using the MM.1S xenograft model in SCID mice, where mice received oral gavage of A35 at doses of 5 mg/kg or 20 mg/kg, or vehicle control for eight weeks. **Results:** A35 demonstrated potent anti-proliferative activity across all tested MM cell lines (MM.1S, H929, KMS12-PE, LP1, OPM2, SKMM2, RPMI-8226, JJN3), with an average IC50 of 1.6 μM (0.5–3.7 μM). Annexin-V/PI staining showed a significant increase of apoptosis in A35 treated cells from 12% in the control to 46% at 2.5 μM and 71% ($p < 0.05$) at 5 μM in LP1 and from 20% to respective 32% and 51% ($p < 0.05$) in MM.1S cells. A35 treatment was associated with a significant G2 cell cycle arrest from 25% to 41% (MM.1S) and 17% to 46% (LP1) ($p < 0.05$). Western blotting revealed a decrease of p-ERK1/2, p-MEK1/2 and p-AKT without affecting the total protein levels. Notably, c-MYC expression decreased markedly, alongside a modest reduction in BCL2 upon treatment. Kinase inhibition profiling revealed FLT3, HASPIN, JAK1, RSK1 and RSK4 to be the top inhibited kinases with a remaining kinase activity < 20% at 1 μM. Next, we investigated the A35 effects in the setting of IMiDs resistance using RPMI-8226 cells, or the H929 LenRes cells with acquired lenalidomide resistance. A35, but not lenalidomide, induced significant cell proliferation inhibition ($p < 0.05$) and c-Myc degradation in both cells, similar to the sensitive parental H929 cells. In vivo treatment with A35 lead to a prolonged median survival of mice from 29 days (vehicle) to 42 (5 mg/kg) and 49 (20 mg/kg). There were no significant differences in weight change between the treatment groups and no major side effects. **Conclusions:** A35 is a promising novel multi-kinase inhibitor with robust anti-myeloma activity in vitro and in vivo, including efficacy in IMiD-resistant models. It represents a potential novel therapeutic option for refractory/relapsed myeloma patients, including those who have failed immunotherapy.

PA-300

Autophagy Disruption Via PIKfyve Inhibition Strikingly Upregulates Cholesterol Metabolism in Multiple Myeloma

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Introduction: Despite marked advances in available treatment regimens for multiple myeloma (MM), chemoresistance and relapse remain major clinical challenges. In MM, autophagy is critical for plasma cell homeostasis and antibody production, underscoring its potential as a therapeutic target. Previous work by our group identified PIKfyve, a phosphoinositide kinase critical for lysosome homeostasis and autophagy, as a novel vulnerability in MM. Given the cytotoxic effects of PIKfyve inhibition in MM, we sought to explore the molecular consequences of targeting PIKfyve in MM. **Methods:** We performed unbiased transcriptomics and proteomics on six human myeloma cell lines (HMCLs), with a wide range of sensitivities to PIKfyve inhibitors, treated with the novel and potent PIKfyve inhibitor PIK001 (500 nM, 16 hrs) or DMSO control. Ex vivo effects of PIKfyve inhibition was also evaluated through single-cell RNA sequencing on six primary MM patient samples treated with PIK001 (500 nM, 16 hrs) or DMSO control. **Results:** Unbiased transcriptomics and proteomics revealed widespread changes in response to PIKfyve inhibition, with lysosomes and autophagy ranked among the top enriched gene sets in PIK001-treated samples, as expected. Notably, cholesterol biosynthesis was the most significantly enriched gene set in PIK001-treated HMCLs and ex vivo samples. Analysis of upregulated proteins across all cell lines revealed robust induction of key enzymes involved in the mevalonate and cholesterol biosynthesis pathways, including HMGCS1, FDFT1, and IDI1. In line with these findings, a 1.5 to 2-fold increase in total cholesterol levels following PIK001 treatment was confirmed. Synergy studies between PIK001 and cholesterol pathway inhibitors, such as fluvastatin, lycorine, and U18666A, showed strong antagonism, highlighting the importance of cholesterol in mediating the effects of PIK001. Furthermore, preliminary data showed that PIKfyve inhibition induces significant colocalization between LAMP1-positive lysosomes and the cholesterol stain filipin, indicating an accumulation of cholesterol in lysosomal membranes. **Conclusions:** Taken together, PIKfyve inhibition induces an increase in cholesterol biosynthesis and its combination with cholesterol pathway inhibitors antagonizes the cytotoxic effects of PIK001. These findings may inform the design of more effective combinations when targeting PIKfyve in MM.

PA-301

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-302

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-303

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.

PA-304

Immunomodulatory Drugs Suppress mTORC1 Signaling to Induce Direct Cytotoxicity and Enhance Antitumor Immunity in Multiple Myeloma

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Introduction: The development of immunomodulatory drugs (IMiDs), including lenalidomide and pomalidomide, has improved outcomes in multiple myeloma (MM). IMiDs bind cereblon (CRBN), activating the CRL4CRBN E3 ligase and promoting degradation of transcription factors IKZF1/3. This mechanism, however, relies on proteasome activity and cannot fully explain the synergy observed with proteasome inhibitors, suggesting additional mechanisms contribute to IMiDs efficacy. **Methods:** N/A **Results:** To better elucidate the mechanisms of IMiDs, we conducted RNA-seq on MM cells treated with IMiDs and found significant suppression of the mTORC1 pathway, specifically reduced phosphorylation of p70S6K, but not 4E-BP1. High mTOR/p70S6K expression in patient datasets correlated with poor prognosis. Inhibition of p70S6K phosphorylation is associated with IMiDs sensitivity. Previous reports have shown that activation of the AMPK pathway can potently suppress mTORC1 signaling. We further found that IMiDs enhance AMPK phosphorylation, leading to Raptor

phosphorylation and mTORC1 inhibition. This effect is CRBN-dependent, as CRBN knockout abrogated AMPK activation and mTORC1 suppression. Patient samples also showed increased AMPK phosphorylation after IMiDs treatment. Consistent with the known role of mTORC1 in autophagy regulation, RNA-seq and Western blotting confirmed that IMiDs can induce autophagy. IMiDs also increased CRBN expression; mTORC1 inhibitors similarly upregulated CRBN, and their combination enhanced IKZF1/3 degradation, supporting a synergistic and positive feedback effect on MM cytotoxicity. Interestingly, from our RNA-seq data, we found IMiDs also downregulated DNA repair pathways, especially CHEK1, which was similarly suppressed by mTORC1 inhibitors. Low CHK1 expression correlated with better survival and was CRBN-dependent. IMiDs impaired DNA repair and promoted DNA damage accumulation, explaining their synergy with melphalan. It is well established that the accumulation of DNA damage can activate the cGAS-STING signaling pathway. We found that IMiDs significantly activate the cGAS-STING pathway in MM cells via CHK1 downregulation, enhancing type I interferon secretion and antitumor immunity. Our group's previous study demonstrated that bortezomib induces immunogenic cell death (ICD) by cGAS-STING activation. We found that IMiDs-treated cells exhibit significantly elevated expression of ICD signature genes. IMiDs also increase surface expression of calreticulin and promote the release of HMGB1, both hallmarks of ICD. Additionally, we found that IMiDs enhance dendritic cell (DC) activation, which in turn activates T cell-mediated immune responses. **Conclusions:** In summary, we found that IMiDs activate AMPK to inhibit mTORC1, inducing autophagy and CRBN upregulation, reinforcing direct cytotoxicity. Concurrently, mTORC1 inhibition suppresses CHEK1, promoting DNA damage, cGAS-STING activation, and ICD, ultimately enhancing antitumor immunity.

PA-305

Computer-Assisted AI to Detect Myeloma Cells

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Introduction: Multiple myeloma remains an incurable disease. If we advance plasma cell/myeloma cell detection by novel approaches, we may be able to work towards a cure. Our team set out to develop computer-assisted AI to identify individual myeloma cells on modified Giemsa-stained slides. Immunophenotyping (CD138/CD56) confirmed the nature of the cells as myeloma cells. **Methods:** Overview: The computer was trained with 100% myeloma and 100% normal blood cells, followed by different dilutions of myeloma cells and blood cells. Finally, spiking experiments were carried out with up to 1 myeloma cell per 1 million normal cells. The recognition of myeloma cells was then confirmed in myeloma patient samples. The detection method is based on a combination of advanced optical microscopy measurement of the stained slides combined with a computer program that identifies the cell types and performs the statistics. Optical system: Digital imaging evolved during the last few years. Currently, it is mainly based on what is called whole slide imaging (WSI), which is basically a system that can scan the whole slide with a given magnification in color, store the data and allow an expert to overview the results on the computer screen. For our method we can use a conventional WSI system, but we also use a new type of a microscopy-based imaging system that allows to measure the full visible light spectrum at every pixel of the object. This spectrum contains much more information relative to the color, and acts as a fingerprint of the underlying tissue. This information must be processed and analyzed in order to extract the relevant information. Computer program: The computer program that analyzes the measured information contains few modules. The first one use AI algorithms that we adopted for identifying the nuclei of all the cells in the image. We found that the nuclei, for this application, provide significant information. Then, different features of the nuclei are calculated such as the size of each nucleus, the shape of it, circularity, roughness of the nucleus envelope, heterogeneity of the chromatin in the nucleus and more. Some of these calculations are performed using conventional image-processing tools, and others use AI. **Results:** We tested different slides, including a mixture of normal and myeloma cells and patients' bone marrow. The results confirm the validity of the methods and provides good results in identifying myeloma cells. Finally, spiking experiments were carried out with up to 1 myeloma cell per 1 million normal cells. The recognition of myeloma cells was then confirmed in patient samples with a ratio of myeloma cells to normal cells of 1:100,000 and even 1:1,000,000. The analysis confirms the ability of the system to measure even a small ratio as 1 myeloma cell to 106 normal cells. **Conclusions:** Computer-assisted AI is able to identify myeloma cells in blood and bone marrow. The method is ready for further application in patient samples.

PA-306

Mezigdomide (MEZI) in Novel Targeted Combinations for Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from the Phase 1/2 CA057-003 Trial

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Introduction: MEZI, an oral CELMoD™ agent, has direct antitumor and immunostimulatory effects in MM, via rapid and maximal degradation of Ikaros/Aiolos. CA057-003 (NCT05372354) is evaluating all-oral, novel triplet regimens with a MEZI+dexamethasone (DEX) (MEZId) backbone plus EZH2 inhibitor tazemetostat (TAZ), BET inhibitor BMS-986158, or MEK inhibitor trametinib (TRAM), in RRMM. Here, we report results from dose-finding cohorts of MEZId plus TAZ, BMS-986158, or TRAM. **Methods:** Eligible patients (pts) had RRMM with progressive disease (PD) during/after the last treatment (Tx), ECOG PS score ≤1, and were intolerant to/ineligible for all available established Tx. Oral MEZI (0.3/0.6/1.0 mg) was given daily (QD) on days (D)1–21 of each 28-D cycle with weekly DEX 40 mg (20 mg if ≥75 y) plus oral TAZ 800 mg twice daily on D1–28, oral BMS-986158 2/3 mg QD 5D-on-2D-off D1–14, or oral TRAM 1.5/2 mg QD on D1–21. Primary aims were to define recommended phase 2 dose, dosing schedule, and safety; secondary aims included efficacy and pharmacokinetics. **Results:** By Oct. 4, 2024, 16 pts received MEZId+TAZ, 20 MEZId+BMS-986158, and 20 MEZId+TRAM. Overall, median (range) age was 63 (37–83) y, time since initial diagnosis was 7.9 (1.2–18.4) y, and 21 (37.5%) pts had extramedullary plasmacytomas. Median (range) no. of prior Tx was 5 (2–20), including IMiD® agents, proteasome inhibitors, and anti-CD38 mAbs (100% each), ASCT (82.1%), and T-cell–redirecting therapy (57.1%); 82.1% had triple-class refractory disease. At data cutoff, 6 (37.5%) pts continued Tx with MEZId+TAZ, 6 (30.0%) with MEZId+BMS-986158, and 12 (60.0%) with MEZId+TRAM. The main reason for discontinuation was PD. Median (range) follow-up was 5.7 (1.3–14.3) mo (MEZId+TAZ), 4.2 (1.0–12.1) mo (MEZId+BMS-986158), and 5.1 (1.9–15.7) mo (MEZId+TRAM). Neutropenia was the most common grade (Gr) 3/4 Tx-emergent adverse event (TEAE) (62.5%–85.0%); Gr 3/4 nonhematologic TEAEs were low; 8 pts had dose-limiting toxicities (1 with 1.0 mg MEZId+TAZ; 1 with 0.3 mg, and 4 with 1.0 mg MEZId+BMS-986158; 2 with 1.0 mg MEZId+TRAM). In the efficacy-evaluable population, ORR was 50.0% with MEZId+TAZ, 35.0% with MEZId+BMS-986158, and 75.0% with MEZId+TRAM. Deeper responses (≥VGPR) were observed with 1.0 mg MEZI in the MEZId+TAZ (50.0%) and MEZId+BMS-986158 (20.0%) cohorts; and with ≥0.6 mg MEZI in the MEZId+TRAM cohort (53.0%); 84.6% pts had ongoing responses with 1.0 mg MEZI. Exposures increased dose-linearly over dose ranges, and across cohorts, showing no drug–drug interaction between MEZI and novel agents. MEZI was pharmacodynamically active, inducing Ikaros/Aiolos degradation and B-cell reduction in all regimens at all dose levels; MEZI 1.0 mg had the greatest effect. T-cell activation and proliferation were observed, independent of study-drug combination. **Conclusions:** MEZId plus TAZ, BMS-986158, or TRAM showed promising efficacy and safety in RRMM, supporting further exploration of these novel all-oral combinations. ©American Society of Hematology (2024). Reused with permission.

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Iberdomide (Iber) Treatment (Tx) Enhances Manufactured Chimeric Antigen Receptor (Car) T Cell Expansion And Functionality And Is Immunostimulatory In Patients Post-Car T Cell Therapy

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Introduction: CAR T cell therapies show high response rates in relapsed/refractory multiple myeloma (RRMM), but many patients (pts) produce suboptimal CAR T cells or lack durable responses due to limited cell persistence and functional exhaustion. Tx to improve CAR T cell expansion and functionality, and maintenance Tx to deepen/extend responses are needed. IBER is an oral CELMoD™ agent that induces enhanced degradation of Ikaros and Aiolos compared with IMiD® agents. IBER increases proliferation, activation, and reduces T cell exhaustion. Here, we assess if IBER Tx of pts with RRMM can improve CAR T cell functionality and stimulate immune responses in pts post-CAR T cell therapy. **Methods:** Peripheral blood samples were collected from pts receiving IBER (1.6 mg)+dexamethasone (DEX) prior to Tx initiation and after 1 cycle in the CC-220-MM-001 (NCT02773030) trial. The functional effect of IBER+DEX on anti-BCMA CAR T cells before and after Tx was assessed in 7 pts by comparing proliferation, phenotypic makeup, antigen-specific cytokine production, and cytotoxic activity. Results were validated with ex vivo Tx of 4 samples from healthy volunteers. Immune activation induced by IBER+DEX was also assessed by flow cytometry in 17 pts previously treated with CAR T cell therapy. **Results:** IBER+DEX Tx of pts with RRMM increased percent of CD4+ T cells, proportion of central and effector memory T

cells, and T cell-expressing activation markers (OX40, CD28, CD38), and decreased proportion of TEMRA (terminally differentiated) T cells in CAR T cell production. CAR T cells from pts on IBER+DEX Tx had higher proliferation rates, increased proportion of CD4+ and HLA-DR+ cells, and decreased proportion of exhausted (PD1+, TIM3+, TIGIT+) cells. Stimulation of CAR T cells produced from pts on IBER+DEX Tx lead to greater TNFα and granzyme-B levels, and significantly more efficiency in killing MM cells than CAR T cells produced pre-Tx. Ex vivo Tx of healthy T cells with IBER increased the proportion of memory CAR T cells and enhanced CAR T cell expansion and functionality. Lastly, IBER+DEX Tx of pts with MM previously exposed to CAR T cell therapy increased T and NK cell proliferation and shifted T cells from a naive to an activated effector memory phenotype. **Conclusions:** IBER+DEX Tx enhanced the proliferation, expansion, and functionality of manufactured CAR T cells in pts with RRMM. Our findings suggest that Tx with IBER prior to apheresis improves expansion, manufacturing success, and potency of CAR T cells. Moreover, IBER remains immunostimulatory post-CAR T cell infusion, suggesting IBER may provide benefit as post-CAR T cell therapy maintenance. Our results provide rationale for IBER as an adjunctive Tx to CAR T cell therapy, supporting further exploration of the effects of IBER Tx peri-CAR T cell apheresis and post-CAR T cell infusion to improve outcomes for pts with MM in clinical practice. This abstract was accepted and previously presented at EHA2025. All rights reserved. AA & MA contributed equally.

PA-308

Efficacy and Safety of Daratumumab-Based Schemes in Over80_Years Newly Diagnosed Multiple Myeloma(NDMM)

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Introduction: Multiple myeloma (MM) is the second most common hematologic malignancy.Frail patients who are ineligible for autologous hematopoietic stem cell transplantation require frontline treatment strategies that are both effective and tolerable, to delay disease progression and preserve quality of life. The incorporation of daratumumab(Dara) into standard first-line regimens VMP(bortezomib/melphalan/prednisone) and Rd (lenalidomide/dexamethasone) has demonstrated improved progression-free survival (PFS) and overall survival (OS). **Methods:** We conducted a retrospective, observational study including over80_NDMM patients who received Dara-based therapy between August2020 and January2025. Clinical and laboratory parameters at diagnosis included disease staging (ISS and R-ISS),cytogenetic abnormalities,renal function,serum albumin, and β2-microglobulin levels. Safety was assessed by recording adverse events (AEs) using CTCAEv5.0 and analyzing treatment modifications. Efficacy outcomes included progression rate and PFS,OS with survival Kaplan–Meier curves. **Results:** A total of 33 patients (17 women,16 men) were included,with a mean age of 82years. Treatment regimens included Dara-BTZ–based combinations in 70% of patients (n = 23;20DVMP, 3DVCP) and D-Rd in 30% (n = 10). Median follow-up was 26.5 months. Baseline values (mean): Creatinine clearance:53 mL/min. Serum albumin:3.6 g/d. β2-microglobulin:5.2 mg/L. Cytogenetics:High-risk:9.1%;Standard-risk:30.3%;Normal karyotype:54.5%: Disease stage (ISS/R-ISS): Stage I:15.2%/15.1%;Stage II:39.4%/57.6%;Stage III:33.3%/9.1% Meantreatment duration:16.8 ± 14.4 months. Median follow-up:5.4years. Progression occurred in 7 patients (21%; 5Dara-BTZ, 2D-Rd). Seven patients (21%) died [3 due to progressive disease]. Median PFS was 40.7months [95% CI:36.8–not reached]: PFS at 1 year: 88.6%[95% CI:77.1–100]PFS at 2 years: 79%[95% CI:64–97.5] Median OS was not reached. OS at 1year:78%[95% CI:63.8–95.4]. OS at 2 years:73.4% [95% CI:58.2–92.7] AEs were reported in 86% of patients (n = 28), mostly grade 1–2 (87%). Most common toxicities included:Hematologic (33%):anemia (20%; G1–3),neutropenia (5.5%; G1–2). Infections (29%):pneumonia (16%; G1–3). Other AEs of interest:Neurologic (18%);hepatic (n = 3), gastrointestinal (n = 2),vascular (n = 4),dermatologic (n = 1),metabolic (n = 1) Serious AEs included: one case of G4 cholestatic liver injury and one fatal septic shock (G5). Treatment modifications occurred in 54% of patients (n = 16):Temporary interruptions: 37%;Drug discontinuation:44%;Dose reductions: 19%. Specific causality was difficult to assign due to regimen complexity, except in the case of cholestatic injury, which led to daratumumab discontinuation. **Conclusions:** Daratumumab-based regimens demonstrated a favorable safety profile in NDMM patients aged ≥80 years, with predominantly mild to moderate toxicity. The observed efficacy (PFSandOS) aligns with results from pivotal clinical trials. Maintenance with Dara-Rd or Dara-BTZ appeared both safe and effective in selected patients.

PA-309

SETD7 is a Novel Therapeutic Target for Multiple Myeloma Carrying t(11;14)

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Introduction: In refractory hematologic tumors, t(11;14) translocation is frequently observed in 85% ofmantle cell lymphoma, 15–20% of multiple myeloma (MM), and 5% of chronic lymphocyticleukemia. Of these, the prognosis of MM patients carrying t(11;14) has been controversialfor many years. However, the latest retrospective analysis revealed that t(11;14) was a poorprognostic factor (Blood Res,60:11,2025). MM cells carrying t(11;14) show an immaturephenotype, such as lymphoplasmacytic morphology, lower CD38 expression, and higherBCL2 expression. Therefore, proteasome inhibitors and CD38 antibodies are less effectivebut a BCL2 inhibitor venetoclax is effective (Cancer Sci,112,3645,2021). However,venetoclax was not approved for MM due to increased treatment-related deaths. Thus, MMwith t (11;14) refractory to immunomodulatory drugs is an unmet need. **Methods:** In this study, we searched for novel therapeutic targets within SET family histonemethyltransferases. Then, we found that SETD7 is highly expressed in MM cells carryingt(11;14) and is associated with inferior survival. SETD7 acts as a transcriptional activatorvia mono- and di-methylation of the lysine 4 residue of histone H3. **Results:** ChIP-sequence analysis of SETD7 revealed a lot of peaks, over 70% of which were localized in the vicinity oftranscription start sites (TSSs). Moreover, we found SETD7 binding to the TSSs of thegenes including ARID1A, PRDM1, and c-FOS, which were associated with poor prognosisof MM. Next, we found that knockdown of SETD7 significantly suppressed the growth ofMM cell lines with t(11;14) but not those without t(11;14). Moreover, a SETD7 inhibitor PFI2significantly inhibited the growth alone and in combination with pomalidomide via down-regulation of ARID1A, IRF4, and MYC in vitro and in vivo. The forced expression of MYCsignificantly mitigated the cytotoxicity of PFI2. **Conclusions:** Although SETD7 can be either an oncogene or a tumor suppressor gene depending onthe type of cancer, there are few data in MM. Based on our findings, we conclude thatSETD7 acts as an oncogene and is a novel therapeutic target for MM. In addition, we foundthat ARID1A/IRF4/MYC axis is a critical down-stream pathway and is a bona fide target ofa SETD7 inhibitor. In line with our results, Bolomsky et al. revealed that ARID1A plays anindispensable role in the expression of IRF4 and MYC in MM (Cancer Cell,42;1,2024). Therefore, our study provides a molecular basis and rationale for the inclusion of SETD7inhibitors into current treatment strategies. The clinical use of PFI2 may significantlyimprove the treatment outcome of MM carrying t(11;14).

PA-310

HUWE1 Inhibition Impacts MYC Expression Leading to Increased DNA Damage in Combination with Bortezomib

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Introduction: Despite significant therapeutic advances, the majority of multiple myeloma (MM) patients develop relapsed/refractory disease, emphasizing the need for novel approaches to improve the efficacy of current treatments. Previous work from our lab highlighted the potential of the E3 ligase HUWE1 as a therapeutic target and developed a series of novel HUWE1 inhibitors, including a lead compound QDD-7. HUWE1 is implicated in many key cellular processes and was recently identified to promote the formation of c-MYC multimers surrounding stalled replication forks as a protective mechanism against DNA damage. Treatment with Bortezomib leads to an increase in c-MYC multimer formation. In this study, we investigate the combination of HUWE1 inhibition with Bortezomib and develop a high throughput assay to screen for inhibitors of HUWE1. **Methods:** MM cell lines (JJN3, OPM2, KMS12, MOLP8) were treated with Bortezomib and QDD-7 simultaneously or sequentially through 4-hour pre-treatment. Cell viability was measured using Cell Titre-Glo® luminescent assay and synergy was calculated using the Bliss Synergy Model (SynergyFinder+). Cells treated with IC50 values of Bortezomib or QDD-7 as single agents and in combination were harvested for protein 2, 4, 6 and 24 h post treatment and analysed for markers of DNA damage and apoptosis through Western Blotting. Auto-ubiquitination of HUWE1 was measured using either UbiQaptureTM combined with Western blotting or with UbFluor, an E2-ubiquitin fluorescent thioester, to measure fluorescence polarisation (FP) in a high throughput assay. **Results:** The novel inhibitor QDD-7 effectively inhibited HUWE1 activity across MM cell lines, as measured using UbiQapture, and this was associated with induction of γH2AX, indicating DNA damage and reduced c-MYC protein expression. Synergy analysis on combinations of Bortezomib and QDD-7 was determined using bliss synergy scores, where >10 indicates synergy, between −10 and 10 shows an additive effect and <−10 is antagonistic. Bortezomib pre-treatment was identified to be the most effective combination with bliss synergy scores ≥ 16.82, while simultaneous combinations were additive (synergy score ≥1.58). Western blot analysis demonstrated that combination treatments increased γH2AX and cleaved caspase-3 expression compared to single agents, indicating an increase in DNA damage and apoptosis, respectively. A novel primary ubiquitination assay incorporating full length HUWE1 was developed and optimised for high-throughput screening of prospective HUWE1 inhibitors. **Conclusions:** Dual inhibition of HUWE1 and proteasome activity demonstrates a synergistic response, associated with an increase in DNA damage and apoptotic activation, suggesting that disruption of c-MYC multimer formation through HUWE1 inhibition can enhance the efficacy of Bortezomib. Future work will use the novel primary HUWE1 activity assay to screen for clinically relevant inhibitors of HUWE1.

PA-311

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), including the development of proteasome inhibitors (PIs), this disease is still considered incurable due to inevitable therapy resistance. Thus, it is essential that resistance mechanisms are elucidated, and novel targets are identified to advance treatment and overcome resistance. Network analysis of 20 MM cell lines was carried out using SynLeGG (Synthetic Lethality with Gene Expression and Genomics) to predict genes that could be targeted to increase PI sensitivity. 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. **Methods:** Five MM cell lines (JJN3, U266, AMO1, OPM2, KMS18) 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 the bivalent SMAC mimetic BV-6. Combination treatments with BV-6 and PIs were analysed using SynergyFinder to calculate Bliss Synergy scores. Scores <−10 indicate an antagonistic relationship, −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 significant sensitisation to carfilzomib (CFZ) ($p < 0.001$). 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). Contrary to previous studies, evidence suggests that sensitivity to this combination is not dependent on TRAF3 mutation status. 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 drug 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 6hrs and 18hrs, suggesting an induction of both intrinsic and extrinsic apoptotic cell death. Preliminary evidence suggests that TNF-α signalling is implicated in mediating sensitivity to this drug combination. **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 include further delineating the mechanism of action of this drug combination, with a particular focus on the NF-κB and TNF-α signalling pathways. Ultimately, the discovery of this synergistic drug combination could have important implications in developing new strategies to overcome treatment resistance in MM.

PA-312

B7-H3 is Associated with Worse Outcomes in Newly Diagnosed Myeloma and Can Be Targeted with a Tri-Specific Killer Engager

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Introduction: B7-H3 (CD276), is an antigen highly expressed on several cancers but is low to absent on healthy tissues. In addition to functioning as a checkpoint receptor, its expression also enhances cancer cell growth. Other cells in the tumor environment can express B7-H3 including myeloid derived suppressor cells (MDSC), osteoclasts, fibroblasts, and tumor associated vasculature. **Methods:** We assessed B7-H3 expression on plasma cells and stroma by immunohistochemical staining (IHC) in decalcified bone marrow biopsies from 116 newly diagnosed, multiple myeloma (MM) patients. All patients had full body imaging within 30 days of diagnosis. We tested for associations between B7-H3 expression and clinical parameters including mutations with pathologic significance, bone lesions, pathologic fractures, and progression free survival (PFS). We also tested the ability of a tri-specific killer engager (TriKE) to improve natural killer (NK) cell mediated killing of B7-H3 expressing elements of the MM microenvironment by live cell imaging assays. This TriKE contains nanobodies that bind B7-H3 and engage CD16 on NK cells while also delivering a recombinant human IL-15 molecule. **Results:** 85% of patients had B7-H3 expression on plasma cells or stroma. Stromal staining was significantly associated with higher numbers of lytic lesions, worse International Staging Score, and shorter PFS. Both plasma cell and stromal expression of B7-H3 was associated with higher risk of pathologic fracture at diagnosis. None of the mutations with known pathologic implications nor cytogenetic risk were associated with B7-H3 expression. Live cell imaging assays showed that B7-H3 TriKE significantly enhanced killing of diverse MM cell lines, CD14+ MDSC, fibroblasts (Hs5), and endothelial cells (HUVEC). Since NK cells from MM patients are known to have functional deficits, we repeated assays with patient-derived NK cells and saw significantly improved killing of MM lines despite slower killing kinetics compared to healthy donor NK cells. **Conclusions:** Our data indicate that B7-H3 is highly expressed by both plasma cells and bone marrow stroma in newly diagnosed MM patients and is associated with bone lesions, pathologic fractures, and worse PFS. To overcome these negative effects, B7-H3 TriKE not only targets MM cells directly but could also alter the tumor microenvironment and attack immunosuppressive cells and tumor vasculature. The ability of B7-H3 TriKE to reinvigorate patient-derived NK cells against tumor lines, further supports its potential utility in the clinic.

PA-313

Novel Therapeutic Targets Kappa Myeloma Antigen (KMA) and Lambda Myeloma Antigen (LMA) are Expressed on Malignant Plasma Cells from Patients with Plasma Cell Dyscrasias but not on Normal Plasma Cells

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Introduction: Kappa myeloma antigen (KMA) and lambda myeloma antigen (LMA) are lipid-associated antigens arising from conformational epitopes in the constant regions of light chains expressed on the surface of malignant plasma cells (PCs). They are not found on normal PCs. Therapeutic monoclonal antibodies have been developed to recognize KMA and LMA. Their expression on a broad range of plasma cell dyscrasias (PCDs) and normal tissues has not been fully documented. **Methods:** Antibodies to KMA and LMA (KappaMab and LambdaMab) and other antibodies were used to compare the expression of KMA, LMA, B cell maturation antigen (BCMA), CD56 and SLAMF7 on bone marrow PCs from patients with a range of PCDs. QuantiBrite beads were used to calculate antigen densities. LMA expression was evaluated using immunohistochemistry (IHC) on a panel of normal human and plasmacytoma tissues. **Results:** Bone marrow aspirates (n = 195) were analyzed from patients with various PCDs including 114 cases of multiple myeloma (MM), 39 MGUS, 13 plasmacytoma, 9 smoldering multiple myeloma (SMM) and 20 AL-amyloidosis. KMA was present on 87 of 121 (72%) and LMA on 56 of 74 (76%) samples. KMA and LMA were never co-expressed. Across all types of PCD, KMA and LMA were expressed on PCs in 60–100% of cases. KMA and LMA were universally expressed with CD38 and SLAMF7 but in some cases (n = 10) were expressed in the absence of BCMA expression. Antigen density of KMA and LMA was similar to BCMA in cases of myeloma but was significantly greater in non-myeloma PCDs (for KMA 1210 v 1121 molecules PE/cell, p = 0.02, for LMA 1436 v 1178 molecules PE/cell, p = 0.03). LMA was expressed on plasma cells from 13 of 14 cases of lambda AL-amyloidosis and KMA from 5 of 6 cases of kappa AL-amyloidosis. Longitudinal samples from two patients whose disease progressed from MGUS and SMM to MM demonstrated an increase in LMA expression and higher antigen density compared to BCMA. LMA expression was restricted to malignant PCs and occasional mononuclear cells in normal mucosal associated lymphoid tissue but not on normal bone marrow PCs. **Conclusions:** KMA and LMA were only expressed on clonal but not on normal PCs. Antigen expression was independent of the Ig subtype, the number of bone marrow PCs and the Ig and FLC serum concentrations. In some cases of MM, the frequency and density of antigen expression increased as MM evolved. Density of KMA and LMA was increased over BCMA especially in non-myeloma PCDs. The broad and selective expression of KMA and LMA on malignant PCs and the high antigen density highlight the potential of these as valuable targets for immunotherapies in a variety of PCDs including AL-amyloidosis.

PA-314

Exploiting Silver Nanoparticle (AgNP) Induced Proteotoxicity for Multiple Myeloma Treatment

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Introduction: Multiple myeloma (MM) is the second most common hematologic malignancy, characterized by abnormal immunoglobulin overproduction and increased baseline proteotoxicity. Proteasome inhibitors (PIs), like bortezomib (BTZ), are frontline therapies that block protein degradation. This induces toxic protein accumulation, further increasing proteotoxic stress, resulting in MM cell death. Resistance to PIs creates an urgency for more effective therapies. Silver nanoparticles (AgNPs) increase protein oxidation and aggregation to selectively induce cell death in cancers with high protein secretory burden. AgNPs are distinct from silver ions (Ag+), which largely induce oxidative stress. The high baseline levels of proteotoxic stress and reactive oxygen species in MM make it an ideal candidate for AgNP therapy. This study evaluates AgNP-induced cytotoxicity in MM, examining differences between AgNPs and PIs on proteotoxic stress pathways and stromal microenvironment. **Methods:** AgNP and BTZ IC50 were determined for MM cell lines (JJN3, U266B1, MM1R, and MM1S) and stromal cells (HS5) through cell viability assays. Proteostat staining quantified protein aggregation to confirm induction of proteotoxicity by both therapies. Western blots assessed effects on ubiquitination, heat shock response (HSP70), integrated stress response (p-eif2α and eif2α), and autophagy (LC3-I, LC3-II, and p62) on MM and stromal cells. Stromal and MM cell co-culture experiments evaluated on-target toxicity (MM death) and off-target toxicity (stromal death) of each drug. AgNP and BTZ synergy was determined through fixed-ratio combination dosing; subsequent mono- and co-culture experiments assessed combined treatment efficacy and effects on proteotoxicity. **Results:** AgNPs and BTZ both induce proteotoxicity through increased protein aggregation, with distinct effects on proteotoxic stress pathways. BTZ treatment resulted in classical indicators of proteotoxicity such as ubiquitinated protein accumulation, increased heat shock response, and integrated stress response activation. AgNPs had little effect on those pathways, with treatment resulting in dysfunctional autophagy. AgNPs alone resulted in less stromal cell death in co-culture at the MM IC50 compared to BTZ. AgNPs and BTZ were highly synergistic in MM cells, with combination treatment at the synergy IC50 resulting in maximal on-target and minimal off-target effects in co-culture. Mechanistically, the combined treatment at the lower doses did not activate indicators of proteotoxicity. **Conclusions:** AgNP-induced cytotoxicity effectively treats MM, inducing proteotoxic stress through a distinct mechanism

from BTZ. AgNPs and BTZ are highly synergistic, allowing lower drug doses to achieve similar treatment efficacy; the combined mechanism is still unclear. Overall, AgNPs show promise as a second-line therapy for PI-resistant MM as well as a dose-sparing adjunct in frontline PI regimens.

PA-315

Tryptophan Metabolism in the Multiple Myeloma Microenvironment

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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 almost always go through cycles of treatment, remission, and treatment-resistant relapse. 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). Depletion of TRP suppresses T effector cell activation and the production of KYN activates pro-survival pathways and MM through the activation of the transcription factor Aryl Hydrocarbon Receptor (AHR). We now show that MM cells can produce KYN independent of DCs through the expression of the TRP catabolizing enzyme Tryptophan 2,3-Dioxygenase (TDO), indicating a mechanism by which MM can become independent of the BMME. **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 catabolizing enzymes with western blot and qPCR. TRP catabolizing enzyme TDO was knocked down with shRNA or inhibited with TDO-specific inhibitor 680C91. In some experiments, MM cell lines were co-cultured with monocyte-derived DC. AHR activation was measured through qPCR of CYP1a1, a transcriptional downstream target. KYN production was measured by ELISA. **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 non-competitive inhibitor 680C91 or knocking down TDO 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. Co-culture with IDO1+ DCs or 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. **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 and could repress T effector activation through the depletion of TRP. TRP metabolism is a novel treatment target in MM and could lead to more effective cell killing and immunotherapy, especially in relapsed/refractory disease.

PA-316

Ex Vivo Evaluation of BCL-2 Family Member Dependencies in Multiple Myeloma: Synergistic Combinations and Biomarkers of Sensitivity and Resistance

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Introduction: Multiple myeloma (MM) is a malignancy of plasma cells, with patients commonly developing resistance to multiple therapies. MM cell fate is controlled by a balance of BCL-2 family members, including BCL-2, BCL-XL, and MCL-1. In this study, we evaluated the cytotoxic activity of BCL-2 family inhibitors, both as single agents, in combination, and with standard MM therapies. We also aimed to identify predictive biomarkers and mechanisms of sensitivity or resistance to this class of agents. **Methods:** Ex vivo chemosensitivity assays were performed in a unique organotypic platform using 98 fresh primary MM samples, spanning smoldering MM to relapsed/refractory stages. Cytotoxic responses to single agents and combinations were quantified using area under the curve and LD50 metrics. Synergy and antagonism were assessed using the BLISS synergy model. Ex vivo data were integrated with molecular (WES, RNA-Seq) and clinical data using Fisher's Exact Test (mutations), enrichment analysis (transcriptional data), and adapted univariate Cox models to identify features associated with increased synergy or sensitivity ex vivo. **Results:** ABBV-467, an MCL-1 inhibitor, was the most potent single agent, with LD50 values in the nanomolar range. It showed particular efficacy against samples with t (14;16), gain1q21, mutations in PTPN11 and HUWE1, "MF" and "PR" transcriptional subtypes, and those overexpressing BAK1. The BCL-2 inhibitor venetoclax was highly effective in MM with t (11;14), gain18q, trisomy 13, mutations in ARID2, XBP1, CYLD and HUWE1, "CD1" and "CD2" subtypes, and those overexpressing BCL2. In contrast, BCL-XL inhibition with A-1331852 showed

limited single-agent activity. Among combinations, MCL1 + BCL-XL inhibition showed the strongest synergy, including in high-risk (HR) MM (hypodiploidy, t(14;16), del17p) and the "LB" subtype. BCL-2 + BCL-XL inhibition was also highly synergistic, especially in t(11;14) samples. MCL-1 + BCL-2 and BCL-2 + BCL-XL inhibition targeted complementary subgroups within the "PR" subtype (linked to poor prognosis). Interestingly, MCL-1 inhibition + Pom demonstrated increased activity in t(14;16) samples, and consistent with preclinical data, BCL-2 inhibition synergized with panobinostat. Molecular features associated with sensitivity to other combinations will be presented. **Conclusions:** BCL-2 and MCL-1 are the dominant anti-apoptotic BCL-2 family effectors in MM. While MCL-1 inhibition may effectively target specific HR MM subtypes, its activity is enhanced when combined with BCL-XL inhibition. These data also indicate that BCL-XL is a primary resistance factor, becoming relevant in the context of MCL-1 or BCL-2 inhibition, where significant synergy is observed. This underscores the pivotal role of BCL-2 family members in MM cell survival, including potential strategies that could exploit these vulnerabilities in certain high-risk subtypes.

PA-317

Decoding the PIM2 Transcriptional Network in Multiple Myeloma: A Novel Therapeutic Vulnerability

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Introduction: Multiple myeloma (MM) remains incurable due to inevitable drug resistance driven by PIM2 kinase overexpression, which correlates with poor prognosis. While ATP-competitive PIM2 inhibitors show limited clinical efficacy despite target relevance, our non-ATP competitive compound JP11646 demonstrates superior activity through PIM2 transcriptional downregulation, suggesting unexplored regulatory mechanisms. **Methods:** Chromatin immunoprecipitation, co-immunoprecipitation, and luciferase reporter assays characterized PIM2 promoter regulation. Wild-type and kinase-dead PIM2 constructs assessed nuclear localization and transcription factor interactions. SP1 binding site mutations in the PIM2 promoter evaluated regulatory requirements. Comparative studies tested JP11646 versus ATP-competitive inhibitors on cell viability and complex disruption. **Results:** Both wild-type and catalytically inactive PIM2 localized to the nucleus, forming a stable complex with MYC that binds the PIM2 promoter. Mutating a critical SP1 binding site at the PIM2 promoter reduced PIM2 transcription by >50%, confirming its regulatory necessity. JP11646 uniquely disrupted the PIM2-MYC-SP1 complex, decreasing PIM2 expression, MYC/PIM2 binding to the PIM2 promoter, and reducing cell viability much more effectively than ATP-competitive inhibitors, which failed to modulate this circuit. **Conclusions:** We identify a transcriptional autoregulatory mechanism sustaining PIM2 overexpression independent of catalytic activity, explaining limitations of conventional inhibitors. Targeting this circuit via JP11646 reveals a novel therapeutic strategy to overcome treatment resistance in MM.

PA-318

Precision Medicine in a Patient with Multiple Myeloma Presenting with t(2;11) and CCND1 Overexpression

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Introduction: Cytogenetic (CG) abnormalities are common in multiple myeloma (MM) and frequently involve the IGH locus (14q32.33). IGH rearrangements lead to specific oncogenes falling under control of the IGH enhancer. One such translocation, t(11;14) [IGH::CCND1], is associated with increased expression of CCND1 (11q13) and B-cell leukemia/lymphoma 2 (BCL-2) protein. Venetoclax, a BCL-2 inhibitor, is used in the treatment of this subset of MM patients. Translocations involving IGK (2p11.2), the light chain locus, and CCND1 are rarely described in MM and its functional significance is relatively obscure. Here, we present a unique case of newly diagnosed MM, with an unusual t(2;11)(p11.2;q13) that was refractory to multiple lines of therapy then demonstrated a rapid and durable response to a venetoclax-based treatment. **Methods:** n/a **Results:** A 71y/o female was diagnosed IgG lambda MM. Labs were notable for M-spike 2.11 g/dL, IgG 2,727 mg/dL, lambda free light chain 5,238.0 mg/L, kappa-lambda ratio 0.0, (R-ISS stage 1). PET/CT showed numerous hypermetabolic lytic lesions. Bone marrow biopsy (BMBx) showed 40% plasma cells (PC), with CG and FISH demonstrating a hypodiploid karyotype (6/20 of metaphase cells) and a balanced translocation of chromosomes 2 and 11. Due to t(2;11)(p11.2;q13), further FISH studies using IGK break-apart and IGH::CCND1 fusion probes were performed, with 85% of interphase cells exhibiting an IGK rearrangement and 82% with a gain of CCND1 without a detectable IGH::CCND1. BCL-2 (3+) and Cyclin D1 were positive by IHC. First line bortezomib, lenalidomide and dexamethasone was started with a partial response. On progression, repeat BMBx was sent for NGS, which confirmed IgK::CCND1. She received two additional lines of therapy with rapid progression. On subsequent BMBx, whole exome sequencing showed that the IGK::CCND1 rearrangement resulted in the fusion of exon 4

of IGK to the 3′ UTR of CCND1. The decision was made to transition to venetoclax, carfilzomib and dexamethasone. 6 months later, workup showed a stringent complete response (sCR) with normal CG studies. The patient has remained in a sCR with persistent Measurable Residual Disease by NGS exceeding 3 years. **Conclusions:** Here we describe a rare case of t(2;11)(p11.2;q13) identified by a gain of CCND1 without IGH::CCND1 in the background hypodiploidy. Cyclin D1 overexpression suggests that the proximity of the IGK enhancer to the 3′ region of CCND1 may be sufficient to upregulate CCND1 transcription. As overexpression of BCL-2 was seen, venetoclax was considered for treatment. This patient represents the only case described of t(2;11)(p11.2;q13) in MM treated with venetoclax. This case highlights the power of molecular diagnostics in identifying rare rearrangements, such as those involving IGK, or when a gain of CCND1 is identified without hyperdiploidy or IGH::CCND1. This approach identified biomarkers that allowed for tailored treatment that was more effective and better tolerated than standard therapy for the patient.

PA-319

Preclinical Activity of Pharmacological Inhibitors Targeting KRAS and pan-RAS in Multiple Myeloma

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Introduction: RAS mutations are among the most frequent oncogenic drivers of both solid tumors and hematologic malignancies. In particular, point mutations in codons 12, 13, and 61 disrupt the intrinsic GTPase activity of RAS proteins, resulting in constitutive activation of key survival and proliferation pathways, including those signaling via MEK/MAPK and PI3 K/AKT. Recently, KRAS G12C-specific inhibitors have demonstrated clinical efficacy in solid tumors such as non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). However, their narrow mutation specificity limits the relevance in hematologic malignancies like multiple myeloma (MM). In contrast, novel KRAS- and pan-RAS-targeting inhibitors with broader activity profiles may offer therapeutic potential for a wider subset of MM patients. **Methods:** We assessed the distribution of KRAS and NRAS point mutations in MM, based on genomic data from n = 992 patients in the CoMMpass study (MMRF release IA22). Additionally, we evaluated the activity of the KRAS-specific small molecule inhibitor BI-2865 and the pan-RAS (RAS-ON) inhibitor RMC-6236 in a panel of RAS-mutant MM cell lines. Cellular responses were measured using proliferation and viability assays (CTG). **Results:** Unlike NSCLC and CRC, where KRAS codon 12 mutations predominate (89% and 65%, respectively), MM exhibits a distinct mutational landscape, with codon 61 mutations being most frequent in both KRAS (37%) and NRAS (70%), followed by mutations in codons 12 and 13. The KRAS-specific inhibitor BI-2865 showed selective activity preferentially in MM lines harboring KRAS codon 12 mutations. The pan-RAS inhibitor RMC-6236 demonstrated different levels of activity across MM lines with various KRAS and NRAS mutations, including those in codons 12, 13 and 61. **Conclusions:** Novel pharmacological KRAS and pan-RAS inhibitors with broader activity profiles show promising efficacy against RAS-mutated MM lines. These agents may significantly extend the therapeutic relevance of RAS-targeted therapies in MM, ultimately offering new therapeutic approaches for a larger number of MM patients.

PA-320

Unc-51 Like Kinase 3 (ULK3) is Essential for Autophagy and Cell Survival in Multiple Myeloma

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Introduction: Despite the availability of effective therapies, multiple myeloma (MM) patients often relapse with refractory disease. **Methods:** To identify novel targets that drive this skeletal malignancy, we assessed RNA sequencing data performed on CD138 + MM patient cells (n = 813) with premalignant, newly diagnosed, and relapsed/refractory disease. These analyses revealed a significant correlation between an autophagy gene signature and MM progression. While basal rates of autophagy are known to be high in MM, Unc-51 Like Kinase 3 (ULK3) significantly correlated with disease progression. **Results:** Here, we report a role for ULK3 as part of a ULK-ATG13-FIP200 effector complex in controlling autophagy and MM cell survival. Further, we generated multi-kinase inhibitors (SG3-014/MA9-060) that block ULK3 enzymatic activity in the nanomolar range and co-crystalized the MA9-060: ULK3 complex to reveal its molecular binding mode. In vivo, ULK3 blockade significantly reduced MM burden, improved overall survival, and protected against cancer-induced bone disease. Furthermore, MM cells resistant to proteasome inhibitors (PI) can be resensitized to PI by co-treatment with MA9-060. Importantly, these findings were validated with specimens from newly diagnosed and refractory MM patients. In fact, potent synergy was observed with MA9-060/PI combination in specimens expressing high levels of ULK3. **Conclusions:** Collectively, these findings indicate a new role for

ULK3-mediated autophagy in cancer and suggest that ULK3 inhibition is an effective treatment strategy for both newly diagnosed and refractory MM disease.

PA-321

Belantamab Mafodotin plus Lenalidomide/Dexamethasone in Newly Diagnosed Patients with Multiple Myeloma: Long-Term Efficacy and Safety Results from the Phase 1/2 BelaRd Study

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Introduction: We present long-term outcomes on the safety/efficacy of belantamab mafodotin (belamaf), administered at an extended dosing schedule with lenalidomide/dexamethasone (Rd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients (pts). **Methods:** Part 1 (dose finding) of the ongoing phase 1/2 BelaRd trial (NCT04808037) assessed the safety/tolerability of belamaf 2.5/1.9/1.4 mg/kg plus Rd, establishing a recommended phase 2 dose (RP2D) of 1.9 mg/kg Q8W (extendable to Q12W), guided by ophthalmologist-assessed ocular adverse events (OAEs; best corrected visual acuity [BCVA] change from baseline and keratopathy) using the Keratopathy and Visual Acuity scale. In Part 2 (dose extension), the safety/efficacy of belamaf RP2D plus Rd is evaluated in 2 groups: in Group A belamaf dosing is guided by ophthalmologist-assessed OAEs, and in Group B dosing is guided by hematologist-assessed patient-reported, 9-question Vision-Related Anamnestic tool (VRA; capturing ocular symptoms & their impact on activities of daily living [ADL], rated as occurring substantial/minimal/none of the time) and Gr≥3 OAEs. Long-term (cutoff 01/03/2025) safety/efficacy results from Parts 1/2 are presented. **Results:** Of Part 1 pts (n = 36; median age: 73 yrs), 25 (69%) are ongoing with treatment, and 11 (31%) discontinued (fatal adverse event [AE]: 8 [22%]; progressive disease [PD]: 1 [3%]; consent withdrawal: 2 [6%]). 17%/75% of pts had stage I/II disease per R-ISS and 8% had high-risk cytogenetics. At a median follow-up of 39 months, the overall response rate (ORR) was 100%. Meaningful BCVA decline (Snellen < 20/50 and ≥3 lines drop in better-seeing eye) was noted in 15% and Gr2/≥3 keratopathy in 11%/3% of ocular exams. Median times to resolution (TTR) of Gr≥2 BCVA/keratopathy were 2/1 months. Most common (≥10%) non-ocular Gr≥3 AEs were fatigue, diarrhea, rash, COVID-19, pneumonia, and insomnia. Of Part 2 pts (n = 30; median age: 76 yrs), 22 (73%) are ongoing with treatment and 8 (27%) discontinued (fatal AE: 6 [20%]; PD: 1 [3%]; consent withdrawal: 1 [3%]). 27%/63% of pts had stage I/II disease per R-ISS and 17% had HRC. At a median FU of 23 months, ORR was 97%. Meaningful BCVA decline was noted in 9% and Gr2/≥3 keratopathy in 9%/< 1% of ocular exams. The median TTR of Gr≥2 OAEs was 2 months. Most common (≥10%) non-ocular Gr≥3 AEs were fatigue and rash. Across the ADL-related questions of the VRA, assessments with 'substantial' time findings were 2%/6% in Groups A/B. Discordance between Gr≥3 OAE and less than 'substantial time' findings reported with the VRA tool occurred in 10/300 and 2/251 ocular assessments in Groups A/B and in none (0/121) of the Group B dosing cycle assessments. The 12/24/36-month time to progression rates for all 66 pts were 98%/98%/94%. **Conclusions:** Consistent with the DREAMM-7/8, belamaf exhibits notable clinical activity in unfit NDMM, achieving rapid, deep, and durable responses. OAEs resolved quickly, without substantially impacting the ADL. No new safety signals emerged.

PA-322

eMMpower: A Longitudinal Multi-Center Chart Review Consortium for Multiple Myeloma (MM)

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Introduction: With the rapidly evolving treatment paradigm in MM, timely, high-quality, representative real-world evidence (RWE) is critical to inform clinical practice and advance MM care. However, existing real-world data (RWD) sources often lack clinical depth, physician-confirmed response, cytogenetics, and diversity in demographics and care setting needed for robust RWE generation. To address these gaps, the eMMpower consortium was established to provide a strong infrastructure with continual, long-term data collection in the US and a GenAI-enabled rapid analytics platform, to help expedite decision-making and evidence generation. In

consultation with MM experts, eMMpower aims to deliver critical insights into MM care. **Methods:** eMMpower is a multi-site retrospective chart review consortium collecting clinically rich, longitudinal RWD that is reflective of demographics of patients with MM, geography, and practice type in the US. eMMpower gathers detailed patient characteristics, treatment patterns and sequencing, and outcomes across the MM care continuum—from frontline therapy in transplant-eligible (TE) and -ineligible (TIE) pts to later-lines of therapy where bispecific T-cell engagers and CAR-T are approved for use. A 5-year data collection plan with annual updates supports robust longitudinal analyses. The current target is 2,000 patients (pts) from 20 high-volume US centers and large health care systems. A clinician-led steering committee with rotating membership sets scientific priorities aligned with emerging clinically-relevant questions unanswered by clinical trials and other RWD with an emphasis on practice-informing RWE. Proposals are reviewed biannually by the committee and are selected based on scientific merit, feasibility, and translational impact. **Results:** As of 3/31/2025, 14 sites joined eMMpower, including 10 academic medical centers (2 Northeast; 3 Midwest; 2 South; 3 West), 3 community networks (2 National; 1 South), and a national patient advocacy organization. The 12-member steering committee approved 7 proposals in 12/2024 (3 frontline-focused, 4 later line-focused). Nine sites have begun data collection, among which 44% see ≥50 new MM pts/year, 68% offer SCT, and 89% offer CAR-T. To date, six sites have provided deidentified data on 499 pts: 260 TE pts on frontline therapy, 161 pts on teclistamab and 78 pts on talquetamab. Seventeen percent of included pts were African American. Data for other novel frontline and later-line treatments will also be collected in the future. **Conclusions:** eMMpower marks a major advancement in RWD collection for MM. Through diverse patient representation in demographics, geography, and practice type, varied clinical settings and robust longitudinal data, it offers a powerful platform for timely and clinically relevant insights through clinician-led research. eMMpower has the potential to redefine the role of RWD in MM—filling key evidence gaps, informing care, supporting innovation and raising treatment standards for patients.

PA-323

LILRB4 Protects Multiple Myeloma Cells from Ferroptosis to Promote MM Progression

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Introduction: Multiple myeloma (MM) is the second most common hematologic malignancy. Although multiple targets on MM cells are discovered and applied in clinical treatment, relapse is almost inevitable in MM patients. In our previous study, a high-risk cell cluster was found from MM patients with overall survival less than 2 years by single-cell RNA sequencing (scRNA seq). In this specific cluster, LILRB4 a novel biomarker for high-risk myeloma patients, was highly expressed, indicating the critical role of LILRB4 in myelomagenesis and drug resistance. However, the mechanisms of LILRB4 in MM development has not been fully understood. Here, we investigated the role of LILRB4 in tumorigenesis and MM cell proliferation. **Methods:** in results. **Results:** Our clinical data revealed that MM patients with elevated LILRB4 expression had poor prognosis and reduced overall survival, underscoring its potential role in disease progression and drug resistance. In vitro experiment showed that LILRB4-overexpressing (LILRB4-OE) MM cells enhanced the cell colony-forming ability, promoted cell proliferation but not affected cell apoptosis. We used LILRB4-OE MM cells to establish myeloma xenograft model and results showed that mice injected with LILRB4-OE MM cells exhibited accelerated tumor growth and reduced survival compared to those receiving LILRB4-negative cells. Transcriptomic profiling of LILRB4-OE MM cells revealed activation of the NF-κB signaling pathway, consistent with our findings and previous literature. Notably, RNA-seq data also indicated activation of the STAT3 pathway and upregulation of its downstream effector PIM1, suggesting that LILRB4 may drive MM proliferation via the STAT3/PIM1 axis. Importantly, treatment with the PIM inhibitor AZD1208 abrogated the proliferative advantage conferred by LILRB4 overexpression. Interestingly, Gene Ontology (GO) enrichment analysis further revealed that cholesterol and sterol metabolic processes were significantly enriched in LILRB4-OE MM cells, indicating altered lipid homeostasis. Ferroptosis is highly related to lipid metabolism and driven by the lethal lipid peroxidation. Recently, more and more evidence proved that inducing ferroptosis improved the effectiveness of immunotherapy, which may be a potential therapeutic strategy for relapsed patients. Given the established link between lipid metabolism and ferroptosis, we investigated the sensitivity of MM cells to ferroptotic cell death. Treatment with RSL3, a ferroptosis inducer targeting GPX4, resulted in significantly increased cell death in LILRB4-knockout (LILRB4-KO) MM cells, which can be reversed by ferroptosis inhibitor, suggesting that LILRB4 plays a protective role against ferroptosis. **Conclusions:** In conclusion, LILRB4 is highly associated with poor prognosis of MM patients and has the ability of tumorigenesis. LILRB4 promotes MM cell proliferation through STAT3/PIM1 signaling pathway and protects MM cells from ferroptosis, which plays critical roles in MM pathogenesis.

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AKR1B1/NAT10 Mediate IL4I1 ac4C Modification to Regulate Tryptophan Metabolism and Promote Multiple Myeloma Proliferation

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Introduction: Multiple myeloma (MM) is a malignant plasma cell tumor with a rising annual incidence rate and cannot be cured. Identifying novel molecular targets for the diagnosis and treatment of MM, as well as improving patient outcomes, is a crucial step in both basic and clinical research. Metabolic disorder is a significant factor in the poor prognosis of MM patients. Aldo-keto reductase family 1 member B1 (AKR1B1), which regulates glucose metabolism, participates in regulating the occurrence and development of various tumors, but its role in MM remains unclear. **Methods:** Analysis of AKR1B1 expression and prognosis in MM patients via gene expression profiling. Immunohistochemistry (IHC) and Western blot (WB) were employed to detect AKR1B1 expression. Co-immunoprecipitation (Co-IP)/MS and RNA sequencing (RNA-seq) were used to screen interacting proteins and key downstream targets of AKR1B1. The impact of AKR1B1 on cell proliferation was assessed through CCK-8, soft agar assays, and xenograft models. Acetylated RNA immunoprecipitation sequencing (acRIP-seq) and mRNA decay analysis were conducted to identify and validate critical downstream targets. Targeted metabolomics was applied to identify differential metabolites in MM cells. Nuclear-cytoplasmic fractionation assays were performed to examine protein nuclear translocation. **Results:** Elevated AKR1B1 expression was significantly associated with shorter overall survival (TT2: P = 0.0019; TT3: P = 0.0003). IHC staining revealed higher AKR1B1 levels in bone marrow tissues of MM patients (n = 20) compared to normal controls (n = 8). AKR1B1 overexpression promoted MM cell growth. KEGG analysis of RNA-seq data indicated that AKR1B1 induced dysregulation of the MAPK signaling pathway, metabolic pathways, and apoptosis. Mechanistic validation demonstrated that AKR1B1 activates p-38 expression, while AKR1B1 knockdown induced cleaved PARP and cleaved Caspase 3 expression to accelerate apoptosis. Co-IP/MS revealed an interaction between AKR1B1 and N-acetyltransferase 10 (NAT10). AKR1B1 interacts with NAT10 to promote interleukin-4-induced 1 (IL4I1) mRNA acetylation, enhancing its translation efficiency and driving MM progression. Targeted metabolomics demonstrated that IL4I1, regulated by AKR1B1, facilitates tryptophan metabolism in MM cells. Tryptophan metabolism was closely linked to activation of the aryl hydrocarbon receptor (AHR) signaling pathway. The reactome enrichment analysis of RNA-seq data highlighted AKR1B1's role in modulating AHR signaling. Overexpression of AKR1B1 and IL4I1 promoted AHR nuclear translocation, while AKR1B1 knockdown inhibited this process, indicating that AKR1B1/IL4I1 activates the AHR pathway. **Conclusions:** AKR1B1 emerges as a novel regulator of ac4C modification and tryptophan metabolism, and targeted inhibition of AKR1B1 may offer a promising therapeutic strategy for MM.

PA-325

RNF5-DNAJA1 Axis Dictates Selinexor Sensitivity of Multiple Myeloma

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Introduction: Selinexor is the only clinically validated and FDA approved Exportin 1 (XPO1) inhibitor. Despite these limited reported mechanisms of selinexor resistance of MM, the underlying mechanisms remain largely unknown. In this research, we performed proteomic assay on selinexor-treated MM cells to explore the re-distribution of proteins in nucleus and cytoplasm and identify key regulators for selinexor sensitivity. We found a new XPO1-RNF5-DNAJA1 complex in regulating mitochondrial function through activating the UPRmt pathophysiological processes. We also assessed the efficiency of targeting RNF5 and DNAJA1 in augmenting sensitivity of MM to selinexor treatment through in vitro and in vivo experiments. **Methods:** we treated LP-1 cells using selinexor and further performed proteomic assay to compare the protein distribution in the nucleus and cytoplasm against vehicle control cells. We suppressed RNF5 expression using shRNA and ectopically over-expressed RNF5 in LP-1 and MM.1S cells, respectively. Establish the xenograft model and bone-lesion model in the NSG mice to evaluate the in vivo anti-tumor effects of Selinexor. Next, we performed bulk RNA-sequencing assay to identify downstream target genes of RNF5-DNAJA1 axis. To elucidate the practical potential of our findings, we evaluated the efficacy of the combination of targeting RNF5-DNAJA1 axis with selinexor both in vitro and in vivo. **Results:** We report a novel mechanism by which XPO1 regulates the translocation of RNF5 from the nucleus to the cytoplasm. In our proteomic analysis, we found that RNF5 was a downstream cargo in the nucleus-cytoplasm translocation process mediated by XPO1. RNF5 induces the K29-linked polyubiquitination of DNAJA1 to control the interaction between DNAJA1 and HSP70, leading to the release of HSF1 into nucleus and activation of UPRmt, thus the re-distribution of RNF5 in the cytoplasm results in improved sensitivity of MM cells to selinexor. Mitochondria in RNF5-DNAJA1 axis disturbed MM cells showed a more swollen morphology, lower levels of OCR, ATP production and UPRmt, proved the protective role of RNF5-DNAJA1 axis in mitochondrial morphology. **Conclusions:** Our study for the first time discovers XPO1 imports RNF5 from nuclear to cytoplasm, and RNF5 consequently modifies K29-linked ubiquitination of DNAJA1 to enhance the recruitment of HSP70. Our study also found that RNF5 induces the K29-linked polyubiquitination of DNAJA1 to control the interaction between DNAJA1 and HSP70, leading to the release of HSF1 into nucleus

and activation of UPRmt, thus the re-distribution of RNF5 in the cytoplasm results in improved sensitivity of MM cells to selinexor. The significance of our study is to prove a theoretical basis for developing treatment strategies targeting the RNF5-DNAJA1 axis to improve sensitivity to selinexor when managing RRMM patients in the clinic.

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Phosphorylation Protects Oncogenic RAS from LZTR1-Mediated Degradation in Multiple Myeloma

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Introduction: Oncogenic mutations in KRAS and NRAS are prevalent in relapsed and refractory multiple myeloma (MM). Given the difficulties in directly targeting RAS, compounded by the heterogeneous genetic landscape and diverse RAS mutations in hematological malignancies, alternative therapeutic strategies are critically needed. Therefore, we conducted multi-omic screening to identify novel regulators of RAS protein stability, aiming to uncover alternative RAS-targeting approaches relevant to these cancers. **Methods:** We used a CRISPR screening approach to identify regulators of KRAS protein stability. **Results:** These screens revealed that PP1C dephosphorylates the conserved T148 residue on both KRAS and NRAS, a critical step that facilitates their proteasomal degradation via LZTR1. Interestingly, PP1C and LZTR1 appear to preferentially regulate RAS stability in hematological cancers. Furthermore, mutations at KRAS A146, a residue adjacent to T148 and frequently found in MM, led to resistance against LZTR1-mediated ubiquitination and degradation of RAS. Our research also uncovered that PAK1 and PAK2 kinases counteract PP1C by phosphorylating T148, effectively protecting RAS from degradation. Consequently, inhibiting PAK1/2 resulted in a reduction in RAS protein expression. **Conclusions:** These findings reveal a novel regulatory circuit controlling RAS stability. This discovery offers a promising therapeutic strategy for targeting RAS-driven hematological malignancies.

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Carfilzomib, Pomalidomide, Dexamethasone ± Daratumumab Delivers Survival Benefit Regardless of Cytogenetic Risk in Early Relapsed Myeloma Patients-A Multi-Center, Prospective Real World Study in China

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Introduction: This study aims to evaluate the efficacy and safety of carfilzomib, pomalidomide, and dexamethasone with or without daratumumab in treating relapsed/refractory multiple myeloma in real-world practice. **Methods:** This multicenter, prospective, real-world cohort study was conducted across eight hospitals in northern China since 2022. Eligible participants included adults diagnosed with RRMM who had received at least one prior line of therapy. Patients were treated with KPd with or without Dara until disease progression. Data on baseline characteristics, cytogenetic abnormalities, and adverse events were collected. Carfilzomib, pomalidomide, dexamethasone, (and Dara) were administered in 28-day cycles. The primary endpoint was the overall response rate (ORR), with secondary endpoints including progression-free survival (PFS) and overall survival (OS). Statistical analyses included χ^2-test, t-test, Kaplan-Meier, and COX regression methods. **Results:** This study enrolled 100 RRMM patients including 69 in KPd and 31 in DKPd with balanced baseline characteristics ($P > 0.05$), of whom 69.1% had high-risk cytogenetic abnormalities according to mSMART 3.0 criteria. The median age was 63.5y (47–84; 46% >65y) with KPd vs 62y (44–84; 42% >65y) with Dara-KPd. Notably, the median number of prior lines was 2 with 45.2% 1 prior line in DKPd vs 69.6% ≥2 lines in KPd. More patients received ASCT in Dara-KPd group (41.9% vs 26.1%). Plasma cell leukemia (PCL) was diagnosed in 14% of patients, while 30.6% had extramedullary disease before starting KPd ± Dara. Most patients exposed to lenalidomide (85%) or bortezomib (97%). After a median follow-up of 11 months (range: 7–18), the ORR was 75.4% (73.3% for KPd vs. 79.2% for Dara-KPd). Kaplan-Meier analysis indicated a median PFS of 22 months (KPd 22m, DKPd NR, $P = 0.687$), while median OS was not reached in the whole cohort ($P = 0.790$). Importantly, PFS/OS data in KPd ± Dara regimen was comparable between high-risk and standard-risk subgroups ($P = 0.501/0.603$). Treatment efficacy was correlated with prior lines, exhibiting superior PFS in first relapse compared to late ones (1 prior line ≥ 3 lines, $P = 0.049$). Hematologic adverse events were common but mostly grade 1 or 2. Cardiovascular toxicities were mild, with hypertension in 8.1% and palpitations in 17.4% of patients. One patient died from severe pulmonary infection. **Conclusions:** In the post-VRd era, this study confirms KPd ± Dara as a preferred therapeutic strategy for RRMM, particularly in lenalidomide/bortezomib-exposed, high-risk populations. Our real-world findings not only validate the regimen's robust efficacy and safety profile in Chinese patients, but more importantly, demonstrate its strength to compromise high-risk biology and deliver superior outcomes in early relapse settings.For RRMM patients, KPd ± Dara represents a safe and effective treatment option.

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Inhibition of DNA Damage Response Factor DNA-PKcs-Mediated H2AX Phosphorylation Enhances Selinexor-Induced Anti-Multiple Myeloma Effects

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Introduction: Abnormal DNA damage response (DDR) in multiple myeloma (MM) promotes genomic instability and drug resistance. DNA-PKcs is a key DDR factor in non-homologous end joining (NHEJ) repair for DNA double-strand breaks. Under certain conditions, it can compensate for ATM to initiate H2AX phosphorylation (γH2AX), which coordinates DDR signaling and promotes DNA repair. Selinexor, an exportin 1 (XPO1) inhibitor, targets the nucleocytoplasmic transport of macromolecules. It suppresses DDR gene expression and homologous recombination (HR) repair. However, it remains unclear whether XPO1 regulates the activation and transport of DDR proteins like DNA-PKcs, and if DNA-PKcs modulates MM cells' sensitivity to Selinexor by influencing DNA damage repair. This study explores the role of DNA-PKcs in Selinexor-induced DNA damage and apoptosis in MM. **Methods:** n/a **Results:** We first discovered XPO1 inhibition by Selinexor or knockdown promoted DNA-PKcs phosphorylation at S2056 and increased γH2AX expression in MM cells, without affecting ATM or ATR activation. Subcellular fractionation showed inhibiting XPO1 reduced cytoplasmic DNA-PKcs but recruited more DNA-PKcs to chromatin and promoted DNA-PKcs phosphorylation on chromatin. We then found Selinexor-induced stimulation of chromatin-bound DNA-PKcs primarily regulated H2AX phosphorylation. Inhibiting DNA-PKcs, via knockdown or its inhibitor Nedisertib, reduced Selinexor-induced γH2AX expression. This reduction likely impairs the recruitment of various DDR factors, disrupting DNA damage repair. Indeed, Using CRISPR/Cas9 gene-editing system and NHEJ/HR reporters in U2OS cells, we observed Selinexor inhibited HR repair without affecting NHEJ repair, and the addition of DNA-PKcs inhibitor Nedisertib enhanced Selinexor's suppression of HR repair and even induced its inhibition of NHEJ repair in U2OS cells. Consistent with these findings, Comet and TUNEL assays confirmed DNA-PKcs inhibition enhanced Selinexor-induced DNA damage in MM cells. Since excessive DNA damage can lead to cell death, we next investigated the role of DNA-PKcs inhibition in MM sensitivity to Selinexor. Results showed DNA-PKcs knockdown promoted Selinexor-induced apoptosis and increased MM sensitivity to Selinexor. The combination of Nedisertib and Selinexor exhibited a significantly synergistic killing effects on MM cells in vitro; in vivo, this combination treatment slowed MM tumor growth. Notably, Nedisertib did not enhance Selinexor-induced apoptosis in PBMCs from healthy donors. **Conclusions:** DNA-PKcs-mediated H2AX phosphorylation promotes DNA damage repair and survival of myeloma cells in response to XPO1 inhibitor Selinexor. DNA-PKcs inhibition increases Selinexor-induced DNA damage and enhances MM sensitivity to Selinexor. The combination of DNA-PKcs inhibitor Nedisertib with Selinexor demonstrates strong synergistic anti-MM effects both in vitro and in vivo. These findings suggest that dual targeting of DNA-PKcs and XPO1 could serve as a promising new strategy for treating MM.

PA-329

A Multi-Step Virtual Screening Framework Identifies Novel GPRC5D Inhibitors for Multiple Myeloma Therapy

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Introduction: GPRC5D, an orphan GPCR overexpressed in multiple myeloma (MM) cells, has emerged as a critical therapeutic target due to its selective expression in malignant plasma cells and minimal presence in healthy tissues. While immunotherapies such as CAR-T cells and bispecific antibodies targeting GPRC5D show clinical promise, challenges including relapse and toxicity underscore the need for small-molecule inhibitors with improved pharmacokinetic profiles. This study addresses this gap by employing a multi-tiered computational strategy to discover novel inhibitors with high binding affinity and drug-like properties. **Methods:** A hybrid virtual screening pipeline was developed, integrating deep learning, molecular docking, and molecular dynamics (MD) simulations. The crystal structure of GPRC5D (PDB: 9IMA) was optimized through energy minimization and MD simulations in a POPC membrane environment. Binding pockets were predicted using SiteMap, identifying a high-scoring cavity near residues ASP238, ASP239, and ASN167. A library of 8,617 drug-like compounds from MedChemExpress underwent sequential screening: PLANET prioritized candidates based on predicted affinity; Vina-GPU refined the selection via docking scores; MM/GBSA calculated binding free energies; and admetSAR3.0 evaluated pharmacokinetic properties, including QED, LogP, BBB permeability, and DILI risk. **Results:** Virtual screening identified 1,694 initial hits, narrowed to 120 candidates through MM/GBSA. The top 10 compounds, ranked by QED scores (0.48–0.68), underwent MD simulations to assess binding stability. Four compounds (1, 2, 7, 8) demonstrated robust interactions: Compound 1 exhibited hydrogen bonds with ASN167, salt bridges with ASP238/239, and π-cation interactions with PHE170 (ΔGbind = −76.986 kcal/mol). Compound 2 formed a

salt bridge network via its piperazine ring (ΔGbind = −79.773 kcal/mol). Compounds 7 and 8 maintained stable RMSD (<2.5 Å after 300 ns) and low residue fluctuations (RMSF <3.2 Å), interacting with MET161 and PHE158. All candidates met drug-likeness criteria: molecular weight < 500 Da, TPSA <140 Å^2, and favorable ADMET profiles, including low hepatotoxicity risk and moderate BBB penetration. **Conclusions:** This study successfully identifies four novel GPRC5D inhibitors with strong binding affinities and optimized pharmacokinetic properties. The interactions with key residues (ASP238, ASP239, ASN167) provide mechanistic insights for rational drug design, while the integrated computational framework demonstrates the efficacy of combining deep learning, docking, and MD simulations for orphan GPCR-targeted discovery. These compounds represent promising candidates for preclinical evaluation, offering a foundation for developing orally bioavailable therapies to complement existing immunotherapies in MM. Future work will focus on in vitro validation, structural optimization, and elucidating GPRC5D's activation mechanisms to advance translational applications.

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Prognostic Determinants of Overall Survival in POEMS Syndrome: A 7-Year Single-Center Retrospective Analysis

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Introduction: POEMS syndrome is a rare and complex plasma cell disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. While outcomes have improved with advances in plasma cell–directed therapies, prognosis varies considerably, especially in patients who develop coexisting hematologic malignancies such as multiple myeloma, AL amyloidosis, or lymphoma. The rarity and heterogeneity of the disease have limited efforts to define reliable prognostic markers. In this retrospective study, we aimed to identify clinical and laboratory factors associated with overall survival (OS) in a large real-world cohort of patients with POEMS. **Methods:** We reviewed 78 patients diagnosed with POEMS syndrome at a tertiary medical center between January 2018 and April 2025. Baseline demographics, laboratory values, treatment approaches, and survival data were collected. Patients were grouped based on whether they had coexisting hematologic malignancies. Most patients received systemic therapy, including regimens based on bortezomib, lenalidomide, and dexamethasone. Multivariate Cox regression was used to identify independent predictors of OS. **Results:** The median age at diagnosis was 55.5 years (range: 21–76), and 69.2% were male. Neurological symptoms were the most common presenting complaint (70.5%), followed by peripheral edema (17.9%). The median time from symptom onset to diagnosis was 8 months. Organomegaly (79.5%), fluid overload (71.8%), and endocrinopathy (48.7%) were frequently observed at baseline. Of the 60 patients who received systemic therapy, 53.3% achieved complete remission and 26.7% achieved partial remission or better. After a median follow-up of 34 months, the estimated 5-year OS rate was 80.0%. In multivariate analysis, age >60 years, serum albumin < 33 g/L, and serum IgA >5.9 g/L emerged as independent predictors of poorer OS (all $p < 0.05$). In subgroup analysis, patients with concomitant hematologic malignancies had significantly higher IgA levels, lower platelet counts, and reduced eGFR compared to those without. These findings suggest a more aggressive disease phenotype and correspondingly worse outcomes in this subgroup. **Conclusions:** This study highlights several practical prognostic indicators for POEMS syndrome. Advanced age, low serum albumin, and elevated IgA levels were each independently associated with reduced survival. The presence of coexisting hematologic malignancies further identifies a high-risk group with more aggressive clinical features. These findings emphasize the importance of early risk stratification and may inform individualized treatment strategies. Prospective multicenter studies are warranted to validate these observations and better understand the biological mechanisms driving outcome differences in POEMS.

PA-331

Real World Outcomes in Cardiac AL Amyloidosis: A Decade of Experience at a Multidisciplinary Amyloidosis Center

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Introduction: Light Chain (AL) amyloidosis results from the deposition of abnormally folded monoclonal light chains in organs, with cardiac involvement being a major prognostic factor. Our institution has a multidisciplinary Amyloidosis Center combining hematology and cardiology expertise to manage complex cardiac AL amyloidosis. Recent advances in systemic therapy, including

proteasome inhibitors, CD38 monoclonal antibodies, and investigational anti-fibril agents, along with specialized cardiac interventions such as advanced heart failure therapies and cardiac transplantation, are being incorporated into the care of patients with cardiac amyloidosis. We aimed to evaluate real-world outcomes in cardiac AL amyloidosis patients at our multidisciplinary Amyloidosis Center over a 10-year period. **Methods:** Our Institution's electronic medical record was queried to identify patients with biopsy-proven AL amyloidosis and cardiac involvement from January 2012 until January 2022. All patients over the age of 18 who followed up at our institution after their initial diagnosis were included. A total of 416 patients met inclusion criteria and were evaluated. Clinical data was reviewed by authors D.B. and A.M. and conflicts were resolved by consensus. The primary endpoint was overall survival (OS). **Results:** Among 416 patients, the median age at diagnosis was 68 (range 31–92), 265 (63.7%) were male, 151 (36.3%) were female, 327 (78.61%) were Caucasian, 78 (18.75%) were African American, and 11 (2.64%) identified as Other race. At diagnosis, 100% had cardiac involvement and 22% had renal involvement. Most patients had advanced-stage disease, with 82.93% of patients having a Revised Mayo stage of 3 or 4. First-line therapies included CyBorD (51.9%), daratumumab-CyBorD (14.7%), bortezomib-dexamethasone (16.8%), clinical trials (5.4%), and others (10.7%). Autologous stem cell transplantation was performed in 10.8% as part of first-line therapy following induction. At five years, OS was 53.6% (95% CI, 26.5–100) for stage I, 73.3% (61.1–87.9) for stage II, 45.5% (36.5–56.7) for stage III, and 32.8% (27.0–39.9) for stage IV. At ten years, OS was 53.6% (26.5–100) in stage I, 47.1% (30.4–73.2) in stage II, 23.9% (13.5–42.3) in stage III, and 22.1% (15.3–31.9) in stage IV. Among patients who survived to 5 years, the probability of reaching 10 years was 100% for stage I, 64% for stage II, and 53% for stage III. Around 67% of stage IV patients who survived to year 5 were alive at year 10. **Conclusions:** Our data underscore the importance of multidisciplinary management in improving survival outcomes for patients with cardiac AL amyloidosis. As demonstrated at our institution, long-term survival is increasingly achievable with integrated hematologic and cardiac care, novel therapeutics, and access to clinical trials—even in those with advanced-stage disease. These findings emphasize the need for timely diagnosis, referral to specialized centers, and unique individualized strategies to optimize outcomes.

PA-332

Clinical Study on the Efficacy and Safety of Aponermin Combined with Dexamethasone-Based Regimen in Multidrug-Resistant Multiple Myeloma

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Introduction: To investigate the efficacy and safety of an aponermin combined with dexamethasone-based regimen in patients with multidrug-resistant multiple myeloma (MM). **Methods:** A retrospective analysis was conducted on clinical data from 26 patients with relapsed/refractory MM treated at The First Affiliated Hospital of Sun Yat-sen University between October 1, 2024, and April 30, 2025. Data included demographic characteristics, R-ISS staging, M-protein subtype, light chain type, cytogenetic abnormalities, and prior treatment regimens. Enrolled patients had received 2–5 prior lines of therapy. The efficacy and safety of the aponermin plus dexamethasone-based regimen were evaluated. **Results:** Among the 26 patients, 65.38% were male, with a median age of 64 years (range: 50–79). R-ISS stages II–III predominated (23/26, 88.5%). The most common M-protein subtypes were IgG (9/26, 34.6%) and IgA (5/26, 19.2%). Cytogenetic abnormalities included 1q21 amplification (14/26, 53.8%) and t(4;14) (6/26, 23.1%). All patients had received 2–5 prior lines of therapy. Following treatment with the aponermin -dexamethasone-based regimen, 17 patients (65.4%) achieved ≥ partial response (PR), 1 patient (3.8%) had stable disease (SD), 3 patients (11.5%) experienced disease progression (PD), and 4 patients (15.4%) were not yet evaluable. Transient transaminase elevation occurred in 2 patients (7.7%), which resolved after hepatoprotective therapy. **Conclusions:** The aponermin combined with dexamethasone-based regimen demonstrated high efficacy and good tolerability in patients with multidrug-resistant MM. For patients ineligible for immunotherapy, this regimen represents a promising therapeutic option worthy of further exploration.

PA-333

Improved Survival in Multiple Myeloma Following Prior Detection of Precursor Conditions: A Nationwide Real-world Study

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Introduction: Multiple myeloma typically evolves from precursor conditions: monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (smolMM). Although diagnostic tools such as peripheral blood electrophoresis allow for less invasive screening, the value of identifying these precursors remains debated, primarily because treatment is deferred until symptomatic MM (symMM). The critical question is whether early detection of precursor conditions confers survival benefits, especially given evidence that clonal evolution intensifies as the disease progresses. **Methods:** Using Korea's Health Insurance Review and Assessment Service database, which covers virtually the entire Korean population, we conducted a nationwide retrospective study to answer this

question. We identified patients newly diagnosed with MGUS (n = 5,500) or multiple myeloma (n = 17,809) from 2009 to 2022 and classified them into three cohorts (Figure S1): the MGUS to symMM cohort (n = 220), consisting of patients who progressed from MGUS to symMM; the smolMM to symMM cohort (n = 447), consisting of patients who progressed from smolMM to symMM; and the de novo symMM cohort (n = 15,067), comprising patients diagnosed directly with symMM without preceding MGUS or smolMM diagnoses. We defined the index date for survival analysis as the first date of MM frontline treatment for all cohorts to mitigate lead-time bias and implemented a 6-month landmark analysis. To address confounding factors, we applied inverse probability of treatment weighting to adjust for difference in age, sex, comorbidities, and treatment intensity. **Results:** Patients who progressed from MGUS to symMM were older (median 71.0 years vs. 66.0 vs. 67.0, $p < 0.001$) with more comorbidities, particularly renal disease (40.9% vs. 14.5% vs. 21.4%, $p < 0.001$). Treatment patterns differed, with the smolMM to symMM cohort receiving more doublet regimens as frontline, especially bortezomib-dexamethasone (26.8% vs. 19.5% vs. 13.4%, $p < 0.001$). The 10-year cumulative incidence of progression was 7.8% (95% CI, 6.6–9.1) for MGUS and 36.2% (95% CI, 33.4–39.0) for smolMM, with median times to progression of 3.7 and 2.0 years. After adjustment for demographics, comorbidities, and treatment patterns, both the MGUS to symMM cohort and smolMM to symMM cohort demonstrated significantly improved overall survival compared to the de novo symMM cohort (HR = 0.57, 95% CI, 0.43–0.76, $p < 0.001$; HR = 0.83, 95% CI, 0.70–0.97, $p = 0.023$). Median overall survival was 7.9 years (95% CI, 6.0-not reached) for MGUS to symMM cohort, 5.5 years (95% CI, 4.8–7.5) for smolMM to symMM cohort, and 4.4 years (95% CI, 4.3–4.5) for de novo symMM cohort. **Conclusions:** This population-based analysis underscores the importance of structured surveillance in precursor MM conditions. By identifying and monitoring high-risk individuals, clinicians may be better positioned to intervene earlier in the disease course, ultimately improving survival outcomes in MM.

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Successful Liver Transplantation for Acute Liver Failure Caused by AL Amyloidosis

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Introduction: Systemic light chain (AL) amyloidosis is a rare, life-threatening condition marked by insoluble amyloid fibril deposition in tissues, leading to organ dysfunction. While the heart and kidneys are most frequently affected, severe hepatic involvement remains rare and is linked to poor outcomes. Often associated with multiple myeloma, AL amyloidosis poses significant therapeutic challenges. We report a rare case of fulminant hepatic failure caused by AL amyloidosis associated with indolent multiple myeloma, successfully managed with liver transplantation and systemic therapy. **Methods:** In February 2024, a 58-year-old man with no significant medical history presented with progressive fatigue and weight loss. In the following months, blood tests revealed isolated thrombocytosis, followed by cholestasis and hepatic cytolysis. A transjugular liver biopsy showed Congo red-positive deposits, confirming hepatic amyloidosis. Upon admission to our centre in mid-July 2024, the patient presented with acute liver failure, characterised by hyperbilirubinemia, severe cytolysis, and hemorrhagic ascites. Serum protein electrophoresis revealed an IgG lambda monoclonal peak of 8.1 g/L and a reduced free light chain kappa/lambda ratio of 0.06. A bone marrow biopsy indicated indolent multiple myeloma with amyloid deposits. Further investigations showed no cardiac or renal amyloid involvement. Treatment with daratumumab and dexamethasone, according to the D-VCD protocol, was initiated promptly. However, the patient's condition deteriorated so rapidly that an emergency liver transplant was considered. Performed on 27 July 2024, the procedure enabled a swift recovery of liver function. One month later, serum lambda light chains had dropped from 242 mg/L to 85 mg/L. Bortezomib was added at reduced dose from the second treatment cycle, leading to VGPR. The patient was discharged in mid-August 2024. Liver biopsies at six months showed no evidence of amyloid infiltration. He is now in the maintenance phase of treatment and has resumed normal professional activity. **Results:** This case illustrates a rare instance of AL amyloidosis with severe liver involvement successfully managed by liver transplantation and systemic therapy. Acute liver failure necessitated urgent multidisciplinary care. The transplant restored hepatic function, and systemic therapy rapidly improved haematological response and reduced amyloid burden. Unlike transthyretin (ATTR) amyloidosis, where liver transplantation is well established, its role in AL amyloidosis remains exceptional. This is due to the rarity of isolated hepatic involvement and frequent cardiac comorbidities, which often preclude transplantation. AL amyloidosis usually presents with significant systemic burden, making patient selection and perioperative management challenging. **Conclusions:** This case highlights the potential of combining liver transplantation with early systemic therapy as a life-saving approach for certain patients with AL amyloidosis and acute liver failure.

PA-335

Assessment of Knowledge and Diagnostic Competence on MGUS Among Primary Care Physicians in Southern Brazil

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Introduction: Monoclonal Gammopathy of Undetermined Significance (MGUS) is a precursor condition to multiple myeloma (MM) and affects approximately 3% of individuals over the age of 50, with prevalence increasing with age. Despite its high prevalence and the estimated risk of malignant transformation (~1% per year), MGUS remains under-recognized in primary care settings. In Brazil, the underreporting and late diagnosis of MGUS may be attributed to a lack of awareness among healthcare professionals and the absence of specific screening protocols. Brazilian studies have identified a significantly lower number of diagnosed cases than expected, highlighting the urgent need for strategies to improve early detection and clinical follow-up. This study aimed to assess primary care physicians' knowledge and diagnostic capacity regarding MGUS in Cascavel, Brazil. **Methods:** A cross-sectional study was conducted using a self-administered online questionnaire distributed via Google Forms to physicians from 36 Basic Health Units (UBS/USF). The instrument assessed familiarity with MGUS, diagnostic criteria, associated clinical features, and management strategies. The survey consisted of 35 questions developed by the study team to capture information relating to awareness and knowledge of MGUS and potential support needs of General Practitioners/Family Doctors. Both quantitative and qualitative data were collected and analyzed using descriptive statistics. **Results:** Out of 117 physicians invited, 34 responded. Most (94.1%) reported no formal training in MGUS, and 58.8% were unfamiliar with the condition. Only 8.8% had previously diagnosed MGUS, and 91.2% indicated they would refer such cases to hematologists. Moreover, 67.6% felt uncomfortable discussing MGUS with patients, and 100% lacked confidence in their ability to manage it independently. **Conclusions:** These findings reveal a significant educational gap among primary care providers, which may delay diagnosis and hinder appropriate monitoring. Most respondents expressed interest in receiving training and educational materials. The study highlights the need for continuing medical education and clear clinical pathways to optimize recognition and care of MGUS in primary settings.

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Effect of Metformin on Progression-Free Survival in Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS): A Phase II Interventional Study in Brazil

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Introduction: MGUS is an asymptomatic plasma cell disorder that precedes multiple myeloma (MM), with an annual progression risk of ~1%. Epidemiological and preclinical evidence suggest that obesity and pesticide exposure may influence MGUS evolution. Recent studies propose that metformin, an antidiabetic agent, may have antineoplastic properties and reduce the risk of MGUS progression by up to 53%. To evaluate whether oral metformin therapy prolongs progression-free survival in MGUS-positive patients, and to assess the influence of obesity and pesticide exposure on MGUS development. **Methods:** This study adopts a single-arm, phase II interventional design based on Simon's two-stage minimax approach. It aims to evaluate the efficacy of metformin in preventing the progression of Monoclonal Gammopathy of Undetermined Significance (MGUS) to multiple myeloma (MM) or other serious clinical outcomes in patients from Western Paraná, Brazil. Inclusion criteria: Only low-risk MGUS patients are eligible for enrollment. Patients must undergo repeat testing to confirm the MGUS diagnosis and exclude CRAB features (hypercalcemia, renal failure, anemia, bone lesions), assessed through laboratory evaluations and low-dose CT scans. Exclusion criteria: Patients with a pre-existing diagnosis of diabetes mellitus are not eligible. An exception is made for individuals whose diabetes diagnosis coincides with MGUS and who begin treatment exclusively with metformin, indicating a glucose intolerance profile rather than chronic diabetes. Participants will receive oral metformin and undergo biannual follow-up with hematologic and metabolic assessments. The primary outcome is the rate of progression to MM or other clinical events over a 3-year follow-up period. Secondary analyses will explore potential correlations between MGUS and obesity or exposure to agrochemicals. The study's primary endpoint is the 3-year progression-free event (PFE) rate, with the hypothesis that metformin will reduce progression risk from the historical rate of 10.8% to 3.6% over the study period. **Results:** (Expected) Projected 3-year events/mortality rate; Metformin group: 3.6%; Historical control: 10.8%. Hypothesis: Metformin modulates the insulin/IGF-1 axis and inflammatory cytokines (e.g., IL-6), decreasing events or progression, improving metabolic and hematologic profiles. This is the first Brazilian trial to evaluate metformin in patients with MGUS. It addresses a critical gap in national data and establishes a foundation for future studies across Brazil and Latin America. **Conclusions:** Metformin may serve as a low-cost therapeutic strategy to delay MGUS progression, particularly in metabolically at-risk populations. The study also highlights the need for improved screening and preventive strategies for MGUS in Brazil.

PA-337

Real-World Outcomes of Primary and Secondary Plasma Cell Leukemia: A Single-Institution Retrospective Study

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Introduction: Plasma cell leukemia (PCL) is a rare and aggressive plasma cell disorder with poor prognosis. The median survival of plasma cell leukemia is in months with slightly improved survival in

patients who undergo hematopoietic stem cell transplantation (HSCT). Multi-agent cytotoxic chemotherapy is generally recommended but carries significant toxicity. Novel agents have shown promise, but there is limited data. PCL may present de novo (primary) or evolve from multiple myeloma (secondary). This single-institution study evaluates treatment outcomes and survival among patients diagnosed with PCL. **Methods:** We conducted a retrospective review of all patients diagnosed with PCL from Jan 1st, 2017 to Jan 1st, 2025. High risk cytogenetics were defined as t(4;14), t(14;16), t(14;20), del(17p), 1q gain and hypodiploidy. We analyzed response rates, HSCT status, overall survival (OS) and progression free survival (PFS). Time-dependent Cox regression analysis was conducted to examine the hazard ratio between the two groups, based on HSCT status. Statistical significance was set at $p < 0.05$ using SAS 9.4. **Results:** Our sample size included 28 patients who had a diagnosis of PCL. We found that amongst those who did not undergo HSCT, the mean age was 70 years, 50% patients had high-risk cytogenetics, 56.25% patients had primary PCL and 62.5% patients were treated with novel agents. However, amongst patients who underwent HSCT, the mean age was 65 years, 50% patients had high-risk cytogenetics, 58.3% patients had primary PCL, and 91.6% of patients were treated with novel agents for induction prior to the HSCT. Amongst patients who had HSCT, 16.7% patients had complete remission (CR), 50% had very good partial response (VGPR), 33.3% patients had partial response (PR), and no one had progressive disease, prior to the transplant. This was significantly different ($p = 0.0002$) from patients who did not undergo HSCT, with 12.5% patients having CR, 6.25% patients with PR, 6.25% patients with VGPR, and 12.5% patients with progressive disease. And response could not be assessed in 62.5% of patients. Given sample size and method of analysis there was no statistically significant difference in OS and PFS between HSCT and Non-HSCT cohorts. However, 33.33% of patients remained in remission after getting HSCT as opposed to 0% patients in the non-HSCT cohort (p-value < 0.001). **Conclusions:** In our single institution study, plasma cell leukemia continues to exhibit poor outcomes. However, the use of novel agents was linked to improved response rates and increased eligibility for HSCT. The small sample size remains a key limitation of our study and larger multi-institutional studies are needed to establish optimal treatment strategies.

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Clinical Characteristics and Long Term Outcomes of POEMS Syndrome from a Tertiary Care Cancer Center

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Introduction: POEMS syndrome is a rare paraneoplastic condition caused by an underlying plasma cell neoplasm. It is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes. Aims & Objectives There is a scarcity of data on this from our region. We conducted this analysis to understand the clinical characteristics and outcomes of POEMS in our population **Methods:** This was a retrospective analysis at the Tata Memorial Centre in Mumbai. All patients diagnosed with POEMS syndrome (n = 34) between January 2013 and November 2024 were reviewed for baseline features, treatment, and outcomes. All data were obtained from the electronic medical record system. **Results:** The median age was 51 years (range, 25–78), and 76% were male. The median time from symptom onset to diagnosis was 9 months (range 2–48). The most common presenting symptoms were parasthesisas and difficulty walking. Demyelinating pattern (78%) of neuropathy was most observed on NCV. Extravascular overload was observed in 76%, with peripheral edema and ascites being the most prevalent. Other characteristics were endocrinopathy (58%), organomegaly (56%), and skin abnormalities (40%). Serum VEGF levels could be measured in 58% (n = 20), with a median of 514 pg/mL (range, 27–1930). Lenalidomide-based regimens were most employed in 88% of patients (n = 28), with maintenance lenalidomide used in 32%. Autologous stem cell transplant (ASCT) was performed for only one patient. The best hematological response of VGPR was reported in 66%,with CR in 19% and PR in 10%. Amongst evaluable patients (n = 15), 60% showed VEGF response of CR. The median duration of follow-up was 50 months. Three deaths were reported. 5-year PFS was 76.6%, with a median PFS of 105 months [95% CI, 96–113], and the 5-year OS was 90.8%, with a median OS of 125 months [95% CI, 109–142]. Univariate analysis revealed no significant factors for overall survival. **Conclusions:** Within the limitations of retrospective analysis, we describe the clinical features and treatment used for patients with POEMS in our context. With timely, precise diagnosis and appropriate treatment, patients have a good overall long-term survival rate despite not receiving ASCT.

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BTK Inhibitors and Bendamustine-Rituximab Demonstrate High Efficacy in Secretory Non-IgM Lymphoplasmacytic Lymphoma

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Introduction: Non-IgM lymphoplasmacytic lymphoma (LPL) is a rare subtype defined by marrow infiltration without IgM paraprotein. Despite biological overlap with Waldenström macroglobulinemia (WM), it is often mistaken for multiple myeloma (MM). Due to its rarity, there are no prospective studies, and evidence

is limited to case reports and small series. No comparative data support current treatment approaches, and clinical outcomes with modern agents such as BTK inhibitors (BTKi) remain anecdotal. **Methods:** We retrospectively identified patients with secretory non-IgM LPL (IgG or IgA) diagnosed at our institution from 2005 to 2025. Diagnosis and response assessment followed IWWM-12 criteria. The primary objective was to compare VGPR rates and PFS with bendamustine-rituximab (BR) vs. BTKi in the frontline setting. Secondary objectives included evaluating outcomes with BR/BTKi vs. rituximab monotherapy and MM-regimens. Multivariable logistic and Cox models were adjusted for age, sex, and isotype (IgG vs. IgA). **Results:** Seventy-two patients were included: 57 (79%) had IgG and 15 (21%) IgA monoclonal protein. Median age at diagnosis was 63.5 years (range 42–87); 38 (53%) were female. MYD88 mutations were detected in 60/63 patients (95%) and CXCR4 mutations in 11/36 (31%). With a median follow-up of 69 months (95% CI 52–85), the 5-year overall survival rate was 96%. Fifty-seven patients (79%) received treatment, with a median time to first treatment of 8.4 months (95% CI 2–28). First-line regimens included BR (n = 16), BTKi (n = 12; zanubrutinib n = 8, ibrutinib ± rituximab n = 4), rituximab monotherapy (n = 11), MM-regimens (n = 5; triplet combinations n = 3, doublets n = 2), and other chemo-immunotherapy/proteasome inhibitor-based combinations (n = 13). Median follow-up after frontline therapy was 49 months for BR and 39 months for BTKi. In the frontline setting, BR and BTKi demonstrated similar efficacy: VGPR rates were 47% with BR and 36% with BTKi (p = 0.60), and the 3-year PFS rate was 76% with BR and 77% with BTKi (p = 0.57). Both therapies outperformed rituximab monotherapy, which showed a VGPR rate of 22% (p = 0.28 vs. BR/BTKi) and a 3-year PFS rate of 34% (median PFS 13 months; p = 0.01 vs. BR/BTKi). Among the few patients treated with MM-regimens, none achieved a VGPR, and PFS was significantly shorter compared to BR/BTKi (3-year PFS rate of 33%; p = 0.04). On multivariable analysis, receipt of either BR or BTKi was independently associated with improved PFS compared to rituximab monotherapy (HR 0.16; 95% CI 0.04–0.69; p = 0.01). No variables were associated with VGPR attainment. **Conclusions:** In the largest reported cohort of non-IgM LPL, BR and BTKis were comparable in efficacy and associated with superior PFS compared to rituximab monotherapy and other non-standard approaches. These findings provide the first evidence-based foundation for treatment selection in this rare population and support aligning therapeutic strategies with those established for WM.

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Modeling Trajectories to Organ Recovery in AL Amyloidosis Using an Ensemble Machine Learning Approach

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Introduction: Organ recovery is a major determinant of clinical outcomes in light chain (AL) amyloidosis. We aimed to better define trajectories to organ recovery in AL amyloidosis using logistic regression (LR) and XGBoost (ML), a machine learning model based on gradient boosting. **Methods:** This analysis included 376 patients (pts) with newly diagnosed AL amyloidosis from 2017–2023, at a quaternary care center. Hematologic and organ responses were assessed at 6, 12, 18, and 24 months using International Society of Amyloidosis criteria. Predictive models were developed using LR and ML to incorporate 37 variables assessed at the time of diagnosis and during treatment. Hyperparameters for ML were optimized using Bayesian search. The dataset was split into training (70%) and testing (30%) subsets. Shapley additive explanation (SHAP) values were used to interpret feature importance. **Results:** In describing clinical trajectories, pts were classified as early responders or non-responders based on organ recovery within 6 months. For pts with renal involvement (n = 238), early response occurred in 67% of pts. At 12, 18, and 24 months respectively, 86%, 75%, and 71% enjoyed sustained responses. For early non-responders, 12, 18, and 24 month response rates were 8.4%, 19%, and 19%. Early response occurred in 59% (n = 273) of pts with cardiac involvement and improved to 85%, 68%, and 70% at 12, 18, and 24 months. For early non-responders, 21%, 26%, and 29% responded at these time points. For pts achieving an early VGPR or better, 64.5% achieved early cardiac response and 70.8% achieved early renal response. In our analysis, ML consistently outperformed LR in the prediction of organ responses at all time points along these trajectories. As an example, for 6-month cardiac response, ML was 85% accurate for response classification with 94% sensitivity and 73% specificity. LR was 63% accurate, 67% sensitive, and 56% specific. SHAP summary plots identified 24-hour urine protein (SHAP = 0.43), serum M-protein (0.33), age (0.32), dFLC (0.20), and NT-proBNP (0.16) as the most impactful predictors of response. ML illustrated distinct non-linear relationships for each variable that were not captured in LR. SHAP values for 24-hour urine protein decreased within a narrow range, indicating a threshold beyond which proteinuria is associated with lower likelihood of response. Detailed model structure, inputs, outputs, and performance for both LR and ML at all time points will be presented. **Conclusions:** This analysis demonstrates that patients with AL amyloidosis follow distinct, time-variable clinical trajectories toward organ recovery. ML provides an accurate and explainable platform for predicting response trajectories that outperforms conventional regression. Our model provides a novel framework for capturing non-linear and dynamic patterns in disease behavior, offering a foundation for earlier risk stratification and more personalized treatment strategies.

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Primary Results from a Phase 2 Response-Adapted Study of Daratumumab, Carfilzomib, and Dexamethasone (DKd) in Patients with High-Risk Smoldering Multiple Myeloma

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Introduction: Half of patients with high-risk smoldering multiple myeloma (HR-SMM) progress to multiple myeloma (MM) within 2 years. Treatment with single agent lenalidomide or daratumumab delays progression and may improve survival (QUIREDEX, AQUILA). Lenalidomide-based multiagent regimens have induced high rates of undetectable measurable residual disease (MRD-neg) which can lead to longer survival outcomes. Finding an effective regimen while minimizing toxicity is most important for asymptomatic patients. The combination of daratumumab, carfilzomib, and dexamethasone (DKd) is effective in relapsed MM and avoids immunomodulatory drug toxicity. This study (NCT04933539) evaluates its use in HR-SMM. **Methods:** This Phase 2, Simon 2-stage, investigator-initiated study enrolled HR-SMM patients, HR defined by Mayo Clinic 2018, PETHEMA 2007, and/or Rajkumar et al Blood 2015 criteria. Patients received 8 cycles (28 days) of DKd [daratumumab 1800 mg SC per USPI, carfilzomib 20/56 mg/m^2 days 1, 8, 15 and dexamethasone 40 mg days 1, 8, 15, 22]. Those with detectable MRD after 8 cycles of DKd received an additional 4 cycles. All patients then received monthly daratumumab maintenance for 24 cycles. The primary endpoint was MRD-neg stringent complete response (sCR) after induction. Responses were assessed by IMWG criteria after each cycle. Very Good Partial Responses (VGPR) were confirmed with mass spectrometry. MRD was assessed by multicolor flow cytometry (MRD sensitivity 10–5) after cycle 8, 12 (if applicable), and yearly. A pre-planned interim analysis assessed futility based on a MRD-neg sCR rates of ≥55%. **Results:** Fourteen patients (median age 58 (range 29–70), 5 men, 9 women; 6 African American/Black, 8 White) were enrolled between Oct 21, 2022, and Jan 22, 2024. Nine (64%) met Mayo 2018 HR criteria. Six (43%) had high-risk cytogenetics (t(4;14), t(14;20), 1q+, del17p). At a median follow up of 2.13 years, 2 patients were off study: 1 died of sudden death (cycle 4) and 1 withdrew consent (cycle 1). Out of 13 evaluable patients, the ORR was 100% (85% VGPR, 15% sCR). After 8 cycles of induction, 1 had an MRD-neg sCR 7.6% (95% CI: 0.19–33%). Of the patients who finished an additional 4 cycles, 1 patient became MRD-neg but remained in a VGPR. One patient deepened his response after a year of daratumumab maintenance and 2 were MRD-neg with a VGPR. In total, 5 patients (38% 95% CI: 18–65%) had at least one MRD-neg bone marrow. One patient had biochemical progression, but no patients have developed SLiM-CRAB criteria. Grade 3 AEs included lymphopenia (n = 1), hypertension (n = 1), lung infection (n = 1), and myocardial infarction (n = 1). No grade 4 AEs occurred. **Conclusions:** The study closed early after not meeting the interim MRD-neg sCR goal of > 55% but notably there was an 100% ORR, and no patients progressed to overt MM. Responses have been durable, with 92% of patients maintaining their best response during the 2 years of daratumumab maintenance. Most toxicities were low grade.

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Safety and Efficacy of Elranatamab in Patients with Daratumumab Relapsed and/or Refractory Immunoglobulin Light Chain Amyloidosis

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Introduction: In AL amyloidosis, plasma cell directed therapies must show efficacy and safety in the setting of cardiac and renal involvement. Based on data in multiple myeloma, we hypothesized that elranatmab, a BCMAxCD3 bispecific antibody, will induce rapid and deep hematological responses in AL amyloidosis patients, with an acceptable safety profile. **Methods:** This is a retrospective, multicenter series on 9 consecutive, Daratumumab-relapsed and/or refractory AL amyloidosis patients who received at least 1 full dose of elranatamab between February-September 2024 at Dana-Farber Cancer Institute/Brigham and Women's Hospital or Columbia University Irving Medical Center. Patients were staged according to the 2004 Mayo Clinic criteria with European modifications. Patients received pre-medications and step up doses (12 mg on Day 1 and 32 mg on Day 3) according to the package insert. Treatment doses of 76 mg were administered weekly thereafter with the schedule modified to Day 1 and 15 in those achieving a ≥VGPR after 1–2 cycles. Patients also received anti-viral and anti-pneumocystis prophylaxis. Cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) were treated per IMWG consensus guidelines. Informed consent and IRB approval was obtained. The data cut-off was February 5, 2025. **Results:** Of the 9 treated patients, 3 were refractory to frontline daratumumab-based regimens with 6 having relapsed disease after a median of 2 prior lines (range 1–4). Three patients had Mayo Stage 3A and 4 had 3B at diagnosis. The median baseline NT-proBNP was 2,164 pg/mL (range: 361–51,140) and baseline dFLC was 154.7 mg/L (range: 26.3–641.8) on C1D1 elranatamab. Three patients met IMWG criteria for overlapping

multiple myeloma. After a median follow up of 8.2 months, there was an ORR of 100% with 89% achieving ≥VGPR and 67% of patients achieving CR. The median time to response was 9 days with, 78% achieving dFCL < 10 mg/L after the first cycle. MRD negativity 10-6 (Clonoseq) was achieved by 4 patients, 10-5 (multiparametric flow cytometry) in one patient, and not available in 4 patients. The median PFS is 8.2 months (range: 1.4–12.3). In the 5 patients evaluable for a cardiac response,2 achieved carVGPR and 3 for carPR. One patient was evaluable for renal response and achieved renCR after 6 cycles. CRS occurred in 67% of patients (Grade 1–2: 5 patients, Grade 3: 1 patient); all occurring within 24 hours of C1D1. One patient developed Grade 2 ICANS within 24 hours of C1D1 that resolved within 3 days without any recurrence. Grade 2 neutropenia occurred in 1 patient and grade 1 thrombocytopenia occurred in another. Two frail patients in a hematological remission with Mayo Stage IIIB amyloidosis passed from progressive multiorgan failure, 103 and 44 days after C1D1, respectively. **Conclusions:** Elranatamab appears highly effective and well tolerated in relapsed refractory AL amyloid patients, including those with advanced cardiac involvement, supporting prospective clinical trials.

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Comparing Smouldering Myeloma High-Risk and Evolving Phenotype Definitions in the Prospective, Nationwide UK Cosmos Study

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Introduction: SMM carries variable risk of progression to MM. Several models aim to identify high-risk (HR) patients. An evolving phenotype (EP) by various criteria also increases risk. As early intervention may benefit HR-SMM, accurate identification is critical. In the prospective UK COSMOS cohort, we compared reported HR/EP criteria, and evaluated whether EP adds risk within HR. **Methods:** SMM patients were risk-stratified at entry using Mayo-2007, -2008, -2018, Rajkumar, Czech Myeloma Group (CMG), IMWG [20-2-20 +CGN], IMWGp [points-based]. Other models were not included in our analysis due to unavailable data or personalised prediction rather than group-stratification. Patients were assessed for EP using Rosiñol, Fernàndez De Larrea (FDL), Ravi, Werly, and Visram criteria. To assess identification of higher risk patients, for all models HR was compared to combined lower risk groups. For 4-tier models, with intermediate-risk (IR) progression ~50% in 2y, HR and IR were combined ("+IR") in additional analysis and compared with lower risk groups. Cox regression and Harrell's C-statistic were used to assess the different models. **Results:** A total of 320 SMM patients were included. In the HR common evaluable set (CS, n = 106), 58 were HR by ≥1 model, only 4 by all, and 14 by one. Best discrimination was seen with Mayo-2018. In the EP CS (n = 113), 74 had EP by ≥1 criterion, only 2 by all, and 42 by one (26 of these by Ravi criteria). Best discrimination was seen with Werly. Concordance was modest

Table (abstract PA-343)

	%Evaluable (n = 320)	%HR or EP	Hazard ratio (95%CI)	p	C-statistic	HR or EP median PFS (m)
HR model (CS n = 106, mFU 28.1 m)						
Mayo-2007	62	16.0	2.43 (0.98–6.05)	0.056	0.545	37.0
Mayo-2008	60	10.4	3.47 (1.26–9.51)	0.016	0.567	26.5
Mayo-2018	59	28.3	4.65 (1.94–11.14)	< 0.001	0.697*	NR
CMG	71	8.5	3.80 (1.26–11.42)	0.018	0.579*	16.4
CMG + IR	71	39.6	7.17 (2.41–21.33)	< 0.001	0.691*	36.4
IMWG	36	17.0	4.52 (1.85–11.05)	< 0.001	0.652*	20.0
IMWG + IR	36	43.4	2.88 (1.16–7.15)	0.023	0.651*	NR
IMWGp + IR	34	14.2	1.51 (0.51–4.50)	0.459	0.543	NR
EP criteria (CS n = 113, mFU = 32.7 m)						
Rosiñol	80	12.4	1.19 (0.26–5.48)	0.823	0.545	NR
Ravi	52	48.7	2.27 (0.68–7.55)	0.181	0.614	NR
Werly	58	28.3	2.34 (1.34–13.35)	0.014	0.731*	NR
Visram	57	18.6	2.26 (0.68–7.52)	0.182	0.570	NR

*p < 0.05.

overall. The Rajkumar (93.2% HR), IMWGp (0.9% HR) and FDL (2.7% EP) models were excluded due to skewed classifications. Combined analysis using Mayo-2018 and Werly showed EP across all risk groups. Among HR patients the 33% with EP had higher progression risk (HR 13.96, p = 0.017, C-index 0.806) and shorter median PFS vs HR alone (8 m vs NR from EP assignment, p = 0.005). **Conclusions:** We validated and compared risk models and EP criteria in SMM in our prospective, nationwide cohort and found that HR and EP classification and model performance varied. Discrimination was best for Mayo-2018 HR and Werly EP. Moreover, EP adds significant risk in HR patients warranting close monitoring. Our results indicate that standardized HR definitions are needed for clinical trial design.

PA-344

Treatment Paradigms and Outcomes for Light Chain Amyloidosis Associated with Waldenstrom's Macroglobulinemia

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Introduction: Waldenstrom Macroglobulinemia is a type of IgM-secreting lymphoplasmacytic lymphoma marked by frequent mutations in MYD88 and CXCR4. WM-associated AL Amyloidosis (WM-AL) is a relatively unexplored clinical entity, with little data on survival outcomes, treatment regimens and prognostic factors. This is distinct from typical AL Amyloidosis that is classically associated with Plasma Cell Dyscrasias. **Methods:** We conducted a retrospective observational study of adults with Waldenstrom Macroglobulinemia-associated cardiac AL amyloidosis (WM-AL) at Cleveland Clinic from January 2012 to December 2022. Patients diagnosed with other amyloidosis types or incomplete clinical data were excluded. Demographic details, diagnostic labs, treatments, and responses were collected from medical records. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians with interquartile ranges (IQR). **Results:** Fourteen patients (10 male, 4 female) were included. Median age at diagnosis was 72 (IQR: 66–78). Organ involvement included cardiac (78.6%), renal (7.1%), liver (7.1%), gastrointestinal (21.4%), and other organs (21.4%) including soft tissue and peripheral nerve. Median difference in involved and uninvolved free light chain (dFLC) was 150.8 mg/dL (IQR: 86.5–193.0). A median of 1 (IQR;1–3) line of therapy was delivered after the diagnosis of WM-AL was made. Patients were mainly treated with the following first-line therapies: Bortezomib-Rituximab- Dexamethasone in 6 (42.9%), Bendamustine-Rituximab (BR) in 2 (14.2%). The remaining patients each received one of the following regimens: VD, Carfilzomib-Rituximab-Dexamethasone, Daratumumab-Rituximab-Dexamethasone, Ibrutinib-Rituximab, Single agent Rituximab, and Clinical trial for WM. None had an autologous stem cell transplant upfront. Second- and Third-line treatments included 2nd generation BTK inhibitors such as Zanubrutinib, Acalabrutinib, BR, Bortezomib-Rituximab-Dexamethasone, CyBorD, Ibrutinib-Rituximab, Daratumumab-Bortezomib-Dexamethasone.In response to 1st line treatment, 35.7% achieved a VGPR or better, 21.4% PR, 7.1% had PD, 14.3% had NR, and 21.4% were not evaluable. Of patients with cardiac involvement, 87.5% of them achieved a cardiac response. **Conclusions:** Prospective data to define optimal treatment regimens for WM-AL are lacking, but our study is the second largest cohort of WM AL Amyloid patients described in the literature. The use of standard WM treatment protocols in WM-Amyloidosis appear to be efficacious, with our study showing the utility of Rituximab based regimens as well as 2nd generation BTK inhibitors in the treatment paradigm. The role of daratumumab remains unclear. Future studies can also look to incorporate investigative therapies for typical AL amyloid like anti-fibril antibodies for these patients.

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The Evaluation of Circulating Tumor Cells as a Prognostic Biomarker in Newly Diagnosed Light Chain (AL) Amyloidosis

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Introduction: Circulating tumor cells (CTCs) emerges as a prognostic biomarker in Multiple Myeloma, independent of other established markers and may refine stratification and possibly affect therapeutic decisions. However, the prognostic impact of CTCs in light chain (AL) amyloidosis remains unexplored. We prospectively evaluated the prognostic impact of the presence of CTCs in previously untreated patients with AL amyloidosis. **Methods:** The presence of CTCs was prospectively evaluated in 218 consecutive untreated patients with AL amyloidosis diagnosed and treated at the

Department of Clinical Therapeutics, Athens. CTCs were assessed in peripheral blood with Next-Generation Flow (NGF) cytometry according to the Euroflow guidelines. A median number of 10 million events (range 8–12.1 × 106) were acquired for each patient and the median limit of detection (LOD) was 2.3 × 10–6 (range 2–3.1 × 10–6). Event-free survival (EFS) was defined as the time between diagnosis and hematologic relapse and/or treatment change and/or death. Overall survival (OS) was considered as the time between diagnosis and death of any cause. The median follow-up period was 24 months (range 3–80 months). **Results:** CTCs were detectable in 129/218 (59%) patients with a median value of 0.00037% (range 0.0002%–11.4%). Among patients with detectable CTCs, the distribution was as follows: 27/129 patients (21%) had CTCs at the level of 10-6, 67/129 (52%) at the level of 10-5, 18/129 (14%) at the level of 10-4 and 17/129 (13%) at levels ≥ 10-3. Patients with detectable CTCs had higher iFLCs (p = 0.02), NTproBNP (p = 0.01), and bone marrow (BM) infiltration (p = 0.05); yet, the association between CTCs and BM infiltration was modest in a linear model. Patients with a IIIa/IIIb cardiac stage had slightly higher levels of CTCs vs. those with stage I and/or II; in contrast, no differences were observed among patients at different renal stages. Regarding treatment, there was no association between CTC levels and depth of hematologic response at 1, 3 or 6 months or organ responses at any time-point. Nevertheless, in the log-rank analysis, the CTC increase per log scale correlated with a gradually worse outcome for both EFS and OS. Most importantly, in a multivariate Cox regression model, CTCs as a continuous variable, conferred an independent prognostic impact (p = 0.011 for EFS and p < 0.001 for OS) compared to the Mayo staging system, dFLC and treatment type (containing Daratumumab or not). The optimal CTC cut-off showing the highest C-index in the multivariate Cox model was for EFS the LOD (HR: 1.44, 95% CI:1.00–2.09; p = 0.04) and 10-4 for OS (HR: 1.88, 95% CI: 0.99–3.56; p = 0.03). MRD-negativity was achieved significantly more frequently in patients with undetectable CTCs (OR:1.9). **Conclusions:** CTCs can be detected in 59% of patients with AL amyloidosis using sensitive NGF. Our data demonstrate that the presence of CTCs has an independent prognostic importance and may be a new useful predictive biomarker for newly diagnosed patients with AL amyloidosis.

PA-346

Efficacy and Safety of Frontline Alternating Bortezomib-Based Regimens Plus Daratumumab in Primary Plasma Cell Leukemia: Interim Results of Eumeleia Phase 2 Trial by the Greek Myeloma Study Group

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Introduction: Primary plasma cell leukemia (pPCL) is a rare and aggressive malignancy with poor prognosis. A phase 2 trial has demonstrated high efficacy of alternating cycles of PAD (bortezomib, doxorubicin, dexamethasone) and CVD (cyclophosphamide, bortezomib, dexamethasone), combined with autologous stem cell transplantation. Our recent retrospective study demonstrated that daratumumab (DARA)-based regimens induce high response rates and prolong survival parameters in pPCL. Given these findings, we evaluated the efficacy and safety of alternating PAD/CVD regimen combined with DARA (D-PAD/D-CVD) in the 1L setting of pPCL followed by DARA monotherapy as maintenance. **Methods:** This is an ongoing investigator-initiated, multicenter, phase 2, single-arm trial aiming to enroll 43 newly diagnosed transplant-eligible or ineligible pPCL patients (pts). Treatment includes a 6-cycle induction with alternating D-PAD/D-CVD, a 2-cycle D-CVD consolidation, and a 24-cycle DARA monotherapy maintenance phase. D-PAD/D-CVD are given in 21-day cycles during induction/consolidation [DARA: 1,800 mg subcutaneously (SC) weekly in Cycle 1–3 (Days 1, 8, 15), then every 3 weeks (Day 1); P/V: 1.3 mg/m2 SC on days 1, 4, 8, 11; A: 30 mg/m2 intravenously on day 4; D: 40 or 20 mg/day orally on days 1, 4, 8, 11; C: 300 mg/m2 orally on days 1, 8], and DARA is administered in 28- day cycles (Day 1) during maintenance. Key inclusion criteria are newly diagnosed pPCL according to the revised International Myeloma Working Group (IMWG) diagnostic criteria of pPCL [≥5% and/or absolute count ≥0.5 × 103/μL circulating plasma cells in peripheral blood (PB) smear or using next generation flowcytometry], age: 18–80, measurable disease, performance status ≤3, adequate bone marrow (BM)/renal/liver function. Main exclusion criteria are severe cardiac/pulmonary dysfunction. This is an interim analysis of the first 20 patients who completed induction or discontinued before this timepoint. **Results:** Between Nov 2021 and Dec 2023, 20 pts (10 pts ≥65 years) were enrolled across six Greek centers. Median time from diagnosis to treatment initiation was 11.5 days (range: 3–44); 19 pts completed the 6-cycle induction phase and were evaluated within 7 days post-induction. Among 19 response-evaluable patients, the overall response rate was 100%, including complete response (21.1%), very good partial response (73.7%) and partial response (5.3%); MRD negativity was achieved in BM in 2 of the 5 pts assessed and in PB in all pts examined (7/7), as for now. Eleven pts were transplant

eligible. Grade ≥3 adverse events occurred in 9 pts (45.0%), mainly cytopenias (7 pts) and infections (4 pts). One patient died 30 days post-baseline from respiratory tract infection (unrelated to treatment). **Conclusions:** In conclusion, these results provide preliminary evidence supporting the efficacy and safety of the induction alternating D-PAD/CVD regimen in the 1L setting of pPCL. Final results from a larger cohort with longer follow-up and maintenance data are awaited.

PA-347

SECURE Study: Early Findings Suggest MGUS Diagnosis Does Not Increase Psychological Distress

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder found in 3.2% of individuals aged over 50. While its progression to multiple myeloma occurs at ~1% per year, management and follow-up of MGUS in the UK remain inconsistent. With increasing interest in screening, understanding the psychological impact of diagnosis is essential. This interim analysis from SECURE, a national prospective observational cohort, investigates risk stratification and psychological outcomes in individuals with incidentally detected MGUS. **Methods:** SECURE is recruiting 2,000 incidentally diagnosed MGUS patients across 30+ NHS sites from Sept 2023 to Dec 2025, with 60-month follow-up. Annual assessments include validated measures of psychological wellbeing: PHQ-9 (depression), GAD-7 (anxiety), HAI (health anxiety), and IUS-27 (intolerance of uncertainty). Risk stratification is based on M-protein concentration, immunoglobulin isotype, and serum free light-chain (FLC) ratios. Outcomes are compared against 2021 UK Office for National Statistics (ONS) data. **Results:** As of May 2025, 687 participants were enrolled across 29 UK sites. Among 317 risk-stratified individuals (median age 71; 52.4% male; 87.1% White), 27.1% were low risk, 46.7% low-intermediate, 24.0% high-intermediate, and 2.2% high risk of progression. Overall, 52.7% had a pathological FLC ratio, 31.5% had non-IgG MGUS, and 17.0% had M-protein 15 g/L. PHQ-9 data (n = 432) showed 14.6% (95% CI [11.3, 17.9]) had moderate to severe depressive symptoms, aligning with the ONS figure of 16% (95% CI [15, 18]). GAD-7 results (n = 411) indicated moderate to severe anxiety in 10.7% (95% CI [7.7, 13.7]), slightly below the ONS estimate of 16% (95% CI [14, 18]). Age-stratified analysis revealed greater psychological burden among younger participants. In those aged 50–69, 21.3% reported moderate/severe depression (ONS: 15%) and 14.6% reported moderate/severe anxiety (ONS: 13%). In contrast, participants aged 70+ had lower rates: 8.9% for depression (ONS: 10%) and 7.3% for anxiety (ONS: 5%). Health-related anxiety (HAI, n = 416) was predominantly low (80.3%), with only 1.4% classified as high. IUS-27 scores (n = 401) had a mean of 48.1 (SD 20.1) and median of 41.0 on a 27 to 135 scale, where higher scores reflect greater intolerance to uncertainty. **Conclusions:** These interim findings suggest that individuals with incidentally diagnosed MGUS experience rates of depression and anxiety comparable to or lower than the general population. Psychological impact appears age-dependent, with younger participants reporting more symptoms. The overall low burden supports the feasibility of MGUS screening strategies. For those with moderate to severe symptoms, referral to mental health services may be appropriate. The use of HAI and IUS-27 offers novel insight into post-diagnosis experience and may inform tailored support.

PA-348

Diagnostic Patterns and Outcomes of Amyloidosis Screening in a Monoclonal Gammopathy Clinic: A Single Center Study

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are precursor plasma cell disorders with potential to progress to symptomatic disease, including light chain amyloidosis (AL). Early identification of patients at risk is critical; delayed diagnosis of AL is associated with poor outcomes. Dedicated MGUS clinics at academic medical centers provide a structured approach for monitoring, enabling timely detection of progression. Incorporating screening tools such as abdominal fat pad aspiration (FPA) enhances early diagnosis of subclinical AL. Understanding transformation risk—estimated at ~1% per year for MGUS and higher for SMM—further supports the utility of such clinics in guiding surveillance and management strategies. **Methods:** The patient cohort included in this study spans January 2022 through May 2025 at a single center academic institution MGUS clinic. The cohort includes those who

underwent both bone marrow biopsy (BMB) and FPA for amyloidosis screening. Reported indications for performing screening FPA were diagnosis of cardiomyopathy, biopsy proven localized amyloidosis, nephrotic range proteinuria and smoldering myeloma. **Results:** Between 2022 and 2025, a total of 417 patients were evaluated in the MGUS clinic. Amongst the MGUS patients, 74 underwent BMB, and 40 bedside abdominal FPA based on clinical indications that included biopsy proven localized amyloidosis (n = 6), nephrotic range proteinuria (n = 8), cardiomyopathy (n = 12), SMM (n = 9) and peripheral neuropathy (n = 5). Imaging studies included 49 PET/CT scans and 54 skeletal surveys to evaluate for multiple myeloma (MM). Systemic AL amyloid was diagnosed in 4 patients by screening FPA (3) and BMB (4). Biopsy-proven localized amyloid cases included 5 pulmonary and 1 laryngeal site. An additional 3 patients who were diagnosed with localized amyloidosis (2 laryngeal, 1 pulmonary) and referred to the MGUS clinic did not have evidence of MGUS. Overall, in the MGUS clinic, 9.5% of patients were screened for AL with FPA. Of all patients seen, 3.1% were found to have AL amyloid. **Conclusions:** While association with progression from MGUS and SMM to MM are well known and frequently monitored in many outpatient settings, monitoring for and diagnosing AL can be easily overlooked. Patients with MGUS and smoldering multiple myeloma benefit from dedicated clinics that employ protocol-driven screening for AL amyloidosis, enabling earlier detection and improved outcomes. For patients with immunoglobulin light chain (LC) abnormalities, FPA and BMB will demonstrate AL in over 85% of patients. Further, reports from Mayo Clinic demonstrate that 9% of all MGUS patients seen are subsequently found to have AL, higher than rates seen at our center, highlighting the need for improved screening practices.

PA-349

EXENT QIP-MS Detection of Stable Monoclonal Light Chain Glycosylation Enables Risk-Stratified MGUS Monitoring

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Introduction: Multiple myeloma (MM) is frequently associated with diagnostic delay, despite earlier detection improving clinical outcomes. MM is consistently preceded by Monoclonal Gammopathy of Undetermined Significance (MGUS). The high prevalence of MGUS (~4.5% of individuals >40 years) and low risk of malignant progression (~1%) make longitudinal monitoring unlikely to be cost-effective or sustainable. Improved diagnostics and identification of novel biomarkers are essential to refine risk stratification and optimise resource allocation. Preliminary data from the Mayo Clinic suggests glycosylation of monoclonal light chains (LCs) is a promising biomarker for MGUS progression, associated with a five-fold increased risk of MM and AL amyloidosis progression, beyond current risk stratification models. This study aims to characterise the frequency and stability of monoclonal LC glycosylation in an incidental MGUS cohort, evaluating its potential as a predictive biomarker for malignant progression. **Methods:** This pilot study included 124 MGUS patients incidentally diagnosed between 2020–2024 at Oxford University Hospital. A trust audit (ID 8776) granted access to 158 serum samples which were evaluated for LC glycosylation by EXENT Quantitative Immunoprecipitation Mass Spectrometry (QIP-MS). The mass spectra were acquired over 10,000–30,000 m/z. Prevalence of glycosylated LCs were compared with previously reported screened cohort data. Stability of glycosylation was assessed using sequential samples. **Results:** Of 124 incidental MGUS patients analysed, 18 (15%) had glycosylated LCs, a significantly higher proportion than 6% previously reported in the screened cohort (P = 0.0013). Demographics and current MGUS risk stratification were comparable between the groups, though the incidental cohort had a greater proportion of non-IgG isotypes (50%) compared to the screened cohort (20%). In the 18 incidental MGUS patients with glycosylation, 14 (78%) involved the primary clone and 4 a non-clonal isotype. 11 of the clonal group had follow-up samples available. Glycosylation remained stable in all 11 over a mean of 29 months (5–52 months), whilst none of the non-clonal glycosylation persisted.

Characteristics of Glycosylated MGUS Cohorts[a].

	Screened MGUS with glycosylation (N = 25)	Incidental MGUS with glycosylation (N = 18)
Age	69 (54–87)	75 (48–94)
Male	14 (56%)	11 (61%)
IgG isotype	20 (80%)	9 (50%)
Abnormal FCL ratio	12 (52%)	13 (72%)
Mayo MGUS risk		
Low-Intermediate	20 (95%)	18 (100%)
High	1 (5%)	0 (0%)

[a]Screened cohort analysed by MASS-FIX (Dispenzieri et al. 2020), incidental cohort analysed by EXENT QIP-MS.

Conclusions: This pilot study demonstrates a higher prevalence of glycosylated monoclonal LCs in incidentally identified MGUS patients compared to previously reported screened cohorts. The observed stability of glycosylation within primary MGUS clones highlights its potential as a predictive biomarker for malignant progression, warranting further evaluation for its use in MGUS risk stratification models.

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Association between Metabolic Syndrome and Increased MGUS Risk in a Large Korean Cohort

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder. Recent studies suggest a potential link between metabolic syndrome (MetS) and MGUS, with MetS possibly contributing to the risk and progression of MGUS through chronic inflammation and metabolic dysregulation. However, the association between MetS and MGUS, particularly in large population-based cohorts, remains underexplored. **Methods:** This study utilized data from the Korean National Health Insurance Service (NHIS), including 4,453,453 individuals, of whom 2,068 were diagnosed with MGUS. We compared baseline demographic and clinical characteristics between MGUS and non-MGUS populations and evaluated the risk of developing MetS using incidence rates (IRs) and adjusted hazard ratios (HRs) from Cox proportional hazards models. **Results:** MGUS patients were older (mean age 60.4 vs. 48.1 years, $p < 0.0001$), more likely to be male (61.0% vs. 54.2%, $p < 0.0001$), and had a higher prevalence of metabolic abnormalities, including diabetes (24.9% vs. 9.9%), hypertension (53.6% vs. 27.2%), and chronic kidney disease (14.0% vs. 2.6%) (all $p < 0.0001$). MetS was associated with a significantly increased risk of MGUS (IR 8.77 vs. 3.72 per 1000 person-years). After adjusting for confounders, MetS remained an independent risk factor for MGUS (HR 1.26; 95% CI 1.15–1.39). Subgroup analyses revealed a stronger association in males (HR 1.40; 95% CI 1.25–1.57), younger adults aged 20–39 years (HR 1.94; 95% CI 1.27–2.96), and middle-aged adults aged 40–64 years (HR 1.37; 95% CI 1.21–1.55). **Conclusions:** MetS and its components are associated with an increased risk of developing MGUS. These findings suggest that metabolic dysregulation may contribute to the pathogenesis of MGUS, highlighting the need for metabolic monitoring in at-risk populations.

PA-351

Cutaneous Manifestation of Monoclonal Gammopathy: Clinical Challenges and Management

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Introduction: Monoclonal gammopathy of clinical significance (MGCS) is characterized by an underlying quiescent clone and symptoms related to the monoclonal immunoglobulin or the clone itself, regardless of tumor burden. The cutaneous manifestations of MGCS can vary greatly, treatment is tailored to the severity of the clinical presentation. **Methods:** We present a series of seven cases of cutaneous MGCS. **Results:** A 59-year-old woman with a 3-year history of urticaria accompanied by fever, leading to a diagnosis of Schnitzler syndrome, associated with an IgM kappa peak. As anakinra was unavailable, she received two courses of rituximab, in addition to steroids and azathioprine, with success. A 69-year-old man with indolent myeloma (SMM) with groin necrosis related to pyoderma gangrenosum. Despite treatment with steroids, the disease relapsed several times even after dapsone and MMF were administered. Ultimately, the disease never relapsed after starting anti-MM therapy. A 57-year-old woman with scleroderma on her head and neck, leading to a diagnosis of Buschke scleroderma associated with an IgG kappa peak. Treatment with Vd resulted in the disappearance of the skin lesions and the monoclonal peak. She relapsed 10 years later and was successfully treated with Rd. A 70-year-old woman with fever, necrotic purpura, arthralgia and acute renal failure, that led to a diagnosis of cryocrystalglobulinemia associated with SMM. Initial therapy consisted of plasma exchanges combined with VCD, followed by lenalidomide maintenance. The disease did not recur after plasma exchanges ceased, but renal function did not recover. A 69-year-old man with a seronegative rheumatoid polyarthritis, with febrile urticaria related to Sweet syndrome. Further testing revealed an IgG lambda SMM. Although symptoms improved with infliximab, they did not resolve, raising the question of whether to start clone-directed therapy. A 70-year-old woman with declive purpura and acute renal failure, leading to a diagnosis of rheumatoid purpura. Further testing revealed an IgA lambda SMM. Although symptoms improved with steroids, relapse occurred upon reducing the dosage. There was no recurrence of skin or renal problems under MM-directed therapy with DRd. A 38-year-old woman with kidney failure, heavy proteinuria and microscopic hematuria, and an IgG kappa peak. She appeared much older than her age, with sagging skin on her face, neck, armpits, and groin. A skin and kidney biopsy revealed the same deposits of gamma heavy chains and C3, leading to a diagnosis of acquired cutis laxa due to heavy chain deposition disease. This was treated with VCD. **Conclusions:** This case series illustrates the range of cutaneous manifestations of MGCS. An accurate diagnosis is essential for effective management. It is also essential to raise awareness among clinicians to ensure timely diagnosis and effective treatment.

PA-352

The Study of Serum VEGF Expression in Different Types of Plasma Cell Diseases

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Introduction: Although VEGF levels are elevated in many other plasma cell diseases besides POEMS syndrome, the clinical characteristics and diagnostic value of VEGF and other plasma cell diseases have not been thoroughly discussed in existing research and clinical practice. The purpose of this study was to analyze the difference of VEGF expression levels in different plasma cell diseases, explore its correlation with clinical characteristics and its diagnostic value. **Methods:** A retrospective study was conducted to select 181 patients with plasma cell diseases,including POEMS syndrome, MGUS, MGRS, pAL, MM, pPCL. We compared serum VEGF levels in patients with various plasma cell diseases, and assessed the relationship between VEGF levels in general and clinical indicators in each disease, with $P < 0.05$ as the level of statistical significance. **Results:** 1. The level of VEGF in patients with POEMS syndrome was significantly higher than that in patients with MGUS, pAL, MGRS, pPCL and MM ($P < 0.01$). VEGF levels in MGUS, pAL and MGRS patients were significantly higher than those in MM and pPCL patients. 2. In the overall analysis of 181 patients with plasma cell disease, It can be seen that the proportion of bone marrow plasma cells and the proportion of abnormal plasma to total plasma cells in POEMS syndrome, MGUS and MGRS were lower than those in pAL, MM and pPCL, while the proportion of serum VEGF was higher than the upper limit of normal value. 3. The disease progression of the high VEGF expression group was later ($P = 0.018$). the survival trend of the high expression group was better ($P = 0.051$). 4. VEGF was negatively correlated with the proportion of plasma cells in bone marrow smear and the proportion of abnormal plasma cells in total plasma cells ($P < 0.05$), and positively correlated with platelet and hemoglobin ($P < 0.05$), besides, VEGF is related to various clinical features in POEMS syndrome. 5. VEGF levels in MGUS patients were positively correlated with WBC and NUET ($P < 0.05$). VEGF levels were positively correlated with serum LDH in pAL patients ($P = 0.038$). VEGF was positively correlated with platelets in MM patients ($P = 0.012$), There was a negative correlation between VEGF and β2MG in pPCL patients ($rs = -0.661$, $P = 0.038$). 6. the cutoff value of the differentiation between POEMS syndrome and MGUS MGRS, pAL, MM, pPCLwas 402.93, 277.21, 424.34, 151.185, 152.91pg/mL, respectively. **Conclusions:** VEGF was negatively correlated with the proportion of total plasma cells and the proportion of abnormal plasma cells. However, when the proportion of abnormal plasma cells in the bone marrow was significantly increased, VEGF levels were inhibited and the correlation with tumor load was weakened. In addition, there are differences in the differential diagnostic threshold of VEGF between plasma cell diseases and POEMS syndrome, which should be carefully screened clinically.

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Analysis of Clinical Characteristics and Prognostic Factors in Patients with Primary Plasma Cell Leukemia

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Introduction: Current evidence on the prognostic benefits of novel agents such as proteasome inhibitors, immunomodulators, and autologous hematopoietic stem cell transplantation for primary plasma cell leukemia (pPCL) remains insufficient. Existing prognostic studies predominantly rely on retrospective data, while the prognostic value of minimal residual disease (MRD) requires further validation. **Methods:** This single-center retrospective cohort study enrolled 38 pPCL patients and 569 newly diagnosed multiple myeloma (NDMM) controls without circulating plasma cells treated at the First Affiliated Hospital of Sun Yat-sen University between January 2014 and April 2024. Clinical characteristics, genetic profiles, treatment responses, and survival outcomes were compared between groups using electronic medical records and follow-up data. For the pPCL cohort, Cox regression analyses identified independent prognostic factors to construct a scoring system, with Kaplan-Meier methodology and log-rank tests evaluating risk stratification efficacy. **Results:** pPCL patients demonstrated significantly poorer clinical indicators and higher cytogenetic abnormality rates, particularly 1q21 amplification (76.3% vs. 40.5%, $p < 0.001$). The transplantation group achieved superior post-treatment MRD negativity (60.0% vs. 13.0%, $p = 0.004$). pPCL patients exhibited inferior long-term outcomes compared to NDMM controls (median PFS: 35.30 vs. 67.87 months, $p = 0.001$; median OS: 38.30 vs. 78.80 months, $p < 0.001$). No significant prognostic differences emerged among pPCL patients stratified by R-ISS staging. Univariate Cox regression identified shared adverse prognostic factors for both PFS and OS: 1q21+ (PFS: HR = 5.508, $p = 0.025$; OS: HR = 4.723, $p = 0.043$), LDH >400 U/L (PFS: HR = 4.199, $p = 0.004$; OS: HR = 4.370, $p = 0.007$), bone marrow SUVmax≥7.2 (PFS: HR = 3.608, $p = 0.022$; OS: HR = 4.346, $p = 0.012$), and non-paramedullary extramedullary disease (PFS: HR = 4.649, $p = 0.010$; OS: HR = 6.057, $p = 0.005$). Post-treatment MRD negativity (PFS: HR = 0.179, $p = 0.008$; OS: HR = 0.241, $p = 0.028$) and transplantation (PFS: HR = 0.192, $p = 0.003$; OS: HR = 0.144, $p = 0.002$) emerged as favorable prognostic factors. Multivariate analysis confirmed paramedullary extramedullary disease as an independent adverse factor for both endpoints (PFS: HR = 11.529, $p = 0.002$; OS: HR = 11.622, $p = 0.004$). Prognostic heterogeneity was observed among pPCL patients. After excluding 5 cases with extremely poor prognosis associated with extramedullary involvement, a prognostic stratification system incorporating 1q21+, LDH >400 U/L, bone marrow SUVmax≥7.2, transplantation status, and post-treatment MRD negativity was developed. Patients scoring ≥4 points demonstrated exceptional outcomes. **Conclusions:** The conventional R-ISS staging system failed to effectively stratify pPCL prognosis. A novel scoring

system (≥4 points) based on 1q21 amplification, LDH levels, bone marrow SUVmax, transplantation status, and MRD status successfully identified a subgroup with excellent prognosis.

PA-354

Profound Decrease of dFLC After One Cycle Predicts Superior Outcome in Patients with AL Amyloidosis Treated with Daratumumab and Bortezomib-Based Regimens

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Introduction: Daratumumab and bortezomib-based treatments are nowadays the standard regimens for AL amyloidosis. The relationship between the decrease in the free light chain after one cycle and clinical outcome is clinically significant. **Methods:** We conducted a multicenter retrospective study on 86 patients to investigate the impact of differences in free light chain (dFLC) reduction after one cycle on the complete hematological response (CHR), organ response, and survival when treated with frontline daratumumab and bortezomib-based therapy. All patients' dFLC was more than 50 mg/L before treatment. **Results:** The CHR rate was 77.9%. Using Receiver Operating Characteristic curve analysis, we predicted CHR based on a dFLC reduction after cycle one (87% change, AUC 0.83, optimal sensitivity 68.4%, specificity 86.6%). We defined dFLC reduction exceeding 87% or achieving very good partial response as an optimal hematological response (O-HR) and sub-optimal hematological response (S-HR) and vice versa. Compared with S-HR groups, O-HR resulted in a high possibility of CHR (90.5% vs. 43.5%, $p < 0.001$), cardiac response (68.9% vs. 36.8%, $p = 0.017$), and renal response (76.6% vs. 50.0%, $p = 0.045$). At a median duration of 25 months follow-up, the estimated 18-month overall survival and major organ deterioration progression-free survival were significantly superior in the O-HR group to that in the S-HR group (91.9% vs. 77.70%, $p = 0.025$) (95.0% vs. 82.6%, $p = 0.020$). **Conclusions:** In conclusion, the profound dFLC reduction observed after cycle one suggests a high likelihood of CHR and organ response, potentially allowing for early modification of therapy in selected patients.

PA-355

Real-World Impact of Anti-CD38 Monoclonal Antibodies and Hematopoietic Stem Cell Transplant in Primary Plasma Cell Leukemia (2021 IMWG Criteria): A Single-Center Analysis

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Introduction: Primary plasma cell leukemia (pPCL) is a rare and aggressive disease with dismal outcomes. Hematopoietic stem cell transplantation (HSCT), whether autologous or allogeneic, is key in achieving durable remissions after front-line therapy. In multiple myeloma, novel agents have improved outcomes, with anti-CD38 monoclonal antibodies (mAb) markedly improving survival. However, real-world reports on the impact of HSCT and especially anti-CD38 mAb therapy in pPCL are scarce. **Methods:** This single-center study explored the impact of front-line therapies on survival in pPCL patients between 2002 and 2024 at our institution. We defined PCL according to the 2021 diagnostic criteria by the International Myeloma Working Group (IMWG), applied retrospectively to patients diagnosed before 2021. We evaluated overall survival (OS) and progression-free survival (PFS) from start of front-line therapy in the entire cohort, as well as by anti-CD38 mAb exposure and by HSCT status. **Results:** Fifty patients were identified. Median age was 69 years (range 41–95), with 50% being male. The median follow-up duration was 18.1 months (IQR 9.6–46.5), and 56% of patients were staged as ISS III. Cytogenetic risk profiles were available for 25 patients, of whom 21 were high-risk (84% of available). The median OS (mOS) for the entire population was 25.3 months (95%CI: 12.7–53.2), and median PFS (mPFS) was 11.2 months (95%CI: 8.0–25.1). Among anti-CD38 mAb exposed (n = 18), mOS was 35.4 months (95%CI: 17.4-NA) and mPFS was 27.9 months (95%CI: 8.5-NA). Patients not exposed (n = 32) had a mOS of 16.4 months (95%CI: 10.9–49.8) and mPFS of 10.9 (6.4–14.7). Patients who underwent HSCT (n = 19) had a mOS of 56.7 months (95%CI: 30.8-NA) and mPFS 27.3 months (95%CI: 14.5-NA). In contrast, patients not undergoing HSCT (n = 31) had a mOS and mPFS of 15.0 months (95%CI: 10.4–35.4) and 6.4 months (95%CI: 4.7–13.5), respectively. In patients who underwent allogeneic HSCT (n = 7), mOS was not reached (95%CI: 10.3-NA) and mPFS 27.3 months (95%CI: 10.3-NA). Further, we analyzed the impact of front-line treatment regimens, where the overall response rate was

86%. Patients receiving doublet had a mOS of 17.4 months (95%CI: 8.8-NA) and mPFS of 7.7 months (95%CI: 1.0-NA). Patients receiving triplet had a mOS 16.2 months (95%CI: 11.9–50.1) and mPFS of 10.9 months (95%CI: 5.0–25.1). In patients receiving quadruplet, mOS was not reached (95%CI: 35.4-NA) and mPFS was 27.3 months (10.3-NA). Univariate analysis indicates diagnosis year after 2018, HSCT, anti-CD38 mAb, IMiD and quadruplet regimen as prognostic factors for PFS ($p < 0.05$). Multivariate modeling suggests IMiD and anti-CD38 mAb as independent predictors. **Conclusions:** Our findings indicate that patients with pPCL exposed to anti-CD38 mAb, and patients who underwent HSCT have superior outcomes in terms of OS and PFS. In particular, allogeneic HSCT is associated with vastly improved outcomes. It is crucial to note the small cohort size, where further studies are needed to confirm our results.

PA-356

Light-Chain Smoldering Multiple Myeloma: Natural History and Risk Stratification Based on the iStopMM Definition

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Introduction: Light-chain (LC) smoldering multiple myeloma (SMM) is a precursor condition of LC multiple myeloma. We recently proposed a new definition of LC SMM based on the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study, defined by an abnormal FLC ratio, elevated involved FLC levels, and >10% clonal bone marrow plasma cells, in the absence of detectable intact monoclonal immunoglobulins or myeloma-defining events. The aim of the current study was to identify a cohort of individuals with LC SMM in a population-based Danish cohort to describe the natural history of the condition and assess progression risk. **Methods:** LC SMM cases were identified from the Danish Lymphoid Cancer Research (DALY-CARE) cohort as individuals with diagnosis of multiple myeloma (MM) after 2011, were alive and had not received MM-related treatment prior to or within 90 days and fulfilled the iStopMM criteria for LC SMM described above. The cumulative incidence was examined overall and by the 20/2/20 risk stratification group using Aalen-Johanson and Kaplan Meier estimation with and without death as competing risk. **Results:** A total of 91 individuals with LC SMM were identified and followed for a median time of 2.2 years. During follow-up, 14(15%) progressed and 36(40%) died. According to FLC analysis, 68% had kappa and 32% had lambda light chain isotype. Bone marrow assessment data was accessible for 87 (96%), confirming plasma cell infiltration of 10–60% within 90 days of diagnosis. In total, 45 had available data on 24-hour urine testing. Of these, 18(40%) had a negative urine protein electrophoresis. The cumulative incidence of progression was 10%(95%CI: 6–20%) 2 years from diagnosis and 27%(95%CI: 11–39) at 5 years. When death was considered a competing risk, the cumulative incidence was 9%(95%CI: 3–15) after 2 years and 19%(95%CI: 10–29) at 5 years. Based on the 20/2/20 risk stratification model, 39% classified as low risk, 48% as intermediate risk, and 13% as high risk. The cumulative incidence of progression was lower (12% at 5 years) in the low-risk group compared to the intermediate or high-risk group (27% at 5 years), considering death as a competing risk, but statistical significance was not reached (Gray's test $p = 0.12$). **Conclusions:** This study provides clinical support for the iStopMM definition of LC SMM and characterizes a cohort with asymptomatic plasma cell dysplasia not covered by existing SMM subgroup definitions. Additionally, the results suggest superior diagnostic sensitivity of serum FLC analysis compared to urine M protein measurements and underscores the need for a revised LC SMM definition. The cumulative risk of progression was approximately 27% at five years, corresponding to an annual risk of 5.4%. These findings help fill a gap in the understanding of the previously uncharacterized subgroup of SMM without detectable M protein. Adoption of this new definition may support earlier identification, improved risk assessment, and more targeted clinical trial design for SMM.

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The Natural History of Smoldering Multiple Myeloma (SMM): Evolution of Incidence and Progression Risk from 2005 to 2022 in a Nationwide Danish Population-Based Cohort

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Introduction: Smoldering Multiple Myeloma (SMM) is an asymptomatic precursor to Multiple Myeloma (MM) and is usually diagnosed during work-up of suspected malignancy, bone disease, neuropathy, or other unspecific symptoms. Due to changes in diagnostic criteria for MM, increased sensitivity and availability of diagnostic tools, shifting population demographics, and greater disease awareness, the characteristics and progression risk of SMM have likely evolved in the last decades. In the present study, we aimed to describe changes over time of SMM incidence, progression risk, and overall survival in a population-based cohort. **Methods:** We used nationwide data from the Danish Lymphoid Cancer Research (DALY-CARE) resource, including the Danish National Multiple Myeloma Registry. We defined SMM as individuals with a ICD coded diagnosis of MM that did not receive anti-myeloma treatment and did not die within 90 days of first registered diagnosis. The cohort was stratified according to year of diagnosis: 2005–2011, 2012–2015, or 2016–2022. Progression was defined as the first day of anti-myeloma treatment. Overall survival was calculated using Kaplan Meier estimation. Finally, progression risk was examined by 2- and 5-year cumulative incidence of progression with death as competing risk using Aalen-Johanson estimation. **Results:** A total of 2,461 individuals with SMM diagnosed from 2005 to 2022 were identified. The median follow-up time was 3.5 (IQR: 1.6–6.6) years. The yearly incidence of SMM doubled from approximately 1.9 cases/100,000 in 2005 to 4.0 cases/100,000 in 2022. The cohort diagnosed in 2016–2022 was slightly older (median age 74(IQR: 67–80)) compared to the previous cohorts (median age 72 years (64–80)) and had more males (57% vs 50%). The median overall survival increased from 5.5 years (95%CI: 5.1–5.9) for individuals diagnosed from 2005 to 2011 to 7.7 years (95%CI: 7.0–8.5) for individuals diagnosed in 2012 or later. The 2-year cumulative incidence of progression decreased from 27.6% (95%CI: 24.3–30.9) if diagnosed 2005–2011, to 18.2% (95%CI: 16.0–20.6) in 2016–2022. Lastly, the 5-year cumulative incidence of progression decreased from 34.3% (95%CI: 30.7–37.8) if diagnosed 2005–2011, to 28.0% (95%CI: 25.0–30.9) in 2016–2022. **Conclusions:** This large population-based study on SMM demonstrates that the risk of progression from SMM to MM has decreased and overall survival has increased over time. These changes likely reflect updated definitions of diagnostic criteria for MM as well as more sensitive diagnostics. In addition, we found that the incidence of SMM increased during the study period, most likely due to a combination of factors including increased M-protein testing and ageing population. These results are important considering recent clinical trials indicating that treatment could be beneficial for selected individuals with SMM and highlights the importance of risk stratification in the management of SMM to optimize both patient care and healthcare resource utilization.

PA-358

A Dynamic Risk Stratification Model for Patients with Smoldering Multiple Myeloma Through Integration of the Evolving Patterns of Monoclonal Protein and Serum Free Light Chains

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Introduction: The Mayo2018 model represents a widely established risk stratification for patients with smoldering multiple myeloma (SMM). In 2023, we presented a preliminary optimization of the Mayo2018 model incorporating evolving patterns of serum M-protein (MP) and involved serum free light chains (FLC) as additional risk factors to more precisely identify high-risk patients who may benefit from intensified monitoring or early therapeutic intervention. This study aims to refine our previous analyses by integrating an expanded patient cohort, extended follow-up data and innovative time-independent cutoffs for the evolving definitions of serum MP and involved FLC. **Methods:** This retrospective study includes 447 patients diagnosed with SMM between February 2009 and July 2023, all meeting the 2014 IMWG diagnostic criteria (Rajkumar SV et al., Lancet Oncol., 2014). Unlike previous approaches limited to the first 12 months after diagnosis, we statistically developed a novel evolving risk factor applicable at any time point during patient follow-up, incorporating the changes in MP and FLC over the preceding 12 months. As in our previous study we then compared the performance of the Mayo2018 model (BMPC >20%, MP > 2 g/dl, serum involved:uninvolved FLC ratio >20; 0 points = low risk, 1 point = intermediate risk, ≥2 points = high risk; Lakshman A et al., BCJ, 2018) enhanced by the dynamic risk factor "evolving serum MP and/or evolving serum FLC" (eMP/eFLC) and by an additional fourth risk category to the respective static model, using the c-index. **Results:** Based on improved cut-point search and clinical applicability, we defined the independent risk factors eMP as a >20% and >0,4 g/dl increase in MP (HR = 5.46, 95% CI [3.60; 8.28], $p < 0.001$) and eFLC as a >40% and >40 mg/l increase in involved FLC (HR = 5.16, 95% CI [3.36; 7.95], $p < 0.001$) within the preceding 12 months of observation. Patients with an eMP and/or eFLC phenotype showed a significantly increased risk of progression (HR = 4.52, 95% CI [3.01; 6.80], $p < 0.001$). Adding the novel combined risk factor eMP and/or

eFLC to the Mayo2018 model as an additional risk factor resulted in having the newly arranged four risk categories "low risk" (= 0 points), "low-intermediate risk" (= 1 point), "intermediate risk" (= 2 points) and "high risk" (≥ 3 points) and improved discrimination of the Mayo2018 risk model compared to the static model (c-statistics for static model: 0.778 vs. dynamic model: 0.817, p = 0.005). **Conclusions:** By applying refined cutoff analyses, we improved our previous definition of the risk factors eMP/eFLC and created a dynamic Mayo2018 model, which is universally applicable for the duration of patient follow-up. Our results show that our novel dynamic eMP/eFLC model more precisely stratifies patients at their individual risk compared to the static model. Further detailed data will be presented at the meeting, including the application of eMP/eFLC in the IMWG 2020 model. Validation of the model is in preparation.

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Diffuse Bone Marrow Activity as Prognostic Biomarker in Patients with Smouldering Multiple Myeloma

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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 via Whole Body MRI (WBMRI) and PET/CT, 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. The aim of this study was the evaluation of DMA as prognostic marker in sMM. **Methods:** This retrospective monocentric study enrolled 80 patients diagnosed with sMM between 2014 and 2025 according to the IMWG criteria. Patients underwent WBMRI (including DWI sequences) and/or PET/CT at baseline. DMA was defined as an ADC value of 550–650 $\mu m^2/s$ on WBMRI or a Deauville score of 2–3 on PET/CT. Prognostic stratification was performed using 20/20/2, IMWG high-precision (with FISH), and PANGEA scores at diagnosis and last follow-up. Statistical analysis was conducted using SPSS v29.0. **Results:** DMA was detected in 43% of patients overall, with higher sensitivity observed in WBMRI (71%) compared to PET/CT (29%). Eighteen patients (22%) progressed to MM over a median follow-up of 20 months (range: 3–111), with a median TTP of 29.5 months. Among those who progressed, 72% had DMA at baseline. Patients with DMA had a shorter TTP (24 vs. 38 months). Even among patients classified as low or intermediate risk by all three scores, those with positive imaging had significantly shorter TTP (26 months). A statistically significant correlation was found between DMA presence and progression (p = 0.01), as well as between DMA and increases in prognostic scores or sFLC ratio during follow-up (p = 0.02–0.05). Among non-progressors with follow-up > 20 months, patients with DMA showed a statistically significant increase in sFLC ratio and PANGEA score over time, suggesting a dynamic evolution despite initial low-risk classification. **Conclusions:** This study supports the role of diffuse marrow activity (DMA) as an independent and dynamic biomarker of progression risk in sMM. Imaging findings correlated with established risk scores and predicted earlier progression, even in patients initially stratified as low or intermediate risk. WBMRI demonstrated superior sensitivity in detecting DMA, while PET/CT proved valuable for confirming metabolic activity. The sequential use of both modalities enhanced diagnostic accuracy. These findings advocate for the integration of DMA into future risk models and suggest WBMRI as a preferred first-line imaging tool in centers where available. Prospective studies on larger cohorts are warranted to validate these observations and refine risk-adapted management strategies. A multicentric prospective study will shortly enroll patients with sMM to evaluate the prognostic impact of DMA.

PA-360

The Significance of a MGUS Tumor Board: Updates After Three Years of Success

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Introduction: For years our large academic medical center faced an issue of access to myeloma physicians at main campus due to the increasing number of referrals for monoclonal gammopathy of

undetermined significance (MGUS). We hired additional advanced practice providers (APPs) at main campus and several regional sites, with MGUS referrals triaged to their clinic. Due to concerns regarding variation in experience with work up of monoclonal gammopathy we created a structured method to approach all MGUS consults. This included standardized educational materials with recommended workflow, the "MGUS Care Path" and a consultation template in the EMR. In August 2021, we formalized a MGUS tumor board focused on discussing cases with possible clinical significance. **Methods:** These cases are presented to main campus plasma cell disorder experts, including three physicians and our APRN/PhD. We meet every 1st and 3rd Monday of the month to provide educational support and standardization for work up of MGUS to avoid missing any cases of clinical significance. We present here our outcomes based on over three years of data from our MGUS tumor board. **Results:** From August 2021 to February 2025, our APPs saw over 800 referrals for MGUS. We discussed 267 of these patient cases based on clinical findings or investigations concerning for monoclonal gammopathy of clinical significance (MGCS). Based on recommendations from the MGUS tumor board we diagnosed a variety of disorders driven by the monoclonal gammopathy. These include type 1 cryoglobulinemia, IgM neuropathy with anti-MAG, TEMPI, warm-autoimmune hemolytic anemia, Schnitzler's disease, smoldering and active myeloma, marginal zone lymphoma, myelodysplastic syndrome, chronic lymphocytic leukemia, light chain amyloidosis, proliferative glomerulonephritis with monoclonal immune deposition. Of the 267 cases, 75 (28.0%) were referred to physicians at main campus, with 25 (9.4%) requiring treatment. **Conclusions:** We previously reported our tumor board findings after 147 patients with 41 (28.0%) found to have MGCS and 16 (11.0%) needing treatment. It was initially surprising that 1 in 4 cases were confirmed MGCS based on tumor board recommended work up. This update after over three years shows consistent distribution, with ~25% MGCS cases. The majority of MGUS patients continue to receive care with our APPs. This allowed the myeloma program at main campus to grow. We hired three additional myeloma physicians in the past two years, expanded the clinical trial portfolio and improved access to cell therapies and physician consultations. We continue to provide CME for attendance at the MGUS tumor board for both APPs and physicians. The tumor board remains a reliable method to triage MGUS consults, providing improved access to physician specialists, while minimizing the risk of missing cases of MGCS. We have also implemented a similar model for anemia consults creating more access to main campus classical hematology providers.

PA-361

Early Venetoclax Salvage in Systemic Light Chain Amyloidosis: A Retrospective Case Series

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Introduction: Systemic light chain (AL) amyloidosis is a rare plasma cell disorder characterized by tissue deposition of misfolded light chains, causing progressive organ damage. The chromosomal translocation t(11;14) is present in approximately 50% of AL amyloidosis patients, compared to about 10% in multiple myeloma, and is associated with suboptimal response to first-line bortezomib therapy. Venetoclax, a selective BCL2 inhibitor, has shown efficacy in t(11;14)-positive hematologic malignancies, including myeloma and AL amyloidosis. Early and rapid reduction of light chains is crucial to achieve organ response and prevent disease progression and related morbidity and mortality. **Methods:** We retrospectively reviewed a database from a quaternary amyloidosis referral centre to identify patients treated with venetoclax-based salvage therapy. Baseline characteristics and response assessments were confirmed through detailed chart review, including electronic medical records, laboratory, and imaging data. **Results:** Seven systemic AL amyloidosis patients treated with venetoclax monotherapy or venetoclax plus daratumumab for inadequate initial response were identified. All patients had ≥10% bone marrow plasmacytosis on initial bone marrow biopsy, with a mean of 18.5%. Median dFLC at diagnosis was 82 mg/L, with an interquartile range of 382 mg/L. All received first-line bortezomib, cyclophosphamide, and dexamethasone; 3 also received daratumumab. The mean age at diagnosis was 62.7 years, with 57% female. Cardiac involvement was present in 6 (86%), and 4 (57%) advanced Mayo 2004 stage III. Venetoclax was dosed at 400 mg daily, or 50 mg with concurrent azole antifungal therapy. To date, patients have received between 4 and 13 monthly cycles of venetoclax (median of 10.5). Hematologic response rate including CR and VGPR was 71% (5/7 patients), with partial response (PR) achieved in the remaining 2 patients. All CRs occurred in patients who began venetoclax within six months of diagnosis due to suboptimal response. Organ responses were observed in 4 patients (57%), including cardiac and renal improvements, even among those without hematologic CR. Venetoclax was generally well-tolerated; 1 patient experienced grade 3 thrombocytopenia, with no grade 3/4 neutropenia, febrile neutropenia or tumour lysis syndrome reported. One patient died due to progressive disease having only achieved a haematological PR. **Conclusions:** Venetoclax is a safe and effective salvage therapy for AL amyloidosis patients with t(11;14), particularly when initiated early after diagnosis. It yields high hematologic and organ response rates, underscoring its potential to improve outcomes in this challenging population. Further studies are warranted to explore its role in frontline therapy and earlier salvage interventions to reduce morbidity and mortality.

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Investigating the Role of the BAFF-APRIL System in Promoting Progression of Smouldering Myeloma (SMM)

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Introduction: The BAFF-APRIL system, comprising two ligands (APRIL and BAFF) and three receptors (BCMA, TACI, and BAFF-R), is a key regulator of B-cell homeostasis and myeloma (MM) survival. To explore how the BAFF-APRIL system may regulate progression from SMM to MM we performed a ligand-receptor and pathway analysis. **Methods:** We utilised our compilated single-cell atlas (64 SMM, 64 MM and 107 healthy donors), including samples from the COSMOS trial (NCT05047107). The soluble sink of the BAFF-APRIL axis was determined by ELISA analysis of sBCMA, sAPRIL, sTACI, and sBAFF protein levels in peripheral blood and bone marrow (BM) plasma of SMM (n = 15) and MM (n = 14) patients, and correlated with results of flow cytometry of BM immune subsets. **Results:** BCMA and TACI were expressed in 60% and 40% of malignant plasma cells (PCs), respectively, being co-expressed in 33% of all PCs, while BAFF-R expression was limited to 10% of PCs. Ligand expression analysis revealed that BAFF and APRIL were expressed by CD14+ and CD16+ monocytes, granulocyte-monocyte progenitors (GMPs), and dendritic cells (DCs), confirming the myeloid compartment as the principal source of these survival signals. Interaction analysis between ligand-receptor pairs and relevant pathways revealed consistent myeloid to PC signalling in both SMM and MM. High BCMA expression was found to correlate with high TACI expression on both PCs and naive B cells. Additionally, a strong positive association was observed between BCMA expression on PCs and BAFF expression on CD14+ monocytes. Additional signalling of BAFF via cDCs was present in MM but absent in SMM. Flow cytometry analysis revealed no significant change in total frequency of either monocytes or cDCs in the BM of MM patients, suggesting a functional cellular shift rather than cell expansion. Stratification by disease stage revealed that both BCMA and TACI transcripts were significantly upregulated in PCs during progression ($p.adj < 0.001$). Similarly, APRIL and BAFF expression increased in PCs but remained stable or declined in myeloid cells. This was consistent with circulating sBCMA levels that were significantly higher in MM compared to SMM ($p = 0.01$). sTACI levels also positively correlated ($p < 0.01$) with tumour burden. Interestingly, BM sAPRIL levels were negatively correlated with tumour burden, suggesting a potential regulatory feedback mechanism. Activation in downstream pathways of BCMA/TACI, MAPK, NF-κB, MYD88 and PI3K/AKT increased with progression, alongside increased transcript expression of members of the APRIL-BAFF axis, implying increased survival signalling via this mechanism. **Conclusions:** Preliminary findings show stage-specific changes in BAFF–APRIL signalling, suggesting that malignant PCs progressively co-opt the immune microenvironment through myeloid–PC interactions and increasing cDC involvement, to support survival and disease progression. BCMA targeting may be most effective in SMM, where lower sBCMA and an ADCC-permissive immune environment support therapies.

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The Impact of HER2-Directed Treatment on Monoclonal Protein (M-Protein) Levels in Patients with Concomitant Breast Cancer and Plasma Cell Disorders: A Case Series

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Introduction: HER 2 positivity has been studied in several solid tumors, especially breast and gastrointestinal. Results from the DESTINY-PanTumor02 Phase II Trial showed durable clinical benefit of HER 2 directed immunotherapy in several solid tumor types. However, HER 2 positivity has been rarely explored in hematologic malignancies. **Methods:** We present a case series of two patients with concomitant breast cancer and plasma cell disorder who witnessed a reduction in their M protein while on HER 2 immunotherapies. Data were collected retrospectively from systematic chart reviews. **Results:** Patient 1: 79-year-old female with IgG kappa multiple myeloma (MM) (del 17p, t(4:14), del 13q) diagnosed in 2014 was started on lenalidomide but stopped shortly after due to side effects (SE). She was switched to Bortezomib and dexamethasone, discontinued in 2016 due to neuropathy, but achieved VGPR. Given age/comorbidities, she was observed until 2018 when rising M spike prompted Bortezomib restart, which was ineffective, leading to third-line treatment with Carfilzomib, pomalidomide, dexamethasone (KPD). P stopped due to suspected seizure. K continued until disease progression. Fourth-line single-agent daratumumab started with initial disease control switched to fifth-line Cyclophosphamide, Bortezomib, and dexamethasone, achieving VGPR. After HER2 + breast cancer diagnosis, myeloma treatment was held post cycle 3 on

Jul, 2022. She completed 12 weeks of Paclitaxel/Trastuzumab by Nov, 2022, followed by Trastuzumab through Aug, 2023. Anastrozole started on Jan, 2023. During Paclitaxel/Trastuzumab treatment, she achieved serologic complete response with undetectable M protein. M protein remained undetectable until Apr, 2024, when recurrence was documented while off HER2 therapy. Therapy with daratumumab and pomalidomide was initiated. Patient 2: 77-year-old female with IgG kappa MGUS (>30 years) and HER2 + breast cancer was started on systemic treatment with Trastuzumab/Pertuzumab; chemotherapy portion of treatment declined. After mass progression, she transitioned to Trastuzumab Deruxtecan. She was switched back to Trastuzumab after 3 cycles due to SE. Dose-reduced ado-trastuzumab emtansine was initiated after disease progression. Interestingly, at time of diagnosis, her M protein concentration was 1.22 g/dL, kappa 38.3 mg/L, lambda 11.2 mg/L, k/l ratio 3.42. While on HER2 immunotherapy, M protein became undetectable in 18 months. During treatment, M protein reappeared at 0.25 g/dL, likely reflecting the drug itself-an antibody-while the k/l ratio remained normal. **Conclusions:** HER2 immunotherapy showed M protein reduction in both cases of plasma cell dyscrasia. A study by Uckun and Qazi found that patients with higher levels of ERBB2/HER2 in MM had poorer outcomes1. Further comparative analysis is needed to identify which patient subsets may benefit from HER2 testing. This case series highlights the potential role of HER2 as a biomarker in plasma cell dyscrasias and its utility in relapsed/refractory MM.

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Clinical Outcomes of Patients with MGUS and Diabetes/Obesity on GLP-1 Receptor Agonists: A Real-World, Propensity-Matched Study

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder with a risk of progression to multiple myeloma (MM). Emerging evidence suggests that metabolic comorbidities, such as diabetes mellitus (DM) and obesity, may influence clonal evolution and immune microenvironment dynamics. In this context, Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated anti-inflammatory and potential anti-neoplastic properties. **Methods:** The association between GLP-1 RAs and clinical outcomes (progression to symptomatic MM, death) in patients with MGUS and concurrent DM/obesity was assessed using real-world data from the TriNetX global health research network. **Results:** Out of 236,250 patients with MGUS in the TriNetX database, 103,913 had diabetes and/or were classified as having overweight or obesity. Among them, 13,360 patients received treatment with GLP-1 receptor agonists, while the remaining 90,553 did not receive GLP-1 RAs. After propensity score matching, the two cohorts consisted of 13,187 patients each. The probability of not progressing to MM at the end of the time window was 91.2% for patients on GLP-1 RAs and 75.4% for patients on other drugs ($p = 0.137$). A non-significant trend of 12.8% reduced risk for progression was observed among patients on GLP-1 RAs (HR = 0.872, 95% CI: 0.727–1.045) compared to other drugs. The probability of being asymptomatic and alive was 32.9% for patients on GLP-1 RAs and 24.9% for patients on other drugs ($p < 0.001$). The median progression-free survival (PFS) was 145.8 months and 121.7 months, respectively. There was a statistically significant 35% reduced risk for progression to MM or death for patients on GLP-1s (HR = 0.650, 95% CI: 0.597–0.709), compared to those on other anti-diabetic drugs. The overall survival (OS) probability was 43.4% and 29.5%, respectively ($p < 0.001$). The median OS was 162.8 and 134 months, respectively. There was a statistically significant 38.3% reduced risk for progression to symptomatic MM or death for patients on GLP-1 RAs (HR = 0.617, 95% CI: 0.566–0.672), compared to those on other anti-diabetic drugs. It was estimated that among patients who progressed to symptomatic MM, 41% were progression-free and alive at the end of the time window among those on GLP-1 RAs and 26.3% among those on other drugs ($p < 0.001$). The median PFS-2 was 162.8 and 131 months, respectively. There was a statistically significant 36.8% reduced risk for disease progression or death for patients with symptomatic MM on GLP-1 RAs (HR = 0.632, 95% CI: 0.581–0.687), compared to those on other anti-diabetic drugs. **Conclusions:** Treatment with GLP-1 RAs in this large, real-world cohort study led to a numerically, but not statistically significant, decrease in progression rates from MGUS to MM, whereas a consistent survival benefit became evident. Our results support the further evaluation of GLP-1 RAs in patients with MGUS/smoldering MM in prospective studies.

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Clinical Profile, Treatment Patterns, Outcomes and Predictors of Survival in AL Amyloidosis: A Retrospective Study from 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. The clinical presentation is heterogeneous, and data from low- and middle-income countries (LMICs) remain scarce, particularly in settings with limited access to novel agents and autologous stem cell transplantation (ASCT). **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. **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%). The median duration of symptoms prior to diagnosis was 6 months (range: 1–24 months). Of the 61 patients evaluable for staging, 30.6% (n = 19) were classified as Revised Mayo Stage III or IV. 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 responses post-induction was 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. Early mortality (within 6 months of diagnosis) occurred in 41.6% (n = 10) of the total deaths. 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 significantly associated with inferior outcomes. **Conclusions:** This study provides key insights into the presentation and outcomes of AL amyloidosis in an Indian cohort, highlighting delayed diagnosis, frequent renal and cardiac involvement, and limited access to advanced therapies including ASCT and daratumumab. High rates of early mortality underscore the need for timely diagnosis, aggressive supportive care, and access to novel agents. Renal involvement and failure to achieve hematologic response emerged as significant predictors of poor prognosis.

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CALM: A Deep Learning Time Series Model for Predicting Progression from Smoldering Multiple Myeloma Using Clinical Data

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Introduction: Current methods of identifying smoldering multiple myeloma (SMM) patients at high-risk (HR) of progression rely primarily on blood- and bone marrow-based assessments of tumor burden, and do not fully leverage the dynamic, longitudinal data routinely generated in clinical practice as SMM patients are monitored. We hypothesized that standard clinical data may contain hidden features that could potentially identify patients at high risk of progression. To test this hypothesis, we developed CALM (Cancer AI Longitudinal Modeling), a 'digital twin' deep learning model designed to predict the risk of progression from SMM to MM using serial laboratory measurements, as opposed to values available at diagnosis alone. **Methods:** We retrospectively analyzed clinical data from 438 patients diagnosed with SMM between 2002 and 2019, with a median follow-up of 4.24 years and a median of 11 laboratory assessments per patient (median interval between measurements: 92 days). At last follow-up, 185 patients (42.2%) progressed to MM, while 253 (57.8%) were censored. CALM utilizes time series measurements of key biomarkers — serum M-protein (M-spike), involved and uninvolved free light chains (FLC), and derived features such as the FLC ratio and log-transformed FLC ratio, along with additional routine laboratory values. CALM leverages a padded Long Short-Term Memory (LSTM) neural network model specifically designed to recognize patterns and trends across sequential data. The LSTM processes each patient's longitudinal data as a sequence, learning to recognize temporal changes that may signal impending progression. Model evaluation was performed using a Cox proportional hazards loss function with 5-fold cross-validation. **Results:** Risk scores computed using CALM achieved a mean concordance index (C-index) of 0.833 ± 0.018, demonstrating strong discriminatory performance for predicting progression to MM with data associated with the last sequence. This represents an 11% increase in predictive potential when compared to baseline risk assessment using the Mayo 2/20/20 criteria alone in the same cohort. To interpret model predictions, we applied Captum's integrated gradients algorithm to quantify the contribution of each feature at each time point to the predicted risk for an individual patient. Higher values of absolute M-spike and the log-transformed FLC ratio were strongly associated with increased risk of progression, with the model showing a clear preference for the log FLC ratio over the raw ratio as a predictive variable. **Conclusions:** CALM leverages routinely collected serial laboratory data to dynamically update individualized risk predictions for SMM patients. This 'digital twin' approach not only provides improved risk stratification over static models but also offers clinicians interpretable feedback on which laboratory trends are driving risk,

potentially informing more personalized monitoring and therapeutic decision-making in clinical practice.

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Mortality and Inpatient Hospitalization Rates amongst Light-Chain Amyloidosis (AL) Patients during the Daratumumab Era: Results from an Analysis of US Medicare Fee-for-Service (FFS) Beneficiaries

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Introduction: Light chain amyloidosis (AL) is a rare hematologic disorder characterized by the misfolding of immunoglobulin light chain produced by clonal plasma cells, followed by aggregation into amyloid fibrils and subsequent organ deposition, which may lead to organ dysfunction and death if not treated. Limited real-world data exist on clinical outcomes in AL patients following the approval of daratumumab as first-line therapy and its inclusion in clinical guidelines, specifically within the Medicare Fee-for-Service (FFS) population. The objective of this study is to assess mortality and inpatient hospitalization rates amongst Medicare FFS beneficiaries with AL who were newly prescribed treatment from January to December/2021. **Methods:** An observational, retrospective analysis of de-identified 100% Medicare Fee-for-Service (FFS) medical and pharmacy claims and enrollment data (Parts A/B/D) from January 1, 2020 to December 31, 2022 was performed. The index date was defined as the earliest diagnosis date (ICD-10 code) of AL within the identification window of January 1, 2021 to December 31, 2021. Patients were required to have: (1) ≥ 1 inpatient or ≥ 2 outpatient claims (≥ 30 days apart) with an ICD-10-CM diagnosis code (E85.81) for AL; (2) continuous medical and prescription insurance enrollment from 12-months pre-index through 12-months post-index (or death); (3) age ≥18 years at index, and (4) ≥1 claim for one of the following treatments within 3 months post-index: bendamustine, bortezomib, carfilzomib, cyclophosphamide, daratumumab, ixazomib, lenalidomide, melphalan, pomalidomide, or venetoclax. Patients with a prior claim for AL at baseline or any claim for stem cell transplant were excluded. Outcomes were assessed during the 12-month post-index period, including all-cause mortality and all-cause inpatient hospitalizations, stratified by daratumumab use (initiated within 3 months post-index-diagnosis). **Results:** A total of 319 patients met all inclusion and exclusion criteria, of which 78.1% (n = 249) and 21.9% (n = 70) were classified as daratumumab users and nonusers, respectively. A majority of patients were age 70+ (79.3%; n = 253), male (55.8%; n = 178), White (79.3%; n = 253), and resided in the South (32.0%; n = 102). The overall annual mortality rate among newly diagnosed/newly treated AL patients was 21.0% (n = 67/319), with a lower rate observed among daratumumab users (19.7%; n = 49/249) compared to daratumumab nonusers (25.7%; n = 18/70). Differences were also observed when assessing all-cause inpatient hospitalization rates during the 12-month post-index period, with 57.8% (n = 144/249) and 48.6% (n = 34/70) seen among daratumumab users and nonusers, respectively. **Conclusions:** Despite recent therapeutic advances, mortality and inpatient hospitalization rates remain high amongst AL patients, underscoring a significant unmet need, particularly within the Medicare FFS population.

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Mesenchymal Stromal Cell Senescence is Associated with Progression from MGUS to Multiple Myeloma

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Introduction: Ageing is associated with an increased risk of progression from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM), suggesting that age-related changes in the bone marrow (BM) microenvironment may contribute to disease evolution. We hypothesise that the accumulation of senescent mesenchymal stromal cells (MSCs) in the BM with age promotes disease progression. **Methods:** MSCs were isolated from BM trephine biopsies of newly diagnosed MGUS patients (n = 9; age 50–84 years), MM patients (n = 8; age 52–86), healthy young controls (n = 8; age 17–32) and older non-cancer controls (n = 8; age 65–94). Senescence was assessed in human and murine MSC cultures by measuring senescence-associated β-galactosidase (β-gal) activity, proliferation and expression of senescence markers via qRT-PCR. The ability of BM MSCs to support MM cell line proliferation was examined in co-culture assays. Expression of potential pro-proliferative secreted factors by MSCs was evaluated using a public microarray dataset (GSE36474) and confirmed by qRT-PCR. Luciferase-expressing 5TGM1 MM cells were injected into C57BL/KaLwRij mice via the tail vein and tumour development in the BM was monitored over four weeks by bioluminescence imaging and serum paraprotein electrophoresis. **Results:** BM MSCs from MGUS and MM patients exhibited a senescent phenotype that was characterised by elevated β-gal activity, increased CDKN2A expression, and reduced proliferation, which was similar to MSCs from older individuals without cancers, and distinct from MSCs of young healthy controls. The proportion of senescent cells in MGUS, MM, and control samples was positively correlated with age ($p = 0.020$; Pearson's $r = 0.4$). Importantly, MGUS patients with high levels of BM MSC senescence showed a significantly increased risk of progression to MM ($p = 0.0047$, log-rank test; HR: 20.3, β-galhi vs β-gallo). Senescent MSCs (whether induced by replicative exhaustion, γ-irradiation, or derived from aged mice) had an increased capacity to

support MM cell proliferation in vitro, when compared with non-senescent controls. Microarray and qRT-PCR analyses identified GREM1, encoding the BMP antagonist Gremlin1, as being significantly upregulated in MSCs from MM patients. Co-culture experiments demonstrated that overexpression of Gremlin1 in OP9 stromal cells enhanced proliferation of KMM1, RPMI-8226 and 5TGM1 MM cells. Notably, treatment with an anti-Gremlin1 neutralising antibody significantly reduced tumour burden in 5TGM1-bearing KaLwRij mice compared with IgG-treated controls. **Conclusions:** This study demonstrates, for the first time, that elevated BM MSC senescence in MGUS patients is associated with a higher risk of progression to MM. Senescent MSCs promote MM proliferation, potentially through increased Gremlin1 expression. Targeting senescence-associated factors such as Gremlin1 may offer new therapeutic opportunities to delay or prevent MGUS progression to MM.

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Prior Plasma Cell Dyscrasia is Associated with Lower Odds of Severe Myeloma-Defining Events at Diagnosis

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Introduction: Clinical guidelines recommend indefinite monitoring of patients with asymptomatic precursor plasma cell disorders (MGUS or smoldering multiple myeloma [SMM]), yet this practice is not grounded in high-quality evidence. Whether such surveillance meaningfully influences clinical outcomes at the time of multiple myeloma (MM) diagnosis remains uncertain. The primary aim of this study was to evaluate differences in symptom burden and healthcare utilization at MM diagnosis between patients with and without a known prior plasma cell disorder (pPCD). **Methods:** We retrospectively reviewed all patients diagnosed with multiple myeloma (MM) between January 2019 and July 2024 at our institution. Patients with a known prior plasma cell disorder (pPCD)—MGUS, smoldering MM, or solitary plasmacytoma—diagnosed ≥3 months before MM were identified. Those with systemic AL amyloidosis or prior plasma cell–directed therapy were excluded. Myeloma-defining events (MDEs) included IMWG 2014 CRAB and SLiM criteria. Healthcare utilization, time from symptom onset to diagnosis, and emergency visits were captured through manual chart review. Logistic regression models were adjusted for age and sex, and descriptive statistics were used to compare the MDE at diagnosis. **Results:** Among 424 patients, 104 had pPCD (n = 71 MGUS, n = 25 smoldering MM, n = 8 solitary plasmacytoma) and 320 had MM without a known pPCD (nPCD). Median time from pPCD to MM diagnosis was 4.6 years. Patients with pPCD had fewer CRAB features at diagnosis (71% vs 92%) and shorter time from symptom onset to diagnosis (4.8 vs 7.6 months, $p < 0.001$). Anemia (38% vs 65%), renal failure (11% vs 23%), bone lesions (44% vs 59%), and PRBC transfusions (16% vs 39%) were less frequent in the pPCD group compared to nPCD. ER visits within 3 months of diagnosis were also lower in pPCD patients (36% vs 64%). On multivariable analysis, pPCD significantly reduced the odds of presenting with a composite adverse outcome—dialysis, fracture, hospital admission, cord compression, hypercalcemia treatment, or transfusion—by 73% (OR 0.27, 95% CI 0.16–0.43, $p < 0.001$). This association persisted after excluding patients without hematology follow-up within 1 year of presentation. **Conclusions:** This study demonstrates that patients with a prior PCD present with fewer MDE and lower acute healthcare utilization at the time of MM diagnosis. While our findings do not define optimal follow-up intervals, they support the clinical value of ongoing surveillance in patients with pPCD. These results contribute to the growing body of evidence suggesting that early recognition and monitoring may attenuate disease-related morbidity at presentation. Ongoing prospective studies such as iSTOP-MM will be critical in determining the broader impact of MGUS screening and longitudinal follow-up.

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Efficacy and Safety of Daratumumab-Based Regimens in Light Chain Amyloidosis: A Retrospective Single-Center Study

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Introduction: Light chain (AL) amyloidosis is a rare plasma cell disorder characterized by misfolded immunoglobulin light chains forming amyloid deposits in tissues and vital organs. Prognosis remains poor, particularly in patients with advanced cardiac or renal involvement. Daratumumab, an anti-CD38 monoclonal antibody, has demonstrated promising efficacy in AL, with reported response rates exceeding 80% in some studies. This retrospective analysis evaluated the real-world effectiveness and safety of various daratumumab-based regimens in patients with newly diagnosed or relapsed/refractory AL amyloidosis. **Methods:** This single-center retrospective study included patients diagnosed with AL amyloidosis who received at least three cycles of daratumumab-based treatment between May 2018 and May 2025. Regimens included combinations such as daratumumab with lenalidomide (DRd), bortezomib (DVd), pomalidomide (DPd), selinexor (SDd), ixazomib (DId), carfilzomib (DKd), or daratumumab plus dexamethasone alone (Dd).

Hematologic responses were assessed per consensus criteria, and organ responses were evaluated based on cardiac and renal improvement indicators. **Results:** A total of 77 patients were analyzed, including 64 newly diagnosed and 13 relapsed/refractory cases. The median age was 58.5 years (range: 36–83). At baseline, 56.1% of patients were classified as Mayo stage III or IV. Cardiac involvement was present in 75.4%, renal involvement in 54.5%, and 31.5% had both. The median baseline NT-proBNP was 2,478 ng/L, 24-hour urine protein was 0.763 g, eGFR was 75.4 mL/min/1.73 m^2, and difference in free light chains (dFLC) was 142.4 mg/L. After 12 months, 77.8% of patients in the DRd group and 58.9% in the DVd group achieved very good partial response (VGPR) or better. Among Mayo stage III–IV patients, 67.3% achieved VGPR or better. Overall hematologic response rates at 1, 6, and 12 months were 60.8%, 80.7%, and 93.0%, respectively. At 12 months, 30 patients achieved complete response (CR), 33 VGPR, and 8 partial response (PR). Cardiac response rates improved from 50.8% at 3 months to 86.7% at 12 months. Among patients with renal involvement, 55.4% demonstrated renal response by month 12. Treatment was generally well tolerated. The most frequent adverse events were neutropenia and anemia (33.4%) and infusion-related reactions (25.4%), all grade 1–2. No thromboembolic events were reported. **Conclusions:** Daratumumab-based therapy is effective and well tolerated in both newly diagnosed and relapsed/refractory AL amyloidosis patients. It induces rapid and sustained hematologic responses and facilitates organ function recovery over time. Most adverse events were mild and manageable. Despite its retrospective design and single-center scope, this study adds valuable real-world evidence supporting the integration of daratumumab into treatment strategies for AL. Prospective, multicenter randomized trials are warranted to confirm these findings and establish optimal treatment protocols.

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Integrative Clinical, Transcriptomic, and Immunohistochemical Characterization of Light Chain Amyloidosis in Bone Marrow and Cardiac Tissue

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Introduction: Systemic light chain (AL) amyloidosis is a rare and potentially fatal plasma cell dyscrasia in which misfolded immunoglobulin light chains form amyloid fibrils that deposit in organs and cause irreversible damage. While the clinical manifestations are heterogeneous and often overlap with other plasma cell disorders such as multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS), the underlying immune and transcriptomic features of AL amyloidosis remain insufficiently characterized. **Methods:** We retrospectively reviewed 50 patients with newly diagnosed primary AL amyloidosis treated at a tertiary medical center in Taiwan. Clinical characteristics, treatment responses, and survival outcomes were analyzed. PD-1 immunohistochemical (IHC) staining was performed on bone marrow and cardiac biopsy tissues. Bulk RNA sequencing was conducted on cryopreserved bone marrow specimens from AL amyloidosis (n = 12), MM with coexisting amyloidosis (n = 5), and MGUS (n = 15) cohorts. Differentially expressed genes (DEGs) were identified using DESeq2, followed by Gene Ontology (GO) and KEGG enrichment analyses. A subset of immune-related DEGs was analyzed separately. **Results:** Cardiac involvement was observed in 80% and renal involvement in 64% of patients. Mayo 2012 staging stratified overall survival (OS) effectively, while renal staging was predictive of dialysis risk. The 3-year OS rate was estimated at 73.97%. Treatment modality significantly impacted prognosis, with better OS seen in patients receiving bortezomib- or alkylating agent-based therapies. In transcriptomic analysis, AL amyloidosis and MM demonstrated distinct expression profiles. A total of 153 DEGs were identified, including upregulation of mitochondrial and immune-regulatory genes in AL. Enrichment analyses revealed pathways related to extracellular matrix remodeling, PI3K-Akt signaling, and PD-1/PD-L1 immune checkpoint regulation. PD-1 IHC staining confirmed higher scores in AL cardiac tissues compared to hereditary cardiac ATTR amyloidosis (mean: 2.00 vs. 0.73, p = 0.046), though PD-1 levels did not correlate with NT-proBNP or OS. Comparison between AL amyloidosis and MGUS identified 738 DEGs, with 595 genes upregulated in AL. These included genes involved in mitochondrial respiration and cardiomyocyte function (e.g., ATP6, ND4, COX1), whereas MGUS samples exhibited higher expression of ribosomal and immune-related genes. GO and KEGG analyses revealed enrichment in muscle differentiation, calcium signaling, and cardiomyopathy-related pathways in AL, aligning with the disease's known cardiac tropism. **Conclusions:** This integrative analysis highlights the clinical heterogeneity and immunogenomic complexity of AL amyloidosis. PD-1 pathway activation and cardiac-specific transcriptomic signatures may underlie the disease's immune suppression and tissue tropism. These findings offer new insights into AL pathophysiology and support further exploration of immune-targeted therapies.

PA-372

Real-World Outcomes and Treatment Patterns in AL-Amyloidosis (AL-A) in Austria: An Analysis from the Austrian Interdiscplinary Amyloidosis Registry (AIDA)

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Introduction: Aim: To create an overview of the treatment landscape for AL-A in Austria. **Methods:** 210 AL- pts. were recruited from Austrian Interdisciplinary Amyloidosis Registry. Statistics were descriptive. **Results:** Pts. : 210 AL-A pts., 45.9% of pts. in AIDA, with (median follow up 7 years) were analysed. (others mostly wt-ATTR). 62.38%. of pts were male. AL-A pts. were younger (median age 66a vs. 78a) compared to wt-ATTR pts. Organ involvement: heart (78.6%), kidneys (58.1%), GI-tract (23.3%), PNS (21.4%). Advanced Mayo stages predominant, resulting in a high number of pts. with severe to moderate renal and/or cardiac insufficiency (4.6%, 42.2%–37.2%, 51.2%). Treatments: 141/210 pts. received a 1st line of treatment (LoT), 35.5% a 2nd LoT, and 20,6% a 3rd or higher LoT, This attrition rate per LoT is above, the one for Myeloma. Median time to next treatment was 9.9 months. 54 pts. received a 1st LoT intending later ASCT, but only 54% received it. This compares inferior to Myeloma. The most frequently used therapeutic regimes were VCd-D (Andromeda) with or without Dara-maintenance resulting in a high rate of high-quality hematologic responses (CR +VGPR = 51.9%). 90 pts. received 1st LoTs not intending later ASCT. Daratumumab based regimes were the most used, but treatment outcomes were much inferior (hematologic CR+ VGPR = 18.9%). Only 40 pts. received 2nd,LoT with modest results. Survival: Median survival was found 45 months and inferior in advanced stages. **Conclusions:** Take home-messages: 1. Efforts needed to improve early diagnosis 2. Necessity to establish disease modifying therapies 3. New therapeutics should be integrated in 1st LoTs preferentially.

PA-373

Subcutaneous Daratumumab + Bortezomib, Cyclophosphamide, and Dexamethasone in Asian Patients with Newly Diagnosed Light-Chain (AL) Amyloidosis: Subgroup Final Analysis of the Phase 3 ANDROMEDA Study

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Introduction: Systemic AL amyloidosis is a rare disorder of clonal CD38+ plasma cells, characterized by deposition of amyloid fibrils leading to tissue damage and organ dysfunction. Subcutaneous daratumumab (DARA SC) is a human CD38-targeting antibody. Combining DARA SC with VCd (bortezomib, cyclophosphamide, dexamethasone) improved outcomes for AL amyloidosis versus VCd alone in the phase 3 ANDROMEDA study. Here, we report a subgroup final analysis of Asian patients in ANDROMEDA. **Methods:** Newly diagnosed AL amyloidosis with measurable hematologic disease, ≥1 involved organ, cardiac stage (Mayo 2004) I-IIIA, eGFR ≥20 mL/min, and no symptomatic MM. Patients were randomized 1:1 to receive DARA SC plus VCd (D-VCd) or VCd. All patients received VCd six 28-day cycles with or without DARA SC. Primary endpoint was overall hematologic complete response (CHR) rate; key secondary endpoints included major organ deterioration progression-free survival (MOD-PFS), survival, and safety. **Results:** Among 388 randomized patients, 60 were Asian (D-VCd, n = 29; VCd, n = 31). Baseline characteristics were well balanced between arms and consistent with the overall population. Median follow-up in the Asian subgroup was 59.1 months, and the median treatment duration was 21.3 months for D-VCd and 5.3 months for VCd. The overall CHR rate was 69.0% for D-VCd and 16.1% for VCd (odds ratio, 11.6; 95% CI, 3.4–39.9; P < 0.0001). With longer follow-up time, higher CHR rates were still observed in the D-VCd arm compared with the VCd arm. MOD-PFS favored D-VCd-treated patients (HR 0.21;95% CI, 0.08–0.58). Median OS was not reached in either arm (HR = 0.19; 95% CI: 0.05, 0.68; p-value 0.0043). The 60-month survival rate was 89.7% for D-VCd arm and 53.2% for VCd arm. 36 participants (D-VCd: n = 15; VCd: n = 21) in Asia subgroup were evaluable for cardiac response, with 66.7% overall cardiac response in D-VCd and 19% in VCd respectively. The cardiac response rate at 6-month was 46.7% and 4.8% in D-VCd and VCd groups, which is consistent with overall population results. Median time to cardiac response (D-VCd: 3.8 months, VCd: 6.0 months) was reached earlier in the D-VCd compared with the VCd. 37 participants (D-VCd: n = 21; VCd: n = 16) in Asia subgroup were evaluable for renal response, with 85.7% overall renal response in D-VCd and 68.8% in VCd, respectively. Median time to renal response (D-VCd: 2.0 months, VCd: 2.8 months) was reached earlier in the D-VCd compared with the VCd. The safety profile of D-VCd observed was generally consistent with the primary analysis. Asia subgroup showed a generally consistent safety profile with the overall population. **Conclusions:** The addition of DARA SC to VCd was superior to VCd alone in Asian patients, resulting in deeper hematologic response, organ response and improved clinical outcomes, including MOD-PFS and OS, with a safety profile consistent with the overall study population. These data support the use of D-VCd in Asian patients with newly diagnosed AL amyloidosis.

PA-374

MGUS Prevalence from a Large-Scale Community Study from Rural India (IMAGe-002B Study)

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Introduction: Considerable variation has been observed in the prevalence of monoclonal gammopathies across the globe. Although the prevalence of monoclonal gammopathy of undetermined significance (MGUS) has been evaluated in two hospital-based studies in India, no data exists on its prevalence in community-based settings amongst the rural Indian population. We aimed to determine the prevalence of MGUS in a rural Indian population in a community-based setting. **Methods:** A cross-sectional study was conducted across 92 villages spreading over 2976 square miles (sq-mi), as part of SIMPLe (Screening Intervention for Myeloma and Prevention of Lifestyle diseases) study. For the complete study population, demographic details, medical history, and blood samples were collected after a thorough medical examination. SPEP was performed in all individuals using on-site capillary zone electrophoresis. SIFE and biochemistry (liver and renal function tests) were performed for those with abnormal SPEP graphs (those with M spike and those with abnormal bulges in alpha, beta-2 or gamma region suspicious of M Spikes). Patients with monoclonal protein on SPEP or SIFE were further assessed for any smoldering/ multiple myeloma features as per IMWG guidelines. Amongst those patients with doubtful reports or isolated light chain disease, they were further subjected to mass spectrometry for evaluation. The data was analyzed using JMP ver. 17.2.0. **Results:** A total of 18,716 individuals were screened and data was analyzed for 16283 (8527 Tribal + 7756 non-tribal) individuals. The prevalence of MGUS in the study population was 111 (0.68%) across age group (12–99y) and was 1.04% above the age of 45y (109 of 10447). Only two patients among our study were younger than 45 (14y and 36y respectively) and neither of them had family history of plasma cell dyscrasia or positivity on family screening. The prevalence was 1.8% above 55y (109 of 6034), and 2.43% above 65y (84 of 3447). The median age of individuals with MGUS was 65y (IQR 57–72) with male preponderance. None of the patients with M protein in this community study satisfied the criteria for SMM/ MM using IMWG criteria. Among those with MGUS, the distribution of heavy and light chains was IgG - 83.78% (n-93), IgA - 16.22% (n-18), with none having IgM paraprotein, Lambda – 69.36% (n-77) and Kappa – 30.63% (n-34). Seven individuals who were initially labeled as light chain MGUS had IgG disease detected on mass spectrometry. Follow up of the 62 patients with MGUS at one year after diagnosis revealed none of the patients had progression to SMM or MM at one year. **Conclusions:** The prevalence of MGUS in the India is low at 1.04% above the age of 45y rising to 2.43% in individuals over 65 years, predominantly affecting older males, with IgG lambda MGUS being the most common type. The background prevalence appears to be lower compared to the Western (both USA ~3% and European ~5%) population.

PA-375

Real-World Outcomes of SLiM-Only Multiple Myeloma: Korean Multicenter Retrospective Analysis

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Introduction: In 2014, the IMWG included SLiM biomarkers (BMPC ≥ 60%, FLC ratio ≥ 100, > 1 focal MRI ≥ 5 mm) into the "myeloma defining events" because they are significantly associated with early progression to active multiple myeloma. However, several subsequent reports demonstrated that patients who met only SLiM biomarkers (SLiM-only MM) showed favorable outcomes compared to the previous reports. Moreover, there have been no subsequent report dealing with patients with > 1 focal MRI lesions. To further elucidate their clinical impact, we carried out a nationwide retrospective analysis. **Methods:** Patients who were diagnosed with MM based on only SLiM biomarkers were included in the analysis. Patients with CRAB features, extramedullary plasmacytoma, solitary plasmacytoma, AL amyloidosis, or plasma cell leukemia were excluded. Baseline characteristics, treatment, and outcomes were retrospectively collected. High-risk cytogenetics were defined by the presence of t(4;14), t(14;16), del(17p), and +1q. **Results:** From 2011 to 2023, 72 cases were collected from 7 tertiary institutes in Korea. The median age was 65 (range, 36–89), and 40 (56%) were male. In terms of the SLiM criteria, 27 patients had BMPC ≥ 60%, 29 patients had FLC ratio ≥ 100, and 34 patients had > 1 focal lesion. Twelve (17%) and seven (10%) patients were ISS-III and R-ISS-III, respectively. Nineteen patients (26%) had at least one high-risk cytogenetics. Thirty-five patients (49%) patients were managed with active surveillance (group 1), while the other thirty-seven patients (51%) received immediate treatment (group 2). In group 1, the median time to progress to CRAB-MM (TTP) was 75.8 months. Patients with > 1 focal MRI lesions only showed significantly prolonged TTP compared to those with BMPC ≥ 60% or FLC ratio ≥ 100 ($p = 0.035$). With 10 patients (29%) progressed to CRAB-MM, their median TTP was 22.6 months (95% CI, 14.4–30.8). Younger patients (≤ 65) were associated with progression to CRAB-

MM (p = 0.046), but other prognostic factors including stage, cytogenetics were not associated with TTP, probably due to small number of patients. In group 2, responses by the first-line treatment were as follows: CR 60%, VGPR 8%, PR 22%. PFS by the first-line treatment was 56.8 months (95% CI, 21.2–92.4). **Conclusions:** In the current study, patients diagnosed with SLiM-only MM exhibited an extended TTP without treatment compared to prior studies, particularly those with only focal MRI lesions. In addition, the first-line treatment resulted in favorable outcomes, which may support the benefit of earlier initiation of treatment for SLiM-only MM.

PA-376

Minimal Residual Disease in Newly Diagnosed Multiple Myeloma Patients not Planned for upfront Autologous Stem Cell transplant: Patient Disposition and MRD Outcomes from a Prospective Clinical Trial

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Introduction: Measurable residual disease (MRD) has the potential to guide treatment and promote judicious use of resources in LMICs. However, data on its feasibility and utility in resource-constrained settings remain limited and warrant further study. Here we report patient disposition, MRD results & characteristics associated with MRD from a prospective study evaluating MRD guided therapy. **Methods:** Newly diagnosed MM patients not intended for ASCT receiving VRd undergo flow-MRD assessment if they achieve at least VGPR post 8 cycles. MRD positive patients are randomised to standard maintenance therapy versus MRD guided consolidation with VRd/KPd till acheivement of MRD negativity for a maximum of additional 12 cycles. **Results:** A total of 279 patients were registered in this clinical trial between July 2022 and June 2024. Of these, 127 (45%) did not undergo MRD evaluation due to the following reasons: : Failure to achieve at least VGPR 50 (17%), deemed unfit for triplet 32 (11%), early mortality 21 (7%), primary refractory disease 12 (4.3%), not keen on for bone marrow 7 (2.5%) and BM MRD not technically feasible in 5 (1.7%). MRD evaluation was performed in 152 patients after completion of eight cycles. The median age was 55 years (range: 32–79), and 109 (72%) were male. Baseline characteristics include, anemia-86 (56.6%), hypercalcemia 47 (30.9%), lytic bone lesions in 142 (93.4%) and creatinine greater than 2 in 24 (15.8%) patients. The ISS and R-ISS stage distribution is as follows: ISS-I 36(23.7%), ISS-II 44(28.9%) and ISS-III 72 (47.4%) and R- ISS-I 19(12.5%), R-ISS-II 80(52.6%) and R-ISS-III 41(27%). Baseline cytogenetic were: Hyperdiploidy in 73 (48%), t (4:14)- 12 (7.9%), t(14:16)- 7 (4.6%), t(11:14)- 7 (4.6%), del17p in 3 (2%), 1q gain/amp in 44 (29%) and del1p on 3 (2%) patients. IMWG responses at the end of eight cycles shows CR in 96 (64%) and VGPR in 54 (36%). MRD negativity at a threshold of 10^{-5} was achieved in 60 (38.8%) patients, while 92 (60.5%) remained MRD positive. Among these groups, MRD positivity was significantly higher among patients in VGPR compared to those in CR (52% vs 10%, p < 0.001). However, other baseline characteristics, including ISS stage and cytogenetics, were not statistically different. At a median follow-up of 21.8 months, the median PFS and OS of the cohort have not yet been reached. Of the 22 progression events, 17 (18.5%) occurred in the MRD-positive cohort and 5 (8.5%) in the MRD-negative cohort (p = 0.041). A total of 6 deaths occurred (all due to disease progression): 4 in the MRD-positive and 2 in the MRD-negative cohort (p = NS). **Conclusions:** MRD assessment is feasible and prognostically relevant in our setting. MRD negativity was less frequent among patients achieving VGPR, while other baseline prognostic markers showed no significant association with MRD status. A substantial proportion of patients did not undergo MRD testing after eight cycles due to suboptimal response, highlighting the need for more effective frontline therapies.

PA-377

Efficacy and Safety of Daratumumab, Lenalidomide, and Dexamethasone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma Patients: A Single-Center Real-World Study in China

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Introduction: To investigate the efficacy and safety of daratumumab combined with lenalidomide and dexamethasone (DRd regimen) in the treatment of transplant-ineligible newly diagnosed multiple myeloma (TIE-NDMM). **Methods:** A total of 70 patients with TIE-NDMM treated with the DRd regimen were consecutively enrolled from March 2022 to April 2025 at Beijing Jishuitan Hospital, Capital Medical University. Clinical data, primarily including gender, age, frailty score, chromosomal karyotype, efficacy, and adverse reactions, were retrospectively collected and analyzed. Survival analysis was performed using the Kaplan-Meier method and Cox regression model. **Results:** A total of 66 patients were enrolled, with a median age of 72 (62–86) years. The overall response rate (ORR) was 92.4% (61/66), and the ≥ very good partial response (≥VGPR) rate was 72.7% (48/66) across all patients. Among 52 evaluable patients, the 6-month minimal residual disease (MRD)-

negative rate was 34.6% (18/52). With a median follow-up of 10.1 months, 6 patients (9.1%) died, including 1 patient (1.5%) who experienced early death within 60 days due to acute myocardial infarction. Central nervous system relapse occurred in 2 patients (3.0%). The median progression-free survival (PFS) and median overall survival (OS) were not reached. Safety was assessed in all patients. The most common grade 3–4 hematological adverse events (AEs) were neutropenia (33.3%) and lymphopenia (22.7%). The primary grade 3–4 non-hematological AE was pulmonary infection (39.3%). Three patients (3.0%) developed grade 3 peripheral neuropathy, and 1 patient (1.5%) experienced ventricular septal hypertrophy during treatment. **Conclusions:** The DRd regimen demonstrates favorable efficacy and safety in treating patients with TIE-NDMM. Attention should be paid to the issues of infection and central nervous system relapse.

PA-378

Steady-State Hematopoietic Cell Mobilization for Newly Diagnosed Multiple Myeloma Patients Receiving Daratumumab-Based Induction Therapy Versus IMiD-Based Induction Therapy: A Real- World Experience

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Introduction: Daratumumab-based induction therapy have recently become the standard of. care for patients with newly diagnosed multiple myeloma who are candidates for autologous stem cell transplantation. Previous reports have shown that daratumumab might impair stem cell mobilization and collection, leading to an increased requirement for plerixafor use and impaired stem cell engraftment. In the context of Daratumumab, protocols for mobilization vary significantly. Therefore, we conducted a single-center retrospective analysis in order to evaluate steady-state stem cell mobilization and harvest in patients receiving daratumumab-based induction therapy versus IMiD-based induction therapy. **Methods:** From Jan 2023 till May 2025, we retrospectively reviewed patients receiving daratumumab-based induction therapy and IMiD-based induction therapy followed by stem cell mobilization in a steady-state protocol using 10 µg/kg granulocyte colony-stimulating factor (G-CSF) for 5 days. **Results:** Overall,110 patients (daratumumab-based 16 patients, IMiD-based 94 patients) were included in the analysis. Patient characteristics were well balanced between groups. There was no significant difference in median days of apheresis to reach the patient-specific CD34+ goal and mean cumulative CD34+ cell collection. Plerixafor was used in 68.7% (daratumumab-based) and 39.3% (IMiD-based) cases ($p = 0.008$). **Conclusions:** Steady-state hematopoietic cell mobilization in patients undergoing daratumumab-based induction therapy is feasible, although patients with daratumumab-based induction therapy more frequently requires plerixafor.

PA-379

Health-Related Quality of life (HRQoL) in Frail Patients with Newly Diagnosed Multiple Myeloma (NDMM) Treated with Isatuximab (Isa), Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) vs VRd Alone

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Introduction: NDMM patients (pts) who meet frailty criteria have worse outcomes vs non-frail pts. A post hoc analysis of the phase 3 IMROZ study (NCT03319667) demonstrated Isa-VRd significantly improved progression-free survival and achieved deep responses vs VRd in both frail and non-frail pts. This study investigated HRQoL in a subgroup of frail pts in IMROZ. **Methods:** We analyzed patient-reported outcomes (PRO) in a subgroup of frail pts (frailty score ≥2 based on age, ECOG performance status, and comorbidities) as defined by the simplified International Myeloma Working Group (sIMWG). PRO instruments, including European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire with 30 questions (EORTC QLQ-C30); EORTC QLQ myeloma module with 20 items (EORTC QLQ-MY20); and European Quality of Life Group 5-dimension, 5-Level Questionnaire (EQ 5D 5L), were administered at baseline (BL), prior to treatment on Day 1 of every cycle, at the end of treatment, and 90 ± 5 days after last study treatment. Meaningful thresholds for within- and between-group improvement/worsening were defined a priori based on published literature (≥10- and ≥5-point change, respectively). Treatment effect was assessed by a mixed-effects model for repeated measures. Time to first deterioration was estimated using the Kaplan Meier method and Cox proportional hazards regression was used to compute hazard ratio and associated 95% confidence interval (CI). **Results:** Overall, 119/446 (26.7%) pts were classified as frail (69 [26.0%] Isa-VRd; 50 [27.6%] VRd). Median follow-up was 59.7 mo overall. In frail pts, Isa-VRd was associated with larger improvements vs VRd in GHS/QoL, pain, fatigue, and physical functioning, with a difference in LS mean change from BL (standard error) [95% CI; p-value] of 3.50 (3.24) [–2.92, 9.91; 0.2825]; –1.90 (4.60) [–11.00, 7.20; 0.6802]; –6.44 (3.90) [–14.16, 1.29; 0.1018]; and 10.67

(4.56) [1.65, 19.69; 0.0209], respectively. Frail pts receiving Isa-VRd showed notable reductions overall in pain (–17.92-point change), >20 points at multiple cycles, and fatigue (–8.48). Similar improvements in appetite loss and disease symptoms were observed in both treatment arms. Change from BL numerically favored Isa-VRd in other scales (role functioning, side effects), except for dyspnea. In frail pts, Isa-VRd vs VRd was associated with statistically longer median time to first clinically meaningful deterioration in physical functioning (6.93 vs 3.12 mo, p = 0.0034), pain (6.93 vs 2.92 mo, p = 0.0060) and role functioning (6.11 vs 2.60 mo, p = 0.0032). **Conclusions:** Isa-VRd was associated with more durable improvements in HRQoL vs VRd in all pts with NDMM, including frail pts. Frail pts on Isa-VRd showed sustained improvements in GHS/QoL and physical function, with significant reductions in pain and fatigue throughout treatment. These findings provide further evidence that Isa-VRd is an effective option with a manageable safety profile for frail pts with NDMM.

PA-380

Isa-VRd Improves Outcomes in High-Risk Newly Diagnosed Transplant-Ineligible Multiple Myeloma Using the IMS/IMWG Consensus HR Definition: Results from the BENEFIT Phase 3 Trial (IFM 2020–05)

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Introduction: Isa-VRd has become a new standard of care (SOC) in NDMM TI based on BENEFIT and IMROZ studies. The IMS has recently standardized the HR definition. We investigated the Isa-VRd regimen in HR patients in the BENEFIT study. **Methods:** The BENEFIT study randomized 270 non-frail TI patients with NDMM in a 1:1 ratio to receive either Isa-VRd or IsaRd. HR status was defined based on the IMS/IMWG consensus. Sustained MRD negativity was defined as 3 consecutive MRD negative assessments (< 10-5 by NGS) at 12, 18 and 24 months. Data are presented in an ITT analysis with missing MRD values considered positive. **Results:** At a median follow-up of 33.4 months, 37 (27%) and 50 (37%) patients across the Isa-VRd and IsaRd arms, respectively, had ended therapy, mostly for disease progression. Using the IMS/IMWG consensus definition, the HR status was identified in 42 (31%) patients in Isa-VRd and 30 (22%) patients in Isa-Rd. Overall, 49/247 (18%) patients from the favorable/intermediate IFM LP score category were reclassified as HR with the new IMS criteria. Among HR patients, the 18-months MRD negativity rate at 10-5 was higher for Isa-VRd than Isa-Rd, 50% (n = 21) vs 27% (n = 8) [odds ratio (OR) for MRD negativity 2.75 (95%CI, 1 to 7.5)]. Similar data were observed using 10-6 negativity threshold, with 19 patients (45%) in the Isa-VRd arm vs 8 (27%) in the Isa-Rd arm [OR 2.27 (95%CI, 0,8 to 6.25)]. Higher MRD negativity rates in the Isa-VRd arm were also observed at 12 and at 24 months at both 10-5 and 10-6 thresholds. Sustained MRD negativity rates were 34% [n = 46, 95%CI, 26 to 43] for the Isa-VRD group and 16% [n = 22, 95%CI, 11 to 24] for the Isa-Rd group, (OR = 2.73 (95%CI, 1.52 to 4.88, p = 0.0007), for the whole cohort. In HR patients, sustained MRD negativity rates were 31% [n = 13, 95%CI, 18 to 47] in the Isa-VRD group and 13% [n = 4, 95%CI, 4 to 31] in the Isa-Rd group (OR = 2.91, 95%CI: 0.84 to 10.6, p = 0.091). Survival data remain immature. In HR patients, the safety profile was no different between both arms. **Conclusions:** The results from the BENEFIT study demonstrated meaningful advantage of the quadruplet-based Isa-VRd regimen compared to IsaRd in HR NDMM HR patients, as reflected in improved MRD negativity rates, including sustained MRD negativity. These data continue to support Isa-VRd as the new SOC for NDMM TI patients aged 65 to 79, replacing the current triplet-based SOC.

PA-381

Severe Infections in Newly Diagnosed Multiple Mieloma Patients Treated Frontline with Bortezomib, Lenalidomide and Dexamethasone (VRD) in Four Reference Centers

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Introduction: Monoclonal gammapathies and multiple mieloma (MM) specifically, are associated with immunosupression and an increased risk of infections. Serious infections are a major cause of morbidity and mortality and are particularly frequent during induction therapy. The identification of clinical and biological risk factors associated with infection is essential to develop preventive and supportive strategies. The aim of this study is to describe the incidence and characteristics of infections and associated risk factors in patients initiating frontline treatment with VRD. **Methods:** Among 360 patients with newly diagnosed MM and treated with VRD into a prospective clinical trial (EudraCT 2019-0026), 279 (77%) were included in four centers with fully available clinical records for retrospective evaluation. Data collection included baseline characteristics of patients and MM. Data on infectious events included focus, implicated agent, severity and timing of infection as well as an exploratory analysis of associated risk factors. **Results:** Among 279 patients, 156 were male (56%), with a mediana age of 63 years (range 32–88), 63 (23%) were over 70 years-old and 183 (66%) received an autologous stem cell transplantation (SCT) as part of initial therapy. A total of 201 (72%) experienced at least a grade 3–5 infection, 154 (55%) presented 1 or 2, infections per patient ranged up to 8. No significant differences were observed in the infection rate according to immunoglobulin type, renal function, dialysis, or presence of extramedullary disease. A total of 308 grade 3–5 infections were identified, respiratory origin was the most common (n = 177), followed by abdominal (n = 64), urinary (n = 40), and septicèmia of undetermined origin (n = 58). Among respiratory infections, 49 were related to Sars-Cov2 (28%), 40 to other viruses (23%) and 30 to encapsulated grampositive bacteria (17%). There were 21 infection-related deaths (7%), mostly within the first three months of induction therapy (13/21), 8 of them with a respiratory origin and 3 due to Sars-Cov2. Patients undergoing ASCT had a higher infection burden (mean 1.9 vs 1.1 infections; $p < 0.01$), although in these patients infections post-SCT were more frequent than episodis in the first months of therapy. There was 1 episode of death due to pneumonia post-SCT among 183 patients submitted to the procedure while 10/13 of mortal infections occuring during the first three months of treatment were in patients > 70 years (77%). **Conclusions:** This study comprehensively analyzes severe infections in MM patients receiving their first line of therapy. First three months of therapy are those at a higher risk of severe infections including infection-related deaths and argue in favor of individualized prophylactic and proactive therapeutic approaches, particularly in vulnerable subgroups identified by age, treatment intensity, or disease biology.

PA-382

Frailty and Social Deprivation Affect Real-World Outcomes in Multiple Myeloma (MM) – an England-Wide Cohort Study from the UNCOVER Study Group and UKMRA Frailty Group

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Introduction: UNCOVER is a blood cancer health data research programme that utilises the National Cancer Registration Dataset (NCRD). NCRD includes information on all patients diagnosed with all types of cancer in all NHS institutions in England (Int J Epidemiol 2020; 49(1):16– 16 h). **Methods:** Data was selected for patients diagnosed with MM (ICD-O-3: 97323, 97343, 97313) between Jan 2014 and Dec 2021 with follow-up until July 2023. Crude and age-standardised incidence rates (IR) were calculated and incidence rate ratios (IRR) estimated using Poisson regression. Overall survival (OS) and net survival (NS) were assessed using Kaplan Meier and Pohar-Perme methods. Multivariable (MV) Cox regression and Fine-Gray models were fitted to estimate all-cause and competing risks mortality. The Poisson model was adjusted for age at diagnosis, gender, ethnicity, index of multiple deprivation (IMD) quintile and region. Cox and Fine-Gray models were additionally adjusted for Charlson co-morbidity index (CCI). International Myeloma Working Group Modified (IMWG) frailty scores (0–1 vs 2–5) could be assigned to patients who received systemic anti-cancer treatment (SACT). Within this subpopulation, OS and NS was estimated for frail and non-frail groups and a multivariable Cox model fitted that included frailty status. **Results:** 39,521 MM patients were identified in total. Crude and age-standardised IR were higher for older people, males and black people. Crude but not age-standardised IR were lower for more deprived areas. Adjusted IRRs increased with age and were lower for females [0.62 ($p < 0.001$)], less deprived areas [0.95 ($p = 0.006$) for IMD5 vs 1), and all provincial regions vs London [e.g. 0.63 ($p < 0.001$) for North West]. Median follow-up was 33.7 (IQR: 14.3–58.7) months. 21,987 (55.6%) patients died with median OS 49.5 (48.5–50.5) months and NS 58.7% and 45.3% at 3 and 5 years. Hazard of all-cause mortality was higher for males [1.06 (1.03–1.08)] and increased with age [10.2 (8.1–12.1) for 81–99 compared to < 40], deprivation [1.29 (1.22–1.34) for IMD1 vs 5], comorbidity [1.46 (1.41–1.50) for CCI >1 vs ≤1], and provincial regions vs London [1.21 (1.15–1.28) for North West]. Among the 23,674 (60%) patients with an IMWG frailty score, 9,487 (40%) were classed as frail and 14,187 (60%) non-frail. Frail patients had a shorter

OS (median 31 vs 78 months, p < 0.001) and NS (58.1% vs 73.1% at 3 years; 26.0% vs 44.5% at 5 years). This extended to high-risk subgroups defined by deprivation or region (5-year NS: 23.9% vs 51.6% for IMD1; 22.6% vs 55.9% for North East). Frailty was independently associated with all-cause mortality (HR 1.75, p < 0.001). **Conclusions:** Deprivation is associated with a higher probability of MM diagnosis and shorter survival once diagnosed in MV analysis. Living in the capital is associated with a higher probability of MM diagnosis but longer survival once diagnosed. Frailty adds to the effect of deprivation and region and is associated with shorter survival.

PA-383

HSPA9 Contributes to Tumor Progression and Ferroptosis Resistance by Enhancing Usp14-Driven xCT Deubiquitination in Multiple Myeloma

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Introduction: Multiple myeloma (MM), the second most common hematological malignancy, is characterized by clonal plasma cell expansion in the bone marrow and monoclonal immunoglobulin secretion. Despite recent advances in the treatment of MM, the therapeutic efficacy of patients remains unsatisfactory, and the majority of patients experience disease progression after initial treatment. Therefore, investigating novel and effective therapeutic strategy is imperative. HSPA9 regulates proliferation, cell cycle, and migration in multiple cancers, but its role in MM is unclear. **Methods:** HSPA9 expression and its prognostic value in MM were analyzed by public databases and IHC. Proteomic sequencing revealed HSPA9 regulated pathways in MM. The functional role of HSPA9 were assessed via CCK-8, soft agar clonogenic assay, TME and xenograft models. Mass spectrometry (MS) was performed to identify the molecular mechanism by which HSPA9 regulates cell malignant proliferation in MM. Rescue experiments elucidated the core regulatory role of HSPA9 and its target protein in MM. **Results:** HSPA9 is highly expressed in MM and augmented level of HSPA9 correlates with poor prognosis. Proteomic analysis suggested HSPA9 is involved in the regulation of ferroptosis in MM. The CCK-8, Fe2+, MDA, TEM assays and xenograft model revealed HSPA9 promotes the malignant survival and impedes ferroptosis of MM cells. MS analysis deciphered xCT (core protein of ferroptosis) as the potential HSPA9-interacting protein. Co-IP identified the C-terminal of HSPA9 directly interacts and maintains xCT stability by diminishing K48-linked polyubiquitination. MS and siUSP screen suggested USP14 as major HSPA9-associated protein. WB detected USP14, but not the active site mutant, deubiquitinates and stabilizes the xCT. CCK-8, trypan blue staining, ferroptosis related assays and xenograft models showed that USP14 promotes cell proliferation by inhibiting ferroptosis in vitro and in vivo. Co-IP, ubiquitination and CHX analysis suggested HSPA9 acts as a scaffold to enhance the interaction between USP14 and xCT, subsequently facilitates the USP14-mediated deubiquitination and stability of xCT. USP14 inhibitor hinders the tumor initiating ability. Rescue experiments revealed HSPA9 modulates cell survival and ferroptosis is USP14-dependent xCT modulation. **Conclusions:** Here, we identified that HSPA9 is significantly overexpressed in MM and correlated with worse outcomes of patients. HSPA9 as a key factor that promoted tumor cell survival by inhibiting cellular ferroptosis. Additionally, we confirmed HSPA9 functions as a scaffold platform for USP14 and xCT interaction, preventing the proteasome-degradation of xCT and further promoting MM progression and ferroptosis resistance. Given that the effects of genetic or pharmacological inhibition of USP14 exerted on xCT ubiquitination and degradation, we conducted further experiments to identify the anti-tumor effects of USP14-specific inhibitor.

PA-384

Impact of CD34+ Cell Infusion Dose on Immune reconstitution and Survival in Multiple Myeloma after Autologous Stem Cell Transplantation

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Introduction: Autologous stem cell transplantation (ASCT) remains a cornerstone therapy for multiple myeloma (MM). However, the optimal CD34+ cell infusion dose and its relationship with immune reconstitution and survival are unclear. Oligoclonal bands (OB), indicating B-cell recovery, may serve as markers of effective immune reconstitution. This study aimed to evaluate the prognostic impact of CD34+ cell infusion dose and to explore its association with OB formation, in order to inform transplant optimization. **Methods:** A total of 176 MM patients who underwent early ASCT were retrospectively analyzed and stratified by CD34+ cell dose ($< 5 \times 10^6$/kg vs. $\geq 5 \times 10^6$/kg). Clinical characteristics, treatment responses, survival outcomes, and OB formation were compared. Prognostic factors were identified via Cox regression, and a nomogram was constructed to predict overall survival (OS). **Results:** Patients receiving a CD34+ cell infusion $\geq 5 \times 10^6$/kg demonstrated significantly improved progression-free survival (PFS: 50 vs. 40 months, p = 0.020) and OS (not reached vs. 76 months, p < 0.001) compared to those receiving $< 5 \times 10^6$/kg. This high-dose group also showed deeper remission (p = 0.034), lower early relapse rates (9.1% vs. 24.2%, p = 0.006), and more durable minimal residual disease (MRD) negativity (≥2 years: 70.5% vs. 51.5%, p = 0.003). Immune reconstitution analysis revealed significant increases in total T cells,

CD8+ T cells, and B cells post-ASCT ($p < 0.001$), alongside a modest reduction in CD4+ T cells ($p = 0.002$) and no significant change in NK cells ($p = 0.248$). OB was detected in 38.6% of patients and was significantly associated with high CD34+ dose (44.5% vs. 28.8%, $p = 0.038$). OB-formation patients exhibited longer PFS (66 vs. 37 months, $p < 0.001$) and OS (not reached vs. 91 months, $p = 0.009$). Combined analysis revealed that CD34+ $\geq 5 \times 10^6$/kg with OB formation conferred the greatest OS benefit ($p < 0.001$), though no marked PFS benefit. CD34+ $\geq 5 \times 10^6$/kg, MRD negativity, and OB formation were independent protective factors. A nomogram incorporating these variables demonstrated strong predictive accuracy (C-index: 0.768; AUC: 0.864, 0.880, 0.749 for 1-, 3-, 5-year OS), supporting its clinical utility. **Conclusions:** This study identifies CD34+ $\geq 5 \times 10^6$/kg infusion as a potential optimal threshold that enhances immune reconstitution and promotes OB formation, thereby improving deep remission and long-term survival after ASCT.

PA-385

Prognostic Value of 1p Deletion in Newly Diagnosed Multiple Myeloma Patients: A Nationwide Multicenter Cohort Study by the Korean Multiple Myeloma Working Party (KMM2306)

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Introduction: The Revised Second International Staging System (R2-ISS) was developed to improve risk stratification in patients with newly diagnosed multiple myeloma (MM) beyond the existing R-ISS. It incorporates three cytogenetic abnormalities: del(17p), t(4;14), and 1q gain/amplification. While 1p deletion (del(1p)) has been associated with poor outcomes in MM, it was not evaluated during the development of R2-ISS. This study aims to evaluate the prognostic value of del(1p) in patients with newly diagnosed MM treated with immunomodulatory agents (IMiDs) or proteasome inhibitors (PIs) as primary therapy, and to explore whether incorporating del(1p) into the R2-ISS improves prognostication. **Methods:** We retrospectively analyzed data from 822 patients with newly diagnosed MM between September 2014 and December 2019 who received either IMiDs or PIs as initial therapy. Patients with complete data ISS, LDH, del(17p), t(4;14), 1q gain/amplification, and del(1p) were included. The primary endpoint was overall survival (OS), which was defined as the time from date of diagnosis to the date of death from any cause or last follow-up. The prognostic value of adding del(1p) to R2-ISS in terms of OS was evaluated using the Harrell's concordance index (C-index). **Results:** The median age was 64 years (range, 29–89), and 477 were male (58.0%). According to the R2-ISS classification: 77 (9.4%) were stage I, 196 (23.8%) stage II, 411 (50.0%) stage III, and 138 (16.8%) stage IV. Del(1p) was detected in 93 patients (11.3%). With a median follow-up of 66.6 months (95% CI: 61.2–71.8), median progression-free survival (PFS) and overall survival (OS) were 29.3 months (95%CI: 27.1–31.4) and 59.1 months (95%CI 59.1–76.8), respectively. Patients with del(1p) had significantly worse PFS and OS compared with those without del (1p), with a median PFS of 25.3 vs. 30.0 months ($P = 0.035$) and a median OS of 42.5 vs. 69.1 months ($P = 0.002$). In multivariate analysis adjusted for R2-ISS, age, sex, and Eastern Cooperative Oncology Group Performance Status, del(1p) remained an independent prognostic factor for OS (HR: 1.58, 95% CI: 1.17–2.12, $P = 0.003$), while the association with PFS showed a non-significant trend toward worse outcome (HR: 1.23, 95% CI: 0.96–1.57, $P = 0.110$). The C-index for OS with R2-ISS alone was 0.613 (95% CI: 0.587–0.638), which improved to 0.620 (95% CI: 0.592–0.646) with the addition of del(1p), though not statistically significant ($P = 0.445$). **Conclusions:** Our study demonstrated that del(1p) is an independent adverse prognostic factor for OS in newly diagnosed MM patients. While incorporating del(1p) to the R2-ISS yielded a modest, non-significant improvement in predictive accuracy, its prognostic relevance supports consideration for inclusion in future MM risk stratification models.

PA-386

Daratumumab, Bortezomib, Thalidomide and Dexamethasone Followed by Lenalidomide Maintenance in Transplant-Eligible Multiple Myeloma Patients: Overall Survival Comparison with the CASSIOPEIA Trial

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Introduction: The Dara-VTd protocol was the first daratumumab-based combination approved in our setting for transplant-eligible newly diagnosed multiple myeloma (NDMM) patients, based on the CASSIOPEIA trial. Despite its approval, the maintenance phase of the original study was not covered by official guidelines, leaving lenalidomida (Lena) as the sole maintenance option for some time. This study presents real-world data (RWD) from the Brazilian Multiple Myeloma Study Group (GBRAM) database, evaluating a novel therapeutic sequence: Dara-VTd induction followed by autologous stem cell transplantation (ASCT), Dara-VTd consolidation, and Lena maintenance. Additionally, we compared the overall survival (OS) outcomes of the GBRAM approach with those reported in the CASSIOPEIA protocol. **Methods:** Analyses from prospectively enrolled NDMM patients (diagnosed post-Jan/2018) and receiving Dara-VTd, followed by ASCT and Dara-VTd consolidation and Lena maintenance (GBRAM RWD cohort). Individual patient data from CASSIOPEIA were reconstructed from published Kaplan-Meier curves using the IPD from KM method and comparative analyses with RWD were conducted using R software (v4.4.1). **Results:** A total of 150 cases from 19 Brazilian centers received Dara-VTd as intent-to-treat. Median follow-up was 37 months (range 9–74). We analyzed 106 patients who completed the full protocol and maintenance follow-up. Median age at diagnosis was 58 years (37–73), with 59 (55.7%) male patients. Racial distribution showed 62 (58.5%) white patients and 44 (41.5%) non-white (mixed-race and black). ECOG performance status was 0–2 in 93 (87.7%) patients, (11.4% unavailable). The most common monoclonal isotype was IgG (49.1%), followed by IgA (25.5%) and light chain (12.2%). ISS staging distribution: I (38.7%), II (25.5%), and III (23.6%). R-ISS was unevaluable in 70 cases (66%); among evaluable cases, R-ISS 2 predominated (15.1%). CRAB features showed bone lesions in 90 patients (84.9%). OS comparison between Dara-VTd followed by lenalidomide (GBRAM cohort) versus Dara maintenance (CASSIOPEIA protocol) showed HR 0.57 (0.21–1.51) P = 0.2. Six deaths occurred, including four from disease progression. **Conclusions:** This study analyzes real-world data from multiple myeloma (MM) patients treated with the Dara-VTd regimen followed by lenalidomide maintenance after autologous stem cell transplantation (ASCT). After a median follow-up of 37 months, a comparative analysis of overall survival (OS) between the Dara-VTd + lenalidomide maintenance approach and the original daratumumab-based regimen from the CASSIOPEIA trial showed no significant difference. However, longer follow-up is required to confirm these findings.

PA-387

Importance of Re-Induction in Patients with Transplant Eligible Multiple Myeloma Refractory to Frontline Therapy

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Introduction: Approximately 10% of transplant eligible multiple myeloma (MM) patients are refractory to induction therapy. The role and outcomes of re-induction therapy for such patients remain unclear. Strategies range from proceeding directly to autologous stem cell transplant (ASCT), or to pursuing a second induction to improve disease control prior to ASCT. We aim to describe the management and outcomes of primary refractory patients in British Columbia, which will serve as a benchmark for further strategies to optimize outcomes in this high-risk group. **Methods:** Patients initiating treatment between January 1, 2015 and September 1, 2022, were included. We identified patients who failed to achieve at least a partial response (PR) or progressed during induction therapy. Survival endpoints were progression free survival (PFS) and overall survival (OS), which were measured both from the time of initial therapy and from ASCT to account for lead time bias introduced with re-induction therapy. We compared outcomes between patients who received re-induction prior to ASCT to patients who did not receive re-induction. **Results:** 422 transplant patients were identified. The cohort for analysis consisted of 39 primary refractory patients (9%). 36% failed to achieve PR and 64% progressed during initial induction. 33% of the patients had high-risk cytogenetics. Cyclophosphamide, bortezomib and dexamethasone (CyBorD) was the frontline induction regimen used in 97%. 64% of patients received re-induction prior to ASCT. Regimens included bortezomib, lenalidomide and cyclophosphamide (VRd) in 60%, and daratumumab, lenalidomide, and dexamethasone in 24%. Of those who received re-induction therapy, the overall response rate was 68% prior to ASCT. The median PFS from initial therapy was 30.2 months. The median PFS from ASCT was 24.5 months. Comparing patients who received re-induction vs those who did not, the median PFS was 38.4 vs 8.5 months respectively (p = 0.001). This was similar when PFS was measured from ASCT (29.4 months vs 3.3 months respectively, p = 0.001). The median OS was 42.8 months. The median OS from ASCT was 38.0 months. Comparing patients who received re-induction vs those who did not, the median OS was 57.3 months vs 17.4 months, p = 0.004. A similar trend was seen when OS was

measured from time of ASCT (51.1 months vs 12.4 months, p = 0.009). **Conclusions:** Our findings confirm the poor survival outcomes in primary refractory MM. Re-induction improved PFS and OS regardless of whether measured at the time of induction or from time of ASCT. This is likely related to improved disease control pre-ASCT. Overall, re-induction strategies should be employed when these high-risk situations are encountered prior to ASCT. While the series is enriched with patients transitioning from CyBorD to VRd, further updates to the dataset will be needed to examine re-induction strategies with more contemporary frontline strategies like VRd and anti-CD3b monoclonal antibody containing regimens.

PA-388

Predicting Multiple Myeloma Mortality Using Long Short-Term Memory Networks (LSTM)

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Introduction: Multiple Myeloma (MM) causes significant morbidity due to complications such as anemia, renal failure, bone lesions, and an increased risk of infections. These clinical manifestations affect patients' quality of life and negatively impact survival. Predicting mortality risk in MM patients remains challenging due to the complex interplay of disease and treatment-related factors that evolve over time. Some studies have shown the utility of using Machine Learning (ML) models in predicting the incidence and relapse trends of Acute Lymphocytic Leukemia. However, little has been published on using LSTM to predict outcomes in MM patients. This study explores the application of LSTM to predict mortality outcomes in MM patients, leveraging sequential data to enhance prognostic accuracy. **Methods:** We extracted mortality data from the Wide-Ranging Online Data for Epidemiologic Research (WONDER) Centers for Disease Control and Prevention (CDC) database. Patients from 1999–2021 were evaluated using established ICD-10 codes for Multiple Myeloma, normalized the data, and encoded demographic variables such as age, gender, and race numerically. A total of 12,654 patients were analyzed using this model. We created an LSTM model capable of identifying and leveraging long-term data patterns for mortality predictions using RStudio. The model was trained using a 20-year sequence length to forecast future data points based on historical trends. **Results:** Mortality analysis demonstrated significant variability across demographic groups. The LSTM model effectively captured nuanced variations in mortality trends based on demographic factors such as age, sex, and geographic location. Mortality increased exponentially with age, as evidenced by a strong correlation ($R^2 = 0.98$), and male mortality rates were consistently higher than female rates by approximately 38% (95% CI: 36–40%). The model's predictive accuracy was evaluated using Mean Squared Error (MSE) and Mean Absolute Error (MAE), achieving a training MSE of 0.0055 and a validation MAE of 0.053, confirming its reliability and precision. Furthermore, integrated performance metrics (MAE = 1.28 deaths per 1.000 patients, $R^2 = 0.986$) reinforce the model's exceptional predictive accuracy and highlight distinct mortality variations across demographic strata. **Conclusions:** This study demonstrates the LSTM model's strong predictive capability in accurately forecasting mortality outcomes in patients with Multiple Myeloma using demographic and temporal data. The model's high accuracy indicates its potential as a valuable clinical decision-making tool to guide personalized interventions and optimize patient management strategies. Implementing LSTM-based predictive models in clinical settings could facilitate early intervention strategies, ultimately enhancing patient outcomes. Future research should focus on integrating additional clinical biomarkers and treatment-related variables to enhance predictive performance and clinical applicability.

PA-389

Uncovering Hidden Prognostic Patterns in Multiple Myeloma: A Novel Unsupervised Deep-Learning Method for Risk Factor Discovery

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Introduction: Current survival analysis models often fail to provide actionable clinical stratification criteria. While the Revised International Staging System (R-ISS) for Multiple Myeloma offers clear decision boundaries, existing machine learning approaches have limitations - relying on metrics unrelated to survival or requiring expert interpretation. We introduce a novel optimization approach derived from the multivariate logrank statistic that enables neural networks to directly learn to derive clusters of distinct survival outcomes from patient features alone. This method successfully stratifies multiple myeloma patients into sharp risk categories while revealing clinically meaningful risk factors in an unsupervised manner. **Methods:** We developed a differentiable adaptation of the multivariate logrank statistic compatible with neural network training that optimizes for survival heterogeneity across patient clusters. We applied this to multiple myeloma laboratory data from the CoMMpass study (n = 722), using standard clinical biomarkers (hemoglobin, calcium, creatinine, WBC, M-protein, free light chains, LDH, albumin, β2-microglobulin). Explainability analyses quantified each parameter's contribution to risk stratification. **Results:** Our approach stratified patients into three distinct risk groups with a C-index of 0.647, outperforming the R-ISS (typical C-index 0.61–0.63). Survival differences were highly significant ($p = 7.3 \times 10–17$), with the high-risk group showing median PFS of approx. 3 years while the low-risk group maintained >70% progression-free survival at 11 years. The model independently identified established risk factors (β2-microglobulin, creatinine, M-protein) while also highlighting the importance of WBC count and specific free light chain patterns not

explicitly incorporated in current staging systems. **Conclusions:** Our novel methodology for optimization of survival heterogeneity can outperform established clinical staging systems, even while relying on standard laboratory parameters alone. The method's ability to discover known risk factors without prior knowledge validates its potential to also identify novel prognostic signatures. This approach is model-agnostic and could yield even greater stratification power when applied to genetic, molecular, or imaging data. By enabling more precise risk assessment, this methodology promises to enhance treatment personalization and resource allocation in multiple myeloma management.

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Validation of a Simplified Prognostic Score for Transplant-Ineligible Multiple Myeloma Patients in a Portuguese Cohort: A Real-World Analysis Based on the Greek Myeloma Study Group Model - MEPS

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Introduction: The Revised International Staging System (R2-ISS) improved risk stratification in multiple myeloma (MM), but its prognostic value in transplant-ineligible (TI) patients remains uncertain. A simplified score proposed by the Greek Myeloma Study Group—based on four adverse features: age ≥75, CKD-EPI < 40 mL/min/1.73 m², ECOG ≥2, and ultra-high-risk cytogenetics (UHR: ≥2 of del(17p), t(4;14), t(14;16), +1q21)—has demonstrated improved prognostic performance. We aimed to validate this Myeloma Elderly Prognostic Score (MEPS) in a real-world cohort of Portuguese TI MM patients. **Methods:** This retrospective study included 300 newly diagnosed TI MM patients from Portuguese hospitals (2010–2024). Each MEPS variable contributed 1 point (score range 0–4). Patients were stratified by R2-ISS and MEPS. OS was estimated via Kaplan-Meier. Variables with $p < 0.05$ in univariable Cox regression were included in multivariable models. Bootstrapping (1000 samples) estimated 95% CIs for overall survival (OS), progression free survival (PFS), and follow-up. Discrimination was assessed with the C-index. Survival differences were evaluated by log-rank and Bonferroni-adjusted pairwise tests. **Results:** Median age was 75 (49–89); 48% female. Median diagnosis year 2017. Frequencies of MEPS features: age ≥75 (53%), ECOG ≥2 (50%), CKD-EPI < 40 (35%), UHR (7%). ISS 3 and R-ISS 3 were seen in 49% and 23%. M-protein types: IgG (62%), IgA (20%), light chain (14%). R2-ISS stages: I (10%), II (29%), III (49%), IV (12%). MEPS groups: low (0 points, 23%), low-intermediate (1, 31%), intermediate-high (2, 31%), high (≥3, 15%). First-line regimens: lenalidomide-based (21%), daratumumab-based (8%), bortezomib-based or Rd (64%). Overall response rate was 83%, with 26% complete response. Second-line therapy was used in 44% and the median of post-progression OS was 22 months (n = 179, 95% CI: 17–29). At 38-month median follow-up, 52% had died. Median PFS and OS were 22 and 38 months, respectively. Median OS by R2-ISS: I (60), II (52), III (31), IV (25) months ($p < 0.001$); by MEPS: low (50), low-intermediate (42), intermediate-high (29), high (20) months ($p < 0.001$). Although the log-rank test did not reach conventional statistical significance ($p = 0.052$), the observed effect size (8 months) suggests a potentially meaningful clinical effect. In contrast, R2-ISS stages III and IV did not differ significantly ($p = 0.999$). Multivariable analysis confirmed age ≥75, CKD-EPI < 40, and ECOG ≥2 as independent predictors ($p < 0.001$); UHR trended toward significance ($p = 0.085$). MEPS showed stronger discrimination than R2-ISS for OS (C-index 0.795 vs. 0.732, $p < 0.001$) and PFS (0.762 vs. 0.676, $p < 0.001$). **Conclusions:** MEPS effectively stratifies TI MM patients into prognostically distinct groups, outperforming R2-ISS in this cohort. Its simplicity and superior accuracy support its clinical applicability in elderly MM management. Further validation in broader cohorts is warranted.

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The Novel High-Risk Multiple Myeloma IMS/IMWG Criteria Identify Previously Overlooked Newly-Diagnosed Patients with Poor Prognosis: Validation and Real-World Application

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Introduction: Novel high-risk multiple myeloma (HRMM) criteria were established by the IMS/IMWG consensus, aiming to refine the classification of high-risk disease beyond traditional staging systems. Our aim was to evaluate these new criteria in the Real World. **Methods:** Consecutive newly-diagnosed MM (NDMM) patients (pts) with available data for IgH translocations, del(1p32), del(17p) and/or TP53 mutations and +1q, and for Sβ2M and serum creatinine (Cr) were prospectively enrolled in this study. Pts were stratified by the

novel IMS/IMWG HRMM criteria [del(17p) and/or TP53 mutations - t(4;14), t(14;16) or t(14;20) with +1q and/or del(1p32) - or monoallelic del(1p32) and +1q or biallelic del(1p32) - or Sβ2M ≥5.5 mg/L with Cr < 1.2 mg/dL] and by established tools: ISS, R-ISS and R2-ISS. **Results:** A total of 332 NDMM pts were included, out of which 60 (18.0%) were identified as high-risk per the novel criteria, 103 as ISS III, 42 as R-ISS III and 18 as R2-ISS high-risk. After a median follow-up of 37.5 months, there were 79 (23.8%) disease progression events and 72 (21.7%) deaths recorded. High-risk pts per novel criteria had a median PFS of 25.5 months and demonstrated double the risk for disease progression or death [HR = 2.15, 95% CI: 1.42–3.25], compared to standard-risk ones. The median OS for these pts was 30.0 months and they had a 2.5-fold risk of death [HR = 2.50, 95% CI: 1.51–4.15], compared to standard-risk. Median TTP was not reached, but high-risk pts had 85% higher risk for disease progression [HR = 1.85, 95% CI: 1.12–3.08], compared to standard-risk. Importantly, the prognostic significance of the novel HRMM criteria was maintained in multivariate analyses for PFS [aHR = 1.86, 95% CI: 1.18–2.96], OS [aHR = 2.26, 95% CI: 1.30–3.91] and TTP [aHR = 2.04, 95% CI: 1.20–3.46]. Out of the 60 patients identified as high-risk per the novel HRMM criteria, the 48 (80.0%) were not categorized as such by established tools. These patients had dismal PFS [HR = 1.94, 95% CI: 1.24–3.05], OS [HR = 1.99, 95% CI: 1.14–3.47] and TTP [HR = 1.79, 95% CI: 1.04–3.11], compared to others. The 4-year OS rates for standard and high-risk pts among those: aged >65 years who did not undergo HDM-ASCT, were 66.8% and 43.3% (p = 0.020) and with ECOG PS≥2, were 60.4% and 30.9% (p = 0.020), respectively. Furthermore, 104 (31.3%) pts were treated with quadruplets. The 4-year OS rates for standard and high-risk pts in this group were 94.9% and 66.5% (p = 0.030), respectively. Finally, the 4-year OS rates for standard and high-risk pts among those categorized: as ISS-2, were 79.7% and 19.8% (p < 0.001) and as R-ISS 2, were: 74.9% and 56.9% (p = 0.030), respectively. Therefore, the novel HRMM criteria seemed to identify a set of pts within each one of these subgroups with adverse prognosis. **Conclusions:** The novel HRMM criteria by the IMS/IMWG consensus seem to identify a group of high-risk pts with particularly adverse prognosis, that were previously overlooked by traditional staging systems and may require tailored therapeutic approaches.

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Temporal Trends in Multiple Myeloma Mortality in Ecuador, 2010–2022: A Nationwide Joinpoint Analysis

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Introduction: There is a lack of detailed research on multiple myeloma (MM) mortality trends specific to Ecuador, a country with its own demographic and healthcare factors that could influence outcomes. Therefore, we conducted the first nationwide assessment of MM mortality in Ecuador. Using 2010–2022 death-certificate micro-data from the National Institute of Statistics and Census (INEC), computed annual crude (CMR) and age-standardised mortality rates (ASMR), and modelled temporal changes with joinpoint regression. **Methods:** This observational, cross-sectional study quantifies crude mortality attributed to multiple myeloma (MM) in Ecuador from 2010–2022 and characterises its temporal trajectory. Mortality micro-data were drawn from the publicly available death-certificate files issued annually by the National Institute of Statistics and Census (INEC) and downloadable in SPSS format from Ecuador en Cifras (https://www.ecuadorencifras.gob.ec/camas-y-egresos-hospitalarios/). Records coded C90.0 (ICD-10) were aggregated by calendar year.To compute the crude mortality rate, we applied the following equation:Crude mortality rate = (Total number of deaths in a calendar year by MM/Estimated mid-year population for that year) * 106. The upper and lower limits of the 95% confidence intervals were calculated using the following formulas: Upper Limit = (1000/n) [d + (1.96 × √d)] Lower Limit = (1000/n) [d - (1.96 × √d)]Temporal patterns were modelled with Joinpoint® regression (≤3 joinpoints; permutation test α = 0.05), yielding segment-specific annual percentage change (APC). This approach pinpoints statistically significant inflexion points, revealing periods of acceleration or deceleration in MM mortality across the 2010–2022 interval. **Results:** A total of 1,642 MM deaths were recorded (57% male); median age 69 years (IQR 17). National CMR varied from 14.99/1,000,000 in 2010 to 16.61/1,000,000 in 2022, reaching a nadir in 2012 (14.10) and a peak in 2019 (23.55). Joinpoint analysis revealed three segments: 2010–2015 (APC +1.22%), 2017–2018 (APC +10.84%), and 2020–2022 (APC –11.72%). Male mortality peaked at 25.65/1,000,000 in 2017 (2010–2019 APC +4.41%, 2021–2022 APC –14.14%), whereas female mortality peaked at 21.45/1,000,000 in 2019 (2010–2018 APC +3.68%, 2020–2022 APC –10.24%). Mortality rates rose step-wise with age, the highest burden occurring in individuals ≥ 80 years. **Conclusions:** MM mortality in Ecuador followed a rise–spike–decline pattern, peaking just before the national adoption of bortezomib and expansion of specialist haematology services, then falling sharply during 2020–2022. Sustained access to novel agents, earlier diagnosis, and strengthened cancer-registry infrastructure are essential to maintain this downward trajectory.

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Propensity Score–Weighted Comparison of Daratumumab-Rd versus Daratumumab-VMP, Rd, and VMP in High-Risk Multiple Myeloma: Insights from the MAIA and ALCYONE Trials

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Introduction: Myeloma is a common hematologic malignancy with improved outcomes, but high-risk patients still fare poorly. In transplant-ineligible NDMM, MAIA showed median PFS of 61.9 versus 34.4 months and OS not reached versus 65.5 months for D-Rd versus Rd; ALCYONE reported median OS of 83.0 versus 53.6 months for D-VMP versus VMP. No direct comparison exists. Objective. To compare progression-free and overall survival of high-risk, transplant-ineligible NDMM patients treated with D-Rd, D-VMP, Rd, and VMP, using a propensity score–weighted analysis of pooled data from the MAIA and ALCYONE trials. **Methods:** A retrospective, IPTW-weighted analysis of de-identified MAIA and ALCYONE phase III data (DUA #2025-0152, YODA Project) was conducted. Only ISS III patients with high-risk cytogenetics (del (17p), amp(1q21), t(4;14), and/or t(14;16)) were included. Propensity scores from multinomial logistic regression (age > 70 years, ECOG 1–2, sex, creatinine clearance > 60 ml/min) yielded IPTW. Weighted Kaplan–Meier curves and robust Cox models compared PFS and OS between D-Rd and D-VMP. **Results:** Of 103 high-risk, transplant-ineligible patients (24 D-Rd, 29 D-VMP, 21 Rd, 29 VMP; Table 1), IPTW balanced age ≥ 70, sex, and CLCR ≥ 60 mL/min (max SMD < 0.10) (Figure 1). Weighted 3-year PFS was 54.8% (95%CI 35% to 86%), 19.5% (95%CI 7.6% to 49.7%), 16.7% (95%CI 7.4% to 38%), and 11% (95%CI 4.1% to 29.2%) mo for D-Rd, Rd, D-VMP, and VMP (Figure 2A); median OS was 59.1, 41.0, 53.,6, and 33.0 mo, respectively (Figure 2B). In the IPTW-Cox model for PFS, D-Rd versus VMP yielded HR 0.29 (95% CI 0.15–0.55; $p < 0.001$), whereas D-VMP (HR 0.92; $p = 0.73$) and Rd (HR 0.80; $p = 0.45$) were not significant. The global Wald test was χ^2 14.9 ($p = 0.002$; c-index 0.602). For OS, no arm differed from VMP (robust Wald χ^2 1.8; $p = 0.60$; c-index 0.561). In ECOG 1–2 patients, 2-y PFS was 57.1%, 32.0%, 35.0%, and 47.0%; 2-y OS was 57.1%, 64.0%, 70.0%, and 70.6% for D-Rd, D-VMP, VMP, and Rd, respectively (all NS). Safety results are presented in Table 2. **Conclusions:** In this high-risk, transplant-ineligible cohort, D-Rd conferred a marked PFS benefit versus VMP (HR 0.29; $p < 0.001$), whereas D-VMP and Rd did not differ significantly. OS differences were non-significant across regimens. These findings underscore the urgent need for prospective head-to-head trials—and real-world data—in elderly, high-risk myeloma patients, particularly those with impaired performance status. **Acknowledge.:** This study, carried out under YODA Project #2025-0152, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The interpretation and reporting of research using this data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The original proposal can be found: https://yoda.yale.edu/data-request/2025-0152/."

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Propensity Score–Matched Comparison of Daratumumab–Rd versus Daratumumab–VMP in Transplant-Ineligible Multiple Myeloma Patients with del(17p13): An Analysis of the MAIA and ALCYONE Trials

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Introduction: Outcomes in transplant-ineligible newly diagnosed multiple myeloma (NDMM) have improved with the incorporation of daratumumab-based regimens. However, prognosis remains poor for patients with high-risk cytogenetics, particularly del(17p13). Although the MAIA trial showed a survival benefit with D-Rd and the ALCYONE trial with D-VMP, no direct head-to-head comparison has been performed, particularly in this high-risk subgroup. Objective. To compare progression-free and overall survival of high-risk, transplant-ineligible NDMM patients treated with D-Rd, D-VMP, Rd, and VMP, using a propensity score–weighted analysis of pooled data from the MAIA and ALCYONE trials. **Methods:** This retrospective analysis used de-identified patient-level data from the MAIA and ALCYONE phase III trials (YODA Project, DUA #2025-0152). Patients with confirmed del(17p13) were selected. One-to-two nearest-neighbor propensity score matching was performed based on age ≥70, ECOG 1–2, CLCR ≥60 mL/min, and ISS stage. Covariate balance was verified post-matching. Kaplan–Meier curves and log-rank tests were used to compare PFS and OS. **Results:** Of 86 patients with del(17p13), 17, 16, 24, and 29 received D-Rd, Rd, VMP, and D-VMP. Median PFS was 40.9, 27.1, 23.1, and 21.5 months ($p = 0.59$) (Figure 1A). The 3-year OS was 58.8% (95% CI 39.5–87.6%), 56.2% (36.5–86.7%), 62.5% (45.8–85.2%), and 65.2% (49.9–85.2%) (Figure 1B). Post-matching balance diagnostics showed standardized mean differences < 0.25 across covariates. Maximum eCDF statistics were < 0.1, and variance ratios remained within acceptable limits (0.5–2.0), confirming distributional balance across matched treatment groups (D-Rd and D-VMP) (Figure 2). After matching, 26 patients were included in the analysis (Table 1). Median progression-free survival (PFS) was 35.0 months for D-Rd and 20.95 months for D-VMP ($p = 0.72$) (Figure 3A). At 3 years, survival (OS) was 60.0% (95% CI 36.2–99.5) in the D-Rd group ($n = 10$) and 62.5% (42.8–91.4) in the D-VMP group ($n = 16$) ($p = 0.49$) (Figure 3B). **Conclusions:** In a propensity-matched cohort of transplant-ineligible NDMM harboring del(17p13), D-Rd and D-VMP achieved comparable 3-year OS, with no significant PFS or OS differences. The numerically longer median PFS for D-Rd remains inconclusive given the small sample. Prospective trials in high-risk cytogenetic subsets are required to refine treatment choices in this vulnerable group. **Acknowledge.:** This study, carried out under YODA Project #2025-0152, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The

interpretation and reporting of research using this data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The original proposal can be found: https://yoda.yale.edu/data-request/2025-0152/."

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Race, Lenalidomide Dosing, and Survival in Newly Diagnosed Transplantation-Ineligible Multiple Myeloma Patients

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Introduction: Lenalidomide (LEN) is central to the management of newly diagnosed multiple myeloma (NDMM). However, LEN dosage reductions may occur, especially in transplantation-ineligible patients who are less fit. These reductions may occur differently in African American (AA) patients due to socioeconomic disparities or baseline neutropenia due to the Duffy-null phenotype. We sought to determine the prevalence and clinical impact of LEN dose reductions in AA patients using a large United States Veterans Affairs (VA) database. **Methods:** This was a retrospective VA cohort study of transplantation-ineligible patients with NDMM treated between Jan 2015 and Dec 2023. Cox proportional hazard models were constructed to determine the difference in LEN dose reductions and all-cause mortality within 5 years between dose-reduced and non-dose-reduced patients, adjusting for age, sex, race, ethnicity, ISS stage, and other covariates. Kaplan-Meier curves examined times to dose reduction and time to mortality. **Results:** Of 1101 patients, the mean (SD) age at diagnosis was 72.1 (8.5) years; there were 341 (31.0%) AA patients. Starting LEN doses were 25 mg in 494 (44.9%), 20 mg in 33 (3.0%), and 15 mg in 198 (18.0%). Starting LEN doses of 15–20 mg produced overall survival (OS) outcomes comparable to those seen with a 25 mg dose (HR 1.01; 95% CI, 1.00–1.03; p = 0.0919). LEN reductions occurred in 303 patients [85 AA (24.9%) and 218 non-AA (28.7%)], comprising 27.5% of all patients. Patients with LEN dose reductions remained on first-line therapy for longer than those who did not: 15.2 months versus 3.9 months. Among the AA patients who experienced a dose reduction, 67.1% (57/85) were initially prescribed LEN 25 mg. Patients prescribed LEN 25 mg were more likely to experience dose reductions (OR 2.79, 95% CI 2.05–3.79; p < 0.001). The median time to first dose reduction was 127.5 days for non-AA and 140 days for AA patients. After adjusting for confounders and removing missingness, AA patients were not more likely to experience LEN dose reductions (HR 0.87, 95% CI 0.73–1.04). Patients older in age, higher starting doses, and neutropenia were more likely to experience reductions. There were no differences in mortality between patients who did and did not experience reductions (HR 0.84, 95% CI 0.68–1.04); instead, baseline thrombocytopenia, older age, and higher ISS Stage were associated with reduced OS. **Conclusions:** In this analysis of over 1000 transplantation-ineligible patients with NDMM, AA patients were not more likely to experience LEN dose reductions. Even after adjusting for race, patients who underwent a dose reduction showed no differences in outcomes. Frontline therapy duration was significantly longer in patients with LEN dose reductions; however, there were no differences in long-term survival.

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Patient Characteristics, Healthcare Utilization and Costs in Multiple Myeloma by Treatment Class Exposure – A German Claims Data Study

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Introduction: Multiple myeloma (MM) accounts for 1% of new cancer diagnoses and 10% of hematological malignancies globally, with an increasing incidence in the US and Europe (Firth 2019; Padala 2021). Treatment typically includes combinations of protease inhibitors (PIs), immunomodulatory drugs (IMIDs), and monoclonal antibodies (mAbs) (Rajkumar 2022). Newer options include bispecific antibodies (BsAbs) and CAR-Ts. This study assessed the real-world burden of disease in incident patients (pts) with MM in Germany, stratified by double- vs. triple-class exposure (DCE-TCE, respectively). **Methods:** Our retrospective cohort study used claims data from AOK PLUS, a German sickness fund covering about 3.5 million pts from 2010–2022; this is prior to the recent novel monotherapy era, so does not capture BsAbs. We included incident pts with a first MM diagnosis (ICD-10-GM: C90.00) between 2012–2022, excluding those with a MM diagnosis within the previous 24-months. Patients were observed during follow-up, for one year or until death, and depending on the number of treatment classes (PIs, IMIDs, or mAbs incl. anti-CD38) were stratified into DCE and TCE. Pts were censored in the DCE group when entering the TCE group. Pts without any of these treatment classes were excluded. We descriptively analyzed pt baseline characteristics, as well as healthcare resource utilization (HCRU) and costs per patient-year (PPY). **Results:** We identified 1849 incident MM pts (male: 52.4%; mean age: 71.3 yr; mean Charlson Comorbidity Index [CCI]: 6.9), resulting in an incidence rate of 4.8/100,000. Of these, 599 pts (32.4%) were categorized as DCE and 126 pts (6.8%) were

categorized as TCE. Compared with DCE pts, TCE pts were younger (mean age: 68.7 vs 65.7 yr), more often male (52.3% vs 63.5%), and had a slightly lower CCI (mean CCI: 5.9 vs 5.6). Although more DCE pts had MM-related hospitalizations vs TCE pts (66.8% vs 58.7%), their mean length of stay was shorter (10.0 vs 18.9d PPY). DCE pts had more visits to the GP (13.4 vs 10.4 PPY) but fewer visits to specialists (hematology, oncology, or radiology; 18.5 vs 19.8 PPY) than TCE pts. Blood and platelet transfusions were given to 50.8% and 33.9% (DCE) or 45.2% and 41.3% (TCE) of pts, respectively. Supportive care was administered to 75.5% of DCE and 81.0% of TCE pts. Prescriptions (DCE: 77,329€, 56.1%; TCE: 127,216€, 71.1%) and MM-related hospitalizations (DCE: 37,680€, 27.3%; TCE: 23,345€, 13.1%) had the highest cost PPY. **Conclusions:** Outpatient data in Germany shows that both DCE and TCE MM is associated with a substantial HCRU burden for pts. Pts visit their specialists and GPs multiple times each month; the probability of hospitalization and need for supportive care is high. New therapies that reduce the frequency of touchpoints with the healthcare system, e.g. by prolonging time in stable remission or reducing adverse event management, will save costs, time, and alleviate the pt and caregiver burden.

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Effects of Two Bortezomib-Based Protocols (VCD and VRD) on Responses and Survival as Induction Treatment of Patients with Multiple Myeloma Eligible for Autologous Stem Cell Transplantation

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Introduction: In patients diagnosed with multiple myeloma (MM) who are eligible for autologous stem cell transplantation (ASCT) current guidelines recommend the VRD regimen (bortezomib, lenalidomide, dexamethasone) as the preferred triplet induction therapy, while VCD (bortezomib, cyclophosphamide, dexamethasone) is considered as an alternative. Some studies comparing these regimens demonstrated superior response rates and survival with VRD, whereas others have found no significant difference. This study was conducted to compare the real world data of VRD and VCD induction regimens in terms of response, survival and side effects in newly diagnosed ASCT-eligible MM patients. **Methods:** Data from 133 MM patients who had been treated at our center between January 2015 and October 2023 were examined retrospectively. All patients were newly diagnosed and ASCT-eligible and received either VCD or VRD as initial therapy. Information on demographics, laboratory results, imaging, pathology, response, survival, side effects was recorded and analysed. **Results:** Of the 133 patients (57,1% male, median age 57), 73 received VCD, 20 received VRD and 40 patients had been treated with VRD following initial VCD. Patients were analyzed as three separate groups. Baseline characteristics were largely comparable across groups. The VRD group had a shorter follow up period and a higher proportion of ISS stage I patients, although R-ISS, R2-ISS and cytogenetic risk were similar between groups. End-of-induction treatment response rates of partial response (PR) and above were higher following VRD regimen compared to VCD (%97 vs % 82) ($p < 0.05$). Post-transplantation day 100 responses were also better in the VRD group but the difference was not statistically significant ($p > 0.05$). In the survival analysis, overall survival was significantly better with VRD compared to VCD (median survival not reached vs 115,8 months) while no significant difference in progression free survival was detected. Among patients receiving maintenance therapy, VRD induction didn't confer a survival advantage ($p > 0.05$). In multivariate analysis, including high cytogenetic risk, maintenance treatment and ISS, no significant survival difference was observed between induction treatment groups. Adverse event profiles were comparable across groups. Additionally in our cohort, once-weekly bortezomib administration when compared to twice-weekly bortezomib administration (73 vs 29 patients, respectively) was associated with fewer neuropathy and didn't result in lower responses and survival. Also R2-ISS differentiated survival among patients better than ISS and R-ISS; PET responses were independently associated with survival. **Conclusions:** In this real world cohort, VRD provided better response rates and overall survival in univariate analysis, but no significant survival difference was detected between induction regimens in multivariate analysis among confounding factors such as maintenance and cytogenetic risk. Both regimens had similar side effect profiles.

PA-398

Overview of First-Line Treatment of Multiple Myeloma Patients from Two Hematology Centers in Slovakia – Data from the RMG Registry

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Introduction: The treatment landscape for multiple myeloma (MM) has undergone significant changes in recent years. The introduction of the monoclonal anti-CD38 antibody daratumumab into first-line regimens has to led to substantial improvements in response rate. The primary aim of this was to evaluate the maximum response and safety of daratumumab-based regimens in the first-line treatment of MM, based on data from the register of monoclonal gammopathy (RMG). The secondary goal was to highlight the importance of systematic data collection in patients with monoclonal

gammopathies in routine clinical practice. **Methods:** A total of 124 patients treated in the first line with daratumumab-based regimens (DVTD,DVMP,DRD,DVRD) between 2023 and 2025 in Two Hematology centers in Slovakia, were included in this analysis. The median age at diagnosis was 65 years (range 36–83), with the majority of patients being male (66; 53.2%) and female (54; 46.8%). Data were analyzed using statistical methods from the RMG registry. We assessed the maximum overall response according to the IMWG criteria and compared it with a historical cohort of 816 patients treated with non- daratumumab regimens (VRD,CVD,VTD,RD, VMP and others) between 2007 and 2022 at our centers. Adverse events were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. **Results:** The analysis confirmed the superior efficacy and safety of daratumumab-based regimens in the first-line treatment of MM, showing higher response rates compared to non-daratumumab regimens. In patients eligible for autologous stem cell transplantation (ASCT), achieving a maximum response of VGPR or better was 92.7% vs.73.4% ($p = 0.0004$). In patients not eligible for ASCT, the response rate was 83.7% vs.40.3% ($p = 0.0000$). Daratumumab regimens were well tolerated and could be fully administered on an outpatient basis. **Conclusions:** The inclusion of daratumumab in induction therapy significantly improves the depth of response in MM patients, with regimens being well-tolerated and suitable for outpatient treatment. The RMG registry proves valuable for tracking diagnosis and treatment outcomes in clinical practice, facilitating access to analytical data for collaborative publications, scientific collaboration, regulatory arguments, and the development of joint guidelines for diagnosis and treatment. The RMG project is fully open for collaboration with all oncology centers and groups in Slovakia, the Czech Republic, and other European countries.

PA-399

Survival Outcomes and Safety of High-Dose Melphalan with Autologous Stem Cell Transplantation in Multiple Myeloma: A Retrospective Study

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Introduction: High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) improves overall survival (OS) in multiple myeloma compared to standard-dose therapy (SDT), particularly before novel agents emerged. Benefits of HDT-ASCT are more pronounced in high-risk cytogenetics. ASCT is safe, with low treatment-related mortality (~1%). Aims and Objectives: This study aimed to retrospectively evaluate survival outcomes among multiple myeloma patients undergoing HDT-ASCT. Objectives included analysing clinical features and assessing PFS and OS. **Methods:** A retrospective analysis was conducted on 186 multiple myeloma cases undergoing HDT-ASCT at a tertiary care centre, Jaslok Hospital and Research Centre,Mumbai,India between 2001 and March 2024. Clinical and laboratory data were analysed using SPSS v22.0 with appropriate statistical tests. **Results:** The cohort included 186 patients, mostly male (70.97%) and predominantly under 60 years (87.09%). At transplantation, 74.19% achieved a very good partial response (VGPR) or better. IgG Kappa was the most common M-protein (36.56%). ISS stage III disease occurred in 25.80%, and high-risk cytogenetics in 31.72%. Newly diagnosed multiple myeloma accounted for 75.80% of cases. Melphalan doses administered were 200 mg/m² in 72.04% (n = 134) and 140 mg/m² in 52 patients. Hospital stays were significantly longer with 200 mg/m² (22.82 days) versus 140 mg/m² (19.15 days; $P < 0.05$). Mean neutrophil engraftment times were comparable (12.54 days at 140 mg/m²; 12.90 days at 200 mg/m², $P > 0.05$), as were platelet engraftment times (14.18 vs. 14.33 days; $P > 0.05$). Grade 3 or higher mucositis rates were similar between doses (20.6% at 140 mg/m² and 21.7% at 200 mg/m², $P = 1.000$). Treatment-related mortality was low (1.61%, n = 3). Median overall survival was 60.1 months (95% CI: 44.8–71.8), and median progression-free survival was 51.2 months (95% CI: 42.1–61.9). **Conclusions:** HDT-ASCT demonstrates substantial clinical benefit and safety, supporting its routine use in eligible NDMM and RRMM patients in India.

PA-400

D-VRd-based Dynamic Frailty-Tailored Therapy (DynaFiT-v2) in Elderly Patients with Newly Diagnosed Multiple Myeloma: a Prospective Study

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Introduction: The anti-CD38 monoclonal antibody daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) has been recommended as first-line therapy for elderly patients with newly diagnosed multiple myeloma (NDMM) However, it remains a substantial challenge to balance its efficacy and toxicity in this vulnerable population, primarily due to the dynamic nature of frailty. **Methods:** We conducted a prospective study to evaluate the feasibility and benefits of dynamic frailty-tailored therapy (DynaFiT-v2) in patients aged ≥ 65 years with NDMM. Patients received eight cycles of D-VRd for induction, with treatment intensity adjusted according to longitudinal changes in the frailty category (according to the International Myeloma Working Group frailty index/IMWG-FI) at each cycle. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), treatment discontinuation (TD), adverse events (AEs), and overall response rates (ORR). PFS and OS were analyzed using the Kaplan-Meier curve and log-rank test. The cumulative incidence

of AE-associated TD was calculated using the Fine and Gray model while accounting for the competing risk of TD caused by disease progression, noncompliance, and deteriorating condition. **Results:** At the time of analysis, 49 patients were enrolled. Of them, 19 (38.8%), 7 (14.3%), and 23 (46.9%) were defined as fit, intermediate fit, and frail at baseline, respectively. 46 patients had two or more geriatric assessments, of whom 19 (41.3%) experienced changes in the frailty category at least once. Improvement was observed in 12/22 (54.5%) of frail patients (18.1% and 36.4% became fit and intermediate fit, respectively) and 3/7 (42.9%) of intermediate fit patients, while 3/17 (17.6%) of fit patients deteriorated. In 22/49 (44.9%) of patients who had completed eight cycles of induction, 5/11 (45.5%) of frail patients became intermediate fit (4/11) or fit (1/11) before proceeding to maintenance. The ORR was 100%, 100%, and 85% for fit, intermediate-fit, and frail patients. Kaplan-Meier curve showed that frail patients had significantly shorter OS and PFS than non-frail (fit or intermediate fit) patients (median PFS, 21.5 months vs. not reached, HR 7.82, 95% CI 0.97–63.07, P = 0.024; median OS, 21.5 months vs. not reached, HR 9.52, 95% CI 1.21–75.01, P = 0.009). During induction, 10/49 (20.4%) patients experienced TD, including 2/7 (28.6%) of intermediate fit patients and 8/23 (30.8%) of frail patients. 3/23 (13.0%) of frail patients discontinued treatment within the first three cycles, mainly because of non-hematologic toxicity (mostly infections). The competing risk of AE-associated TD was significantly higher in frail patients than their non-frail counterparts (P = 0.019). **Conclusions:** This individualized D-VRd-based DynaFiT therapy is feasible and may benefit heterogeneous elderly patients with NDMM, particularly those classified as frail by the IMWG-FI.

PA-401

Intensified Cyclophosphamide, Bortezomib, Dexamethasone (iCyBorD) for the Treatment of Newly Diagnosed Multiple Myeloma with Acute Kidney Injury

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Introduction: There is no standard treatment for newly diagnosed multiple myeloma (NDMM) presenting with acute kidney injury (AKI). The MYRE trial noted no additive benefit of bolus cyclophosphamide (Cy) to bortezomib (Bor) and dexamethasone (D) for NDMM and cast nephropathy not requiring dialysis. A retrospective study demonstrated daratumumab's (dara) efficacy in NDMM with AKI, though dara isn't universally available in this setting. We report the outcomes of treatment with lower dose, hyperfractionated Cy with CyBorD (iCyBorD) in NDMM patients with AKI. **Methods:** This retrospective study included adults with NDMM and AKI between 1/1/14 and 1/1/24 at the University of California, Davis. Patients received iCyBorD (Cy 250 mg/m2 every 12 hours for 4 doses, Bor 1.3 mg/m2 days 1, 4, 8, 11, D 20 or 40 mg day 1–4, 8–11) followed by imid based therapy after 1 cycle, standard weekly (w)CyBorD, or a non-CyBorD regimen. The primary endpoints were IMWG defined overall renal response (ORR), and time to initial and best renal response. Secondary endpoints included MM response and toxicity. **Results:** 68 patients were included: 12 each received iCyBorD, wCyBorD, and dara based regimens with 32 treated with non-dara treatments. Baseline eGFR was similar in the iCyBorD and wCyBorD groups and higher in non-CyBorD patients. ORR rates with iCyBorD of 92% (n = 11) were superior to responses with dara and other non-dara regimens at 42% (n = 5) and 44% (n = 14), respectively (p = 0.0272; p = 0.0057). wCyBorD resulted in 75% (n = 9) ORR rate. iCyBorD resulted in a median time to initial renal response of 11 vs 64 days with dara based treatments (p = 0.04). Time to initial renal response with wCyBorD and non-dara regimens were 38 and 37 days, respectively. Time to best renal response was comparable at a median of 26, 44, 64, and 37 days with iCyBorD, wCyBorD, dara and non-dara based regimens, respectively (P = 0.16). After 1 cycle, eGFR improvement in the iCyBorD group was 162% compared to 46%, 19%, and 19% in the wCyBorD, dara and non-dara groups, respectively. Time to best myeloma response was comparable amongst all groups: median of 45, 83, 66, and 85 days with dara, non-dara, iCyBorD, and wCyBorD regimens, respectively (p = 0.21). Among those treated with iCyBorD, 5 (42%) grade (G) 3 neutropenia, 1 (8%) G 3 thrombocytopenia and a 1 gastric ulcer perforation events occurred. No instances of neutropenic infections were noted. Among wCyBorD patients: 1(8%) each G3 neuropathy, and pancreatitis events occurred. Among dara treated patients, 2 (17%) G3 neutropenia, and 1 (8%) lung infection events occurred. Among non-dara treated patients, 3 (9%) G3 neutropenia, and 1 (3%) G3 thrombocytopenia events occurred. **Conclusions:** One cycle of iCyBorD was effective at inducing rapid renal responses while yielding similar toxicity profiles to other regimens. iCyBorD is an effective treatment for NDMM presenting with AKI, and may be considered in settings where dara is unavailable.

PA-402

Incidence and Timing of Infections in Patients with Newly Diagnosed Myeloma Treated with Contemporary Regimens

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Introduction: Patients with multiple myeloma are at high risk for infections due to their compromised immune system, other co-morbidities and treatment-related factors. Understanding this risk of infections in patients treated with contemporary regimens in the real world setting is important to develop preventive and management strategies. **Methods:** To evaluate risk and incidence of infections in newly diagnosed myeloma (NDMM) patients we analyzed the infectious complications (i.e infections of at least grade 3) in newly diagnosed consecutive myeloma patients, treated in a single center (Department of Clinical Therapeutics, Athens). The analysis included 539 patients, that started treatment between 1/1/2020 and 31/12/2024, thus including patients from the start of COVID period. **Results:** Median age was 67 years; 56% were >65 years, 54% were males. Per ISS, 34%, 36% and 30% were stage 1, 2 & 3 respectively, 21% had high risk cytogenetics, 16% had eGFR< 30 ml/min/1.73 m2 and 4% required dialysis at the time of diagnosis. Treatment included a PI in 78%, lenalidomide in 77%, PI +lenalidomide in 56% (VRd in 33%) and anti-CD38 in 38% (Daratumumab-VRd in 18%). The median follow-up of the cohort is 2.5 years and 20% of the patients have died. During their first line therapy 26% of the patients had at least one grade ≥3 infection. The rates of infection were higher in the first 3–6 months from start of treatment; the rate of grade ≥3 infections at 3, 6, 12 and 18 months was 10%, 15%, 16% and 19% respectively. Lower respiratory tract infections (grade ≥3) were the most common (in 64 (12%) of all patients) and grade ≥3 COVID-19 in 35 (6.5%); the cause of death was mainly infectious in 32 patients (6%). Factors associated with higher risk of infections during the first 6 months from start of treatment included ECOG PS≥2 ($p = 0.002$), eGFR ($p = 0.003$), increased serum LDH (>ULN) ($p = 0.045$). The use of anti-CD38-based induction regimens was associated with a numerically higher risk of infections (vs non-anti-CD38) at 6 months (18% vs 15%, $p = 0.396$) or at 12 months (22% vs 17%, $p = 0.183$); however, focusing on patients treated with Dara-VRd vs VRd, the addition of daratumumab to VRd was associated with significantly higher rates of Grade³3 infections at 6 months (21% vs 13%, $p = 0.067$) and at 12 months (26% vs 15%, $p = 0.023$). Based on the results of multivariate analysis we developed a risk score with 1 point for eGFR< 30 ml/min/1.73 m2 and LDH >ULN and 2 points for ECOG PS≥2: the 6, 12 and 18 months Grade≥3 infection rate at 6 months was 9%, 19% and 30%, at 12 months was 13%, 23%, 33% and at 18 months was 16%, 26% and 40% for the three risk groups respectively ($p < 0.001$). **Conclusions:** In conclusion, in this real-world contemporary cohort, infectious complication are frequent and their burden is higher during the first 3 months from the start of therapy. Use of anti-CD38 antibodies further increases this risk. Strategies to reduce infectious complications should be implemented in routine clinical care.

PA-403

Predictors of High-Risk and Ultra High-Risk Multiple Myeloma from the Australia & New Zealand Myeloma and Related Diseases Registry (MRDR)

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Introduction: A significant proportion of newly diagnosed myeloma patients(NDMM) have high-risk multiple myeloma (HRMM): overall survival (OS)< 5y, and ultra high-risk MM (UHRMM), variably defined as OS < 2–3 y. This study aims to define the predictors of HRMM and UHRMM based on overall survival, in NDMM in MRDR, a prospective registry involving 60 sites across Australia and New Zealand, from 2012 to 2020. **Methods:** NDMM patients with >5 years follow up were included, and classified into UHRMM, HRMM and SRMM (standard risk MM) according to OS < 3 y, 3–5 y and >5 y respectively. Baseline demographics and clinical characteristics were compared using Pearson's chi square test; survival analyses with Kaplan Meier method; univariate and multivariate logistic regressions used to identify predictors of HR disease. **Results:** In 2649 patients analysed, median OS and PFS were 80 m (IQR 37 m – NR) and 33 m (IQR 16 m – 67 m), respectively. 24% had UHRMM, 13% HRMM and 63% SRMM. Most patients received frontline VCd (71%) with only 7% treated with Rd and 2% with VRd. 17% were primary refractory (PR) to frontline therapy and 20% had early relapse (ER) within 12 m of diagnosis. PR patients were older with no difference in performance status (PS), ISS or presence of high risk cytogenetics abnormalities (HRCA); 70% had no HRCA, consistent with well-defined functional high risk (FHR) disease. ER patients were older, had worse PS, higher ISS, more end organ damage and t(14;16). When analysing patients based on OS, those with UHRMM and HRMM were older with poorer PS, higher ISS, more end organ damage, high risk cytogenetic abnormalities (HRCA) and co-morbidities than patients with SRMM. When comparing the two high risk groups, patients with UHRMM were older than those with HRMM with worse PS, more hypercalcaemia, renal insufficiency and cardiac disease. With regards to treatment and response, UHRMM patients were less likely to receive frontline ASCT consistent with the age difference and there was a higher proportion of PR and ER compared to the HRMM group. Multivariate regression (MVR) identified age >70 years, ECOG PS, ISS, presence of 1 HRCA as predictors of UHRMM and HRMM when compared to the SRMM group.

Within the UHRMM group, presence of 2 or more HRCA was identified on MVR as predictive of UHRMM when compared to HRMM and SRMM groups. ASCT did not abrogate the increased risk associated with poor PS, high ISS stage and HRCA in the UHRMM group when compared to HRMM and SRMM groups. **Conclusions:** This large real-world cohort treated prior to the availability of VRd therapy, highlights the inferior survival in over 1/3 of patients with NDMM. Whilst age, PS, ISS and HRCA remain important predictors of high-risk disease, patients with FHR, who remain difficult to accurately define at diagnosis, account for a significant proportion of the high risk cohort, a major barrier to pursuing frontline risk adapted therapy.

PA-404

A Randomized Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone (KRd) with Elotuzumab-KRd in Transplant-Eligible Patients with Newly Diagnosed Myeloma: Initial Results for 3-Year PFS and OS

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Introduction: The treatment approach in newly diagnosed multiple myeloma (NDMM) has evolved dramatically. Adding monoclonal antibodies (mAbs) directed against CD38 to a triplet consisting of bortezomib (V), lenalidomide (R) and dexamethasone (d; VRd) was a major achievement improving outcomes. In a recent phase 3 study of a German group in transplant-eligible (TE) NDMM subjects, VRd and the mAb elotuzumab (targeting SLAMF7) however, did not prove superior over VRd alone. As the irreversible proteasome inhibitor carfilzomib (K) is thought to be more effective than V, we decided to compare KRd plus elotuzumab (E; associated with less severe respiratory infections than anti-CD38 mAbs) with KRd. **Methods:** For this phase 3 study (registered as NCT03948035), TE NDMM pts up to 70 years (yrs) were randomized 1:1 to receive six cycles of KRd or E-KRd, single (tandem, if < CR/high risk NDMM) HDT/ASCT, followed by four consolidation cycles (KRd/E-KRd) and R or ER maintenance (maint). For induction (28-day cycles), pts received K on D1/2, 8/9 and 15/16 (20 mg/m² IV on D 1/2 in C1 and 36 mg/m² thereafter), R (25 mg PO, D1–21) and d (36/40 mg D 1, 8, 15, 22). E was given on D 1, 8, 15, and 22 (C1/C2) and on D 1 and 15 (C3–6; 10 mg/kg IV). For maint, pts. received continuous R 10 mg (R maint) or E 20 mg/kg IV on D1 plus R 10 mg, (ER maint) until PD/toxicity. Minimal residual disease (MRD) was analyzed by next-generation flow. The 1st co-primary endpoint, the rate of pts who were in > VGPR and were MRD-negative post induction, was met showing superiority of E-KRd over KRd. Here, we present initial results for the 2nd co-primary endpoint: 3-year PFS rate since randomization. We estimated 3-year rate for KRd to be 58%. The data extract was 01/28/2025. **Results:** 579 pts (of whom 574 received treatment) were randomized between 08/2018 and 10/2021 at 52 sites. Median age was 60 (range, 31–71) yrs and 15.4% had ISS stage III disease. After a median follow-up of 46.4 (0.03–74.0) months (mos) for KRd and 47.4 (range, 1.1–73.1) mos for E-KRd, median PFS/OS could not be estimated. The 3-year PFS rate was comparable between groups: 72.2% (97.47% CI, 66.0–77.7) for KRd versus 78.7% (97.47% CI, 72.9–83.6) for E-KRd (OR, 1.421 [97.47% CI, 0.920–2.195]; Chi-square p = 0.0703). For OS, HR was 1.563 (97.47% CI 0.976, 2.504); Log-rank p = 0.0608. During maint, the rate of treatment-related AEs was 78.1% with R versus 80.9% with ER (p = 0.4583). The rate of grade 3–5 related AEs was 39.9% (R) versus 46.1% (ER; p = 0.1820). With 249/574 (43%) of pts still on treatment, median duration of maint was comparable between the arms: 27.8 (range, 0.4–55.0) mos for R versus 28.5 (range, 0.1–55.8) mos for ER. **Conclusions:** In our study, the addition of elotuzumab to KRd (ind/cons) and to R (maint) showed a clear trend in favor of the elotuzumab arm regarding 3-year PFS and OS rates without reaching statistical significance yet. This was mainly due to a better-than-estimated PFS in the KRd arm. ER maint was not associated with more toxicity than R.

PA-405

Nuanced Treatment Decision for Newly Diagnosed Multiple Myeloma Patients Between 65 and 75 Years Old

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Introduction: Multiple myeloma (MM) is a clonal plasma cell malignancy that accounts for approximately 10% of all hematologic cancers. While MM has always been a disease of older adults, the median age at diagnosis is slowly increasing, paralleling trends in population aging. Recently, DETERMINATION trial reaffirmed the role of autologous stem cell transplantation (ASCT) as part of frontline therapy, offering significant progression-free survival (PFS) benefits for patients aged 65 years or younger. While age 65 has traditionally served as a threshold for transplant eligibility, it lacks biological or clinical justification. This study aims to evaluate contemporary treatment patterns and outcomes in newly diagnosed MM patients aged 65 to 75 years. By comparing patients aged < 70 and ≥70 years, we seek to characterize differences in treatment selection, transplant utilization, and clinical outcomes, thereby informing a more tailored approach to treatment planning in this key population. **Methods:** This is a longitudinal cohort study conducted between January 2015 and December 2023 at 2 academic centers. A total of 561 patients aged between 65 years and 75 years at MM diagnosis were retrospectively identified and included. Their medical records were reviewed and analyzed for demographics, baseline disease characteristics, details of treatment, treatment outcomes, and survival. **Results:** Patients were categorized into 4 groups: Group 1 age 65–69 + ASCT (N = 183); Group 2 age 65–69 + no ASCT (N = 133); Group 3 age 70–75 + ASCT (N = 15); and Group 4 age 70–75 + no ASCT (N = 230). There were no differences between the 4 groups with regards to ISS stage, risk status and basline laboratory results. Triplet regimen was most often used across all groups. Interestingly, about 1/4 of patients in both Group 2 and Group 4 were treated with doublet regimen. ASCT was associated with associated with improved PFS regardless of age (Group 1 39.1M vs Group 2 17.3M vs Group 3 24.2 months vs Group 4 20.7 months). For patients between 65 and 70, this trend translated into overall survival gain (P < 0.001), but for patients between 70 and 75 PFS gain did not lead to overall survival gain (P = 0.102). Quadruplet regimens demonstrated significantly longer PFS compared to triplet or doublet regimens across all groups. **Conclusions:** Upfront ASCT offers PFS gain for newly diagnosed MM patients upto 75 years old.

PA-406

Efficacy and Safety of Bortezomib, Pomalidomide and Dexamethasone (VPD) in Newly Diagnosed Multiple Myeloma: Single-arm, Phase-II Investigator Initiated Prospective Clinical Trial

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Introduction: The data on the use of pomalidomide in Newly Diagnosed Multiple Myeloma (NDMM) is limited. Primary objective of this study was to determine the efficacy of VPD regimen by measuring Minimal Residual Disease (MRD) by flow-cytometry after 9 cycles of VPD. Current abstract is reporting the final results of PRIME trial with longer follow up. **Methods:** Both transplant eligible and ineligible patients with NDMM aged between 18 and 70 years as defined by the IMWG were recruited. Transplant patients planned for 9 cycles and non-transplant patients for 12 cycles of VPD. Eligible patients underwent Autologous HCT after 4–6 cycles of VPD. After Auto HCT 3–5 cycles of VPD given as consolidation therapy. Maintenance treatment was given as per institutional practice. A 2-tube 8-colour antibody panel was used for MRD analysis using Flowcytometry (BD FACS CANTO-II) and analysed on Kaluza version 1.3 software. A valve of < 0.001% was considered as MRD negative. **Results:** A total 50 patients were enrolled between April 2020 to March 2024. Median follow up was 27.3 months (range 9.0–59.6 months). The median age was 58 years (38–71), and gender ratio was 1:1. High risk cytogenetics were seen in 50.0% (n 25) patients. According to revised international staging system for myeloma (RISS) stage I, II and III were present in 12% (n 6), 50% (n 25) and 38% (n 19) of patients respectively. Out of 50 patients 49 (98.0%) had completed 4 cycles and 47 (94.0%) patients had completed 9 cycles of VPD. After 4 cycles 15 (30.0%) patients were in stringent complete response (sCR), 3 (6.0%) patients in CR, 29 (58.0%) in very good partial response (VGPR) and 2 (4.0%) in partial response (PR). After 9 cycles 23 (46.0%) patients were in sCR, 2 (4.0%) in CR, 19 (38.0%) in VGPR, one (2%) in PR and 2 (4.0%) patients had progressive disease. Overall response rate after 4 cycles of VPD was 98.0% and after 9 cycles was 90.0%. After 4 cycles of VPD 21 (42.0%) patients were MRD negative and MRD negative rate improved after 9 cycles to 62.0% (31 patients). Three years event free survival was 75.6% (95% CI: 61.0–85.4) and 3 years overall survival (OS) was 86.9% (95% CI: 72.9–93.9). Eleven patients underwent auto HCT. No patient failed stem cell mobilization. Grade 3–4 toxicities include hematological toxicities (10%), infections (10%) and skin rash (4%). Majority of nonhematological adverse events were grade 1 to 2 and protocol was well tolerated. A total six deaths occurred, four were due to pneumonia (COVID 19 and bacterial) and two due to progressive disease with sepsis. **Conclusions:** VPD has shown improved depth of response (MRD negativity) and overall response rate. Early follow up results showed promising PFS and OS results. VPD may be a promising induction regimen instead of Dara VRD in resource constrain setting where Daratumumab is not readily accessible. Phase 3 randomized trials are the way forward to its clinical use in frontline setting.

PA-407

Prognostic Subgroups in Hyperdiploid Myeloma and the Role of Modern Treatments

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Introduction: Chromosomal abnormalities are important prognostic factors in multiple myeloma (MM). A hyperdiploid karyotype is considered currently of standard risk and there are doubts whether more intensive treatment or transplantation is needed. Also, the clinical impact of chromosome number and of additional–structural–chromosomal aberrations assessed by conventional karyotype has not been clearly defined. **Methods:** We retrospectively reviewed the clinical, laboratory and treatment data of 80 patients with hyperdiploid MM to assess the abnormalities frequently found by cytogenetic analysis and their relationship to prognosis, especially in the era of modern treatments. **Results:** The median age was 58 (31–83) years, ISS stage was I,II,III in 21, 24 and 35 patients, while 30/68 had R-ISS III. 71 patients (89%) were treated with at least one of the novel agents (bortezomib, lenalidomide, daratumumab), 34(42.5%) underwent autologous transplantation (ASCT), one allo-SCT and 2 received CAR-T cells. All patients had cytogenetic and 52/80 FISH analysis. Twenty patients had 47–50 chromosomes and 60 had >50 (>65 in 7). Most patients (74, 92.5%) had both numerical and structural abnormalities. Thirty-one had < 3, 34 had 3–5 and 15 had ≥6 structural abnormalities. Chromosome 13 deletion was common (33 patients, 41.5%) as were abnormalities of chromosome 1 (40%) and t(11;14)(q13;q32) was observed in 6 patients. No high-risk abnormality involving 14q32 was found by karyotype or FISH. Patients with less structural abnormalities (0–2) tended to be younger and have less stage III disease (28% vs 48%, p = 0.058). By univariate analysis, there was a trend for a worse outcome with increasing number of structural abnormalities, median OS 122, 91 and 28 months, 5year OS probability of 79.2%, 57% and 23% for < 3, 3–5 and ≥6 structural abnormalities respectively, p = 0.071. No significant difference in survival was found by chromosome number. However a group of patients with high hyperdiploidy (51–65 chromosomes) and < 5 structural abnormalities showed a better outcome than the rest: median OS 91 vs 29 months, 5year OS 67% vs 32.3%, p = 0.053. Yet, this group had inferior survival when compared to 60 patients with a normal karyotype (5year OS 67% vs 81%, p = 0.003). This difference in survival was eliminated when only patients who received daratumumab in the first 2 lines were considered (p = 0.67). Patients aged ≤ 67years had a longer survival with ASCT: medOS 133 vs 64 months, 5year OS 83% vs 53.6%, p = 0.001. In multivariate analysis, significant factors were ASCT, age and a trend for −13/del13q. **Conclusions:** In conclusion, the conventional karyotype can evaluate hyperploidy, which affects a significant percentage of MM patients, and define subgroups with different prognosis, such as high hyperdiploidy with < 5 structural abnormalities. ASCT is beneficial for hyperpdiploid MM. Newer treatments, such as anti-CD33 antibody, improve the prognosis of this group even further, becoming similar to that of normal karyotype.

PA-408

Long-Term Safety and Efficacy of Autologous Hematopoietic Cell Transplantation for Multiple Myeloma in the Era of Quadruplets

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Introduction: Quadruplets have been introduced as the mainstay of induction treatment in multiple myeloma (MM) patients eligible for autologous hematopoietic cell transplantation (AHCT). We studied the long-term safety and efficacy of AHCT in a large real-world cohort of MM patients receiving quadruplets compared to historic controls induced with triplets. **Methods:** We enrolled consecutive patients, of our JACIE-accredited center, that received AHCT over the last decade (2013–2023) for MM. Patients were divided into 2 groups: 79 patients were induced with daratumumab-based quadruplets (Group A) versus 187 patients with bortezomib-based triplets (Group B). All patients received high-dose melphalan (200 mg/m2) as conditioning regimen, with dose reduction (140 mg/m2) in 6 patients with chronic kidney disease. Median patient age at transplant date was 59 (41–71) years for group A and 57 (35–70) for group B. Disease status at transplantation was complete response (CR), very good partial response (VGPR), partial response (PR) and progressive disease (PD) in 34/28/11/5 in group A vs 55/64/63/5 in group B. Variables included in the analysis were also CD34+ stem cell yield, time to neutrophil and platelet engraftment and post-transplant outcome regarding overall survival. **Results:** We studied 266 patients with multiple myeloma, within the above follow-up period. No second AHCT or allogeneic transplantation was performed in the study period. There were no transplant-related deaths. Within this period, 5-year OS was 83% in Group A patients vs 60% in Group B patients (p = 0.003). There was no statistically significant difference in the disease status at transplantation between the two groups. CD34+ stem cell yield was not different in the two groups, 3.91 (1.70–9.48) in group A vs 3.89 (1.38–9.63) × 10^6/kg in group B (p = ns). There was no impact in median time to neutrophil engraftment, 10.6 (in group A (9–13) vs 11.5 (7–26) days in group B (7, (p = ns). However,

patients in group A had significantly shorter median time to platelet engraftment, 12.8 (8–26) vs 14.2 (7–68) days (p = 0.045). **Conclusions:** Our data confirm that AHCT is safe and effective for MM in the era of quadruplets. Daratumumab-based quadruplets offer an optimal graft yield and seem to exert an enhanced impact on platelet engraftment, probably due to their alkylator-sparing advantage. The significant benefit in overall survival highlights the importance of incorporating novel agents into the first-line setting, even in transplant-eligible patients, so as to improve total outcomes in this still incurable disease.

PA-409

Real-World Experience with Daratumumab Maintenance After ASCT in Newly Diagnosed Multiple Myeloma (NDMM): Preliminary Data From a Single-Center

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Introduction: The addition of daratumumab to first-line treatment regimens for newly diagnosed multiple myeloma (NDMM) has shown superior depth of response and progression-free survival (PFS) in phase III trials such as CASSIOPEIA and PERSEUS. These studies established daratumumab-based maintenance, either as monotherapy or in combination with lenalidomide (D-R), as a standard post-transplant approach. Based on this evidence, a daratumumab-based maintenance strategy was progressively adopted in our routine clinical practice. **Methods:** A retrospective real-world analysis was conducted including 19 patients with NDMM who received maintenance with daratumumab, either as monotherapy or combined with lenalidomide, following autologous stem cell transplantation (ASCT). Median age at diagnosis was 59 years (range: 44–69), and 36.8% were female. At diagnosis, 31.6% of patients were ISS stage I, 52.6% stage II, and 15.8% stage III. R-ISS stages were I (31.6%), II (52.6%), III (10.5%), and unknown (1 patient). High-risk cytogenetics [del(17p) or t(4;14)] were present in 10.5% of cases; 21.1% showed gain of 1q, with two cases also presenting complex karyotype. All patients underwent daratumumab-based induction (D-VTd: 73.7%, D-VRd: 21.1%, DVMP: 5.3%) and received melphalan conditioning prior to ASCT. Post-transplant consolidation was given in 94.7% of cases. Maintenance therapy consisted of daratumumab alone (63.2%) or in combination with lenalidomide (36.8%). Five patients discontinued treatment without relapse. **Results:** Response deepened across treatment phases. Post-induction, 10.5% achieved sCR, 21.1% CR, and 52.6% VGPR. After ASCT, 42.1% reached sCR. Following consolidation and during maintenance, the sCR rate increased to 55.6% and 73.7%, respectively. Estimated PFS was 93.6% at 2 years, 81.1% at 3 years, and 71.2% at 5 years. Two patients relapsed (one on daratumumab, one on D-R), and one case showed progression without strict criteria, managed by adding lenalidomide. **Conclusions:** This real-world cohort shows that daratumumab-based maintenance post-ASCT is well tolerated and highly effective. Most patients achieved deep responses, with sustained PFS over time. Combination with lenalidomide (D-R), as used in PERSEUS, offers a clinically relevant option and allows for adjustment of treatment intensity based on individual response. Future clinical trials may consider evaluating treatment discontinuation in standard-risk patients with sustained MRD negativity.

PA-410

Cytarabine plus G-CSF as Second Attempt in Very Poor Mobilizer Myeloma Patients after Cyclophosphamide Plus G-CSF and Plerixafor: Efficacy of Peripheral Blood Stem Cell (PBSC) Collection

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Introduction: Daratumumab plus bortezomib, thalidomide and dexamethasone (D-VTd) strategy represents the current standard of care in transplant-eligible patients with newly diagnosed multiple myeloma (NDTEMM). Data from the trials, metanalysis and real-world experiences showed that, using conventional strategy with cyclophosphamide (CTX) combined with granulocyte colony-stimulating factor (G-CSF) and plerixafor, the median number of CD34+ collected was significantly lower in patients receiving D-VTd. We evaluated the efficacy and safety of cytarabine (Ara-C) plus G-CSF in the subgroup of poor mobilizer myeloma patients following historical mobilization strategy with CTX plus G-CSF and plerixafor.

Methods: This observational, retrospective study was conducted across 5 Italian centers. 19 patients affected by NDTEMM and treated with D-VTd induction regimen (8 F and 11 M - mean age 57.5 years [range 43–68]) were included in this analysis. The number of induction cycles was 4. One 57-year-old man patient with IgGλ MM, ISS stage I, had previously undergone chemotherapy using the R-CHOP scheme (rituximab, cyclophosphamide, epirubicin, vincristine and prednisone) due to asynchronous non-Hodgkin's lymphoma. All patients were treated with intermediate-dose CTX (2–4 g/m2) plus G-CSF (non-pegylated G-CSF only) at the dose of 5 µg/kg/day in the morning from d5 by subcutaneous injection. On day 12, prior to stem cell collection, only if peripheral CD34+ count was ≤20 µL, patients received 10 µg/kg/day G-CSF via two consecutive subcutaneous injections plus plerixafor (0.24 mg/kg/day) as a subcutaneous injection, without benefit. After the declaration of mobilization failure (CD34+ cell count < 20 µL), all poor mobilizer patients received a second chemo-based strategy to harvest stem cells. The chemotherapy consisted of ARA-C (800 mg/m2 d1 and d2 or 1.600 mg/m2 d1, according to the medical decisions) plus G-CSF 5 µg/kg/day in the morning from d5 until the day of apheresis. **Results:** All patients achieved adequate CD34+ cell collection without plerixafor. The median of CD34+ cells harvested was 7.6 × 106/kg (range 4.3–11.3), with 17/19 (89%) of patients yielding more than 5.0 × 106/kg. The median number of apheresis was 1 (range 1–2). No red blood cell and platelet transfusions were used. One patient (5%) had febrile neutropenia. 16/19 patients (84%) underwent transplant as planned, receiving a conditioning regimen with high-dose melphalan (200 mg/m2 d2), followed by infusion of autologous PBSC on day 0, and received G-CSF 5 µg/kg from d5 until neutrophil engraftment. The post-transplant course was regular. The time of neutrophil and platelet engraftment was 12 days (range 9–150) and 14 days (range 10–25), respectively. The median length of hospitalization was 21 days (range 17–22). **Conclusions:** Our study showed that the mobilization with Ara-C plus G-CSF, without plerixafor, was highly efficient and safe for patients with MM who were very poor mobilizers after CTX plus G-CSF and plerixafor.

PA-411

Daratumumab as Post-Asct Maintenance in Multiple Myeloma Patients with Lenalidomide Intolerance/Toxicity: Results From a Single Center Over the Last 5 Years

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Introduction: Maintenance therapy after autologous stem cell transplantation (ASCT) in multiple myeloma (MM) improves progression-free survival, with lenalidomide being the most commonly used agent. However, its use can be limited by intolerance or toxicity. Daratumumab, an anti-CD38 antibody with proven efficacy in MM, could be an alternative in these cases. This study describes the experience of a single center using daratumumab as maintenance therapy in patients not eligible for lenalidomide over the past five years. The objetive of this study is to evaluate the efficacy of daratumumab maintenance in terms of response and disease control in MM patients post-ASCT with intolerance/toxicity to lenalidomide. **Methods:** A retrospective, descriptive, single-center study (HU Príncipe de Asturias, Madrid) of MM patients receiving daratumumab maintenance post-ASCT from April 2020 to May 2025. Demographic, clinical, laboratory data, and treatment response were analyzed. Clinical management was conducted according to the recommendations of the Spanish Myeloma Group. **Results:** Seven MM patients who received daratumumab maintenance after ASCT due to lenalidomide intolerance or toxicity were included. The median age was 58 years (interquartile range [IQR] 53.5–60), with a female predominance (57.1%). High-risk cytogenetics were present in 85.7%, and 71.4% were ISS-R stage 2. The most common MM subtypes were IgG Kappa and Kappa light chain (28.6% each). Pre-ASCT treatment included bortezomib- and daratumumab-based regimens. Daratumumab was administered prior to transplantation in 42.9% of patients. Conditioning regimens were MEL-200 (71.4%) or BUMEL (42.9%). At day +100 post-ASCT, 3 patients (42.9%) were minimal residual disease (MRD) positive, 2 were negative, and 2 had no available information. The median duration of daratumumab maintenance was 24 months (IQR 18–28). At the last evaluation, 3 patients (42.9%) remained MRD positive and 4 had no available data. No biochemical progression was detected during treatment in any case. Three patients completed therapy without evidence of progression to date. **Conclusions:** In our experience, daratumumab as post-ASCT maintenance therapy in MM patients with lenalidomide intolerance/toxicity was associated with good disease control, no biochemical progression during follow-up, and adequate tolerance. These results support its use as a safe and effective alternative in this clinical context.

PA-412

Optimization of Post-Autologous Hematopoietic Stem Cell Transplant (Asct) Maintenance Therapy in Multiple Myeloma (Mm): Analysis of a Single-Center's Results Over the Last 5 Years

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Introduction: In recent years, treatment for patients under 70 years with multiple myeloma (MM) has evolved toward a 4-drug immunochemotherapy regimen, followed by autologous stem cell transplantation (ASCT) and a maintenance therapy for at least 2 years, typically with lenalidomide (LEN) monotherapy. However, in cytogenetically high-risk (HR) MM or suboptimal responses, this approach may be insufficient. The phase III AURIGA study showed that maintenance with daratumumab (DARA) plus LEN in patients with measurable residual disease (MRD)-positive status after ASCT improved MRD negativity rates and prolonged progression-free survival (PFS) compared to LEN alone. The objetive is to analyze post-ASCT maintenance treatments administered to MM patients at our center, focusing on their impact, especially in cytogenetically HR MM. **Methods:** Retrospective, single-center observational study (HU Príncipe de Asturias) conducted from April 2020 to May 2025 on MM patients receiving post-ASCT maintenance therapy. Clinical and cytogenetic data, type of treatment and outcomes were collected. **Results:** 23 MM patients were included, with a median age of 58 years(IQR 48–68); 74% were male and 14 (61%) had cytogenetic HR features. Most patients (69.6%) received only one prior line of therapy (56.5% had not received DARA during induction). Maintenance therapies were: DARA-LEN (48%), DARA alone (30%) and LEN monotherapy (13%). 52% had completed maintenance and 78% showed no clinical or biochemical evidence of disease progression. Among the 19 patients who received DARA-LEN or DARA, 4(21%) experienced disease progression. Among patients (3) who received LEN monotherapy, 1 (33%) showed progression. In the HR subgroup who received induction without daratumumab (n = 8), the maintenance regimen was DARA-LEN (62.5%), DARA (25%) and LEN (12.5%). Serial MRD evaluations on day +100 post-ASCT and after 1 or 2 years revealed: persistent MRD positivity (n = 3), sustained MRD negativity (n = 1), MRD negativity turning positive at 2 years (n = 1) and incomplete follow-up data in 3 cases. 3 patients (37%) experienced disease progression(1 during maintenance and 2 after it), while 62.5% remained progression-free. Among HR patients who received daratumumab during induction (n = 6), maintenance regimens were DARA (50%), DARA-LEN (33.3%), and LEN (16.7%). Only one had MRD positivity at day +100 and after 2 years, with evident clinical progression. In this subgroup, 66.6% had MRD negativity at day +100 post-ASCT, one had MRD negativity at 1 year and 5 patients (83.3%) remain progression-free. In summary, among patients receiving DARA-LEN or DARA maintenance the progression rate was 21% (17.6% in HR patients) compared to 33% in those receiving LEN monotherapy. **Conclusions:** Maintenance therapy with DARA (either alone or with LEN) appears effective with a lower progression rate compared to LEN monotherapy—even among cytogenetically HR patients. Our findings suggest that post-ASCT daratumumab remains beneficial even in previously exposed patients.

PA-413

Impact of Cumulative and Relative Dose Intensity of Bortezomib, Lenalidomide, and Dexamethasone (VRD) on Depth and Duration of Response in Newly Diagnosed Multiple Myeloma (MM)

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Introduction: Although VRD is a widely used standard of treatment for newly diagnosed MM, the cycle schedules and number of cycles to administer vary across different trials. The actual impact on outcome of the cumulative dose and dose intensity in different treatment regimens has not been explored in detail. This substudy evaluates the individual cumulative doses and dose intensity of bortezomib, lenalidomide, and dexamethasone in newly diagnosed MM patients treated with VRD (bortezomib, lenalidomide, dexamethasone) in an institutional prospective trial (EudraCT: 2019-002626-67) using up to eight 4-week cycles of VRD. **Methods:** The trial recruited 360 patients with newly diagnosed MM across several centres from a single institution. Individuals with full dosing information, receiving at least 8 weeks of treatment and two or more treatment cycles (N = 304; 84%) were eligible for this substudy. VRD schedule consisted of 8 cycles of lenalidomide (len) 25 mg/day 21/28 (adjusted if renal insufficiency), bortezomib (btz) 1.3 mg/m2 days 1,4,8,11 and dexamethasone (dex) 20 mg days 1,2,4,5,8,9,11,12 (half dose for patients > 70 years). Irrespective of age, autologous stem cell transplantation (SCT) was offered to patients considered eligible and was performed after cycle 6. Dosing data for bortezomib, lenalidomide, and dexamethasone included the cumulative dose across all cycles and were expressed as percent of maximal dose per schedule, dose intensity was calculated as the dose of each individual drug divided by the total duration of the 8 cycle treatment. We evaluated the association of cumulative doses and dose intensities with depth of response per IMWG criteria and duration of response (DoR) defined as time from partial response to relapse or

death from any cause. **Results:** Patients age ranged from 31 to 88 years old (median 62) and 166 were male (55%), 18% had a creatinine clearance < 30 ml/min. Mean treatment duration was 47.5 weeks (for patients receiving SCT) and 29.7 weeks (non-SCT). Older patients (>70 years) received significantly lower cumulative doses of all drugs, btz 72% (Standard Deviation 23) vs 83% (SD 21), len 60% (SD 28) vs 78% (SD 26) and dex 39% (SD 13) vs 77% (SD 25), $p < 0.0001$ all comparisons. Partial response or better was achieved in 299/304 cases (98%), Cumulative doses below 75% of btz, len or dex were all associated with lower probabilities of achieving VGPR or better, 75 vs 91%, 82 vs 89% and 80 vs 93% for btz, len and dex respectively ($p < 0.001$ all comparisons). Median DoR was 5 years and cumulative doses below 75% were again associated to shorter DoR ($p < 0.001$). **Conclusions:** Dose reductions of btz, len or dex below 75% expected cumulative dose were associated wih lower rates of CR and shorter duration of response. Our findings highlight the critical relevance of treatment optimization and toxicity management to maintain full induction treatment.

PA-414

Cost per Responder Model of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) for Transplant-Ineligible or Transplant-Deferred Newly Diagnosed Multiple Myeloma

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Introduction: In the phase 3 CEPHEUS trial, eight 21-day cycles of subcutaneous daratumumab (D) with bortezomib (V), lenalidomide (R), and dexamethasone (d) followed by monthly DRd until progression (DVRd/DRd) was associated with a higher rate of minimal residual disease (MRD) negativity compared to eight 21-day cycles of VRd followed by monthly Rd until progression (VRd/Rd) in patients with transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma (TIE or TD NDMM; 60.9% vs 39.4% at 58.7 months; $p < 0.0001$). An economic assessment of the value associated with achieving and sustaining MRD-negative status with DVRd/DRd versus VRd/Rd was conducted. **Methods:** CEPHEUS trial data were used to develop a cost per MRD-negative patient model from a United States (US) mixed payer perspective (80% Medicare, 20% commercial). Model inputs included costs for first-line (1L) and second-line (2L) drug acquisition, medical visits, MRD testing, and adverse event management. Cost per MRD-negative patient was calculated using the cumulative proportion of patients achieving MRD-negative status (10-5 threshold) at 60 months after randomization. Cost per patient achieving sustained MRD negativity (i.e., MRD-negative for ≥12 months) was calculated using the proportion of patients with MRD-negative status on ≥2 occasions that were ≥12 months apart during the 60 months post-randomization. Costs were reported in 2025 US dollars. **Results:** At 60 months, the total cost per MRD-negative patient was $640,189 lower for the DVRd/DRd cohort compared to the VRd/Rd cohort. The key drivers for these cost savings were 1) the higher proportion of patients achieving MRD-negative status in DVRd/DRd cohort (60.9%) vs VRd/Rd cohort (39.4%) and 2) the lower 2L treatment costs per MRD-negative patient for the DVRd/DRd cohort ($186,371) compared to the VRd/Rd cohort ($958,840), attributable to the lower proportion of patients having progressed to 2L treatment in the DVRd/DRd (11.2%) vs VRd/Rd cohort (33.3%). The cost per patient achieving sustained MRD-negative status was $1,964,539 lower for the DVRd/DRd cohort relative to the VRd/Rd cohort, primarily attributable to the higher proportion of patients achieving sustained MRD negativity with DVRd/DRd (48.7%) than VRd/Rd (26.3%), and to the lower 2L treatment costs per patient achieving sustained MRD-negative status for the DVRd/DRd cohort ($233,060) compared to the VRd/Rd cohort ($1,436,436). **Conclusions:** DVRd/DRd was associated with a lower cost per MRD-negative patient, and cost per patient achieving sustained MRD-negative status compared to VRd/Rd in patients with TIE or TD NDMM. These findings provide evidence of the economic value of 1L DVRd/DRd, complementing the superior efficacy benefits observed compared to VRd/Rd in the CEPHEUS trial.

PA-415

Definition of Transplant Ineligibility in Newly Diagnosed Multiple Myeloma: A Systematic Review

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Introduction: High dose melphalan followed by autologous stem cell transplantation (ASCT) has been the standard of care for eligible patients with newly diagnosed myeloma (NDMM). A substantial proportion of patients are deemed ineligible for ASCT due to age,

comorbidities, functional status, or frailty. Criteria defining transplant ineligibility remain inconsistent and poorly characterized. This systematic review examined randomized controlled trials (RCTs) in transplant-ineligible NDMM, focusing on how transplant ineligibility is defined. **Methods:** This study built on a previously published systematic review, the protocol for which is registered on Open Science Framework. We included phase II and III RCTs that exclusively enrolled transplant-ineligible NDMM patients published through October 2023. For each study, we collected data on reported criteria for transplant ineligibility and patient characteristics in the main manuscript and/or protocol/supplement. **Results:** Of 264 identified RCTs, 50 (19%) exclusively enrolled transplant-ineligible patients (88% available as full manuscripts). Study protocols and supplementary data allowing for detailed analysis of enrollment criteria were available for 32 studies (64%). Among 50 transplant-ineligible trials, only 22 (44%) explicitly defined ineligibility criteria. Of these, 20 (40%) trials used age as a cut-off with/without other criteria including: age alone (n = 1, 2%), combination of age/comorbidities (n = 15, 30%), age/comorbidities/personal preference (n = 2, 4%), age/significant comorbidities/insufficient stem cells/patient preference (n = 1, 2%), and age/no access due to cost or other reasons/patient preference (n = 1, 2%). The remaining two trials (4%) used investigator judgment (n = 1, 2%), and comorbidities/patient preference (n = 1, 2%). Notably, only two studies explicitly specified which comorbidities constituted transplant ineligibility. All trials using age cut-offs for transplant ineligibility (n = 20, 40%) uniformly applied a threshold of ≥65 years. The median age of participants in these trials ranged from 62 years to 78.5 years, with an increasing trend over time (p = 0.003). While 58% of trials reported ECOG or Karnofsky performance status, none utilized these scores as formal criteria for transplant ineligibility. Among a total of 14 trials (28%) that reported enrolling patients with ECOG 3–4, these patients represented 1–26% of enrolled patients. Standardized frailty tools were employed in 24% of studies (IMWG 16%, simplified frailty score 8%). **Conclusions:** RCTs enrolling transplant-ineligible patients with NDMM demonstrated considerable variety in defining ineligibility. This heterogeneity in eligibility criteria has important implications for interpreting trial results and clinical practice. While the decision to pursue transplantation should remain individualized, the absence of consistent, evidence-based definitions of transplant ineligibility complicates both research interpretation and clinical decision-making.

PA-416

Optimizing Belantamab Mafodotin Doses for the Treatment of Transplant-Ineligible Newly Diagnosed Multiple Myeloma in the DREAMM-9 Study

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Introduction: DREAMM-9 (NCT04091126), an ongoing randomized Phase 1 dose and schedule evaluation study, assessed belantamab mafodotin (belamaf) + bortezomib, lenalidomide, and dexamethasone (VRd) in autologous stem cell transplant (ASCT)-ineligible newly diagnosed multiple myeloma (TI NDMM). Early, deep anti-myeloma responses and no unexpected safety signals were reported for all cohorts.1 Here we report data on doses and schedules in 3 cohorts that support dose recommendations for TI NDMM. **Methods:** Patients (pts) ≥18 years (yrs) ineligible for ASCT and with no prior MM treatment were dosed in cohorts with differing belamaf doses/schedules. All cohorts received belamaf and standard VRd for Cycles 1−8 (21-day cycle), then Rd for Cycles 9+ (28-day cycle). Primary endpoint was safety/tolerability. Efficacy endpoints included overall response rate (ORR, % of pts with a confirmed partial response or better); complete response rate (CRR, % of pts with a complete response or better [>CR]); and minimal residual disease negativity rate (MRD[-], % of pts with >CR and reached MRD negativity at 10-5 threshold by next-generation sequencing). Responses were assessed per International Myeloma Working Group criteria (2016). **Results:** As of Mar 4, 2024, a total of 108 pts were enrolled in 8 cohorts1: 12 pts were treated in each of the 1.9 mg/kg Q3/4W (1.9 SHORT),

1.9 mg/kg Q6/8W (1.9 STRETCH), and 1.4 mg/kg Q6/8W (1.4 STRETCH) cohorts. ORR % (CRR %) was 100 (75)/100 (92)/100 (91), respectively. Median time (months) to >VGPR was: 1.9 SHORT, 2.8; 1.9 STRETCH, 2.9; 1.4 STRETCH, 2.1. In pts with >CR, MRD[-] rates were 100% (n = 9)/73% (n = 8)/50% (n = 5). Of the pts who received ≥1 dose of belamaf, 67% (n = 8)/25% (n = 3)/33% (n = 4) of pts in the 1.9 SHORT/1.9 STRETCH/1.4 STRETCH cohorts had Grade 3+ (Gr3+) belamaf-related AEs. Ocular exam findings (Gr3+) based on keratopathy and visual acuity scale were reported in 83% (n = 10)/92% (n = 11)/75% (n = 9) of pts, respectively, comprising 26%/10%/18% of all assessments. AEs led to belamaf dose interruptions/delays in 83% (n = 10)/75% (n = 9)/83% (n = 10). Belamaf dose reductions were seen in 42% (n = 5)/83% (n = 10)/42% (n = 5) of affected pts. Median (days) time to first bilateral decrease in BCVA to 20/50 or worse in pts with 20/25 or better in ≥1 eye at baseline was longer with Q6/8W schedules (1.9 STRETCH, 245.5; 1.4 STRETCH, 263.5) than Q3/4W (1.9 SHORT 76.0): these BCVA decreases resolved in a median of 1.4 STRETCH 70.0, 1.9 STRETCH 135.0, and 1.9 SHORT 163.0 days. **Conclusions:** Of the cohorts described the results indicate that belamaf + VRd induced deeper MRD[-] responses at the higher initial dose (1.9 mg/kg), with improved tolerability at the longer schedules (Q6/8W). In line with Terpos et al2, these data show that belamaf 1.9 mg/kg with an extended schedule achieved the positive benefit: risk ratio for the treatment of pts with TI NDMM. 1. Usmani et al. Blood, 2024 2. Terpos et al. Haematologica, 2024. **Funding:** GSK (209664).

PA-417

Evaluating a Value-Based, Measurable Residual Disease (MRD) - Focused Clinical Pathway in Patients with Newly Diagnosed Multiple Myeloma

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Introduction: Widespread variation in myeloma treatment adversely affects patient outcomes. All4Cure is a collaborative ecosystem for oncology of patients, clinicians and researchers that developed a clinical pathway for NDMM to achieve and maintain MRD negativity. This report describes an observational cohort study that examines the outcomes of NDMM patients treated On- vs. Off-Pathway, and an interim analysis following accrual of 225 patients (out of 450), focusing on baseline demographic, clinical and treatment characteristics. **Methods:** Data were collected retrospectively from electronic medical records of NDMM patients initiating treatment at community oncology practices ≥4/18/2024. Patients were classified into three cohorts: On-Pathway Platform (enrolled in All4Cure, n = 10), On-Pathway Documentation (pathway available via All4Cure's website, n = 128), and Off-Pathway (n = 87), using a pathway adherence scoring system that includes use of an anti-CD38 antibody in front-line treatment. Baseline demographics, clinical characteristics, and comorbidities were compared. Therapy regimens and treatment sequences were also analyzed. **Results:** Median age at diagnosis was 68 years; 141 (63%) were male, 147 (65.3%) were white and 34 (15.1%) were black. No significant demographic differences between cohorts were observed. Sixty percent of Platform patients, and 77.3% of Documentation patients were eligible for transplant vs. 59.8% in Off-Pathway (p = 0.018). Other clinical characteristics (e.g. subtype, cytogenetics) were similar across groups. The most common comorbidities were hypertension (n = 162, 72%), renal disease (n = 93, 41.3%), and diabetes (n = 50, 22.2%), without significant differences between cohorts. Front-line treatment included 15 distinct regimens. Nearly half of patients (46% overall, 53.5% for combined On-Pathway cohorts vs. 34.5% for Off-Pathway cohort p = 0.0066) were treated with a 4-drug regimen (anti-CD38 antibody, IMID, proteasome inhibitor and dexamethasone). Three-drug regimens with lenalidomide, bortezomib and dexamethasone were used in 14.6% overall (2.3% On-Pathway vs. 33.3% Off-Pathway, p < 0.0001), and 2-drug regimens containing lenalidomide or bortezomib plus dexamethasone were used in 2.8% overall (0.8% On-Pathway vs. 6% Off-Pathway, p = 0.0363). The group differences are an expected consequence of the pathway adherence scoring. **Conclusions:** This real-world study showed no difference in most demographic and clinical characteristics across cohorts defined by adherence to a clinical pathway. Wide variability in front-line treatment was observed, with fewer than half of patients receiving the current 4-drug standard of care. Consistent with the study design, On-Pathway patients were 55% more likely to receive an anti-CD38 based quadruplet regimen. As follow-up data accrue, this study will assess whether clinical pathway adherence leads to improved MRD-negativity and other effectiveness outcomes in patients treated at community oncology centers.

PA-418

Mortality and Trends of Multiple Myeloma in Brazil: A 27-Year Analysis

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy primarily affecting older adults. Global disparities in diagnosis, access to care, and mortality are well documented, particularly in low- and middle-income countries. In Brazil, socioeconomic and geographic heterogeneity may influence

outcomes. Understanding long-term trends and demographic patterns is critical for developing equitable public health strategies. **Methods:** An ecological study was conducted using mortality data from the Mortality Information System (SIM) and population estimates from Brazilian Institute of Geography and Statistics (IBGE). Mortality rates due to MM aged ≥40 years between 1997 and 2023. Analyses included stratification by sex, age, race, region, and occupation. Trends were assessed by Joinpoint regression and age-period-cohort (APC) models were used to explore the effects. **Results:** A total of 63,105 deaths were recorded in Brazil. Men accounted for 51.2% of deaths. Age-adjusted mortality increased from 0.40 per 100,000 in 1997 to 0.85 in 2023. Race analysis showed that white individuals accounted for 60% of deaths, followed by mixed-race (26%) and Black individuals (7.8%). Workers in and construction (10%) had elevated mortality followed by agriculturists and workers in livestock, forestry, and fishing (8.2%). For the cohort, there is an increase in relative risk in males (1990) and a recent rise among females (male RR 1.45; female RR 1.53). There was a decline trends for males [(−1.87%); CI: −2.52; −1.19)] and less for females [(−0.43%); CI: −0.65; −0.21)], with sharper declines in ages 40–49 (men: −2.22%; women: −2.83%). **Conclusions:** Mortality from MM in Brazil rose overall from 1997 to 2023, more in males and less in females. Elevated mortality was found among construction workers and white race. These findings underscore the urgent need for targeted policies addressing occupational exposures, regional inequalities, and timely access to diagnosis and treatment.

PA-419

Retrospective Analysis of Newly Diagnosed Multiple Myeloma Patients with Partial or Worse Response to First-Line Induction Therapy

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Introduction: A small proportion of newly diagnosed multiple myeloma (NDMM) patients do not respond to initial treatment and show adverse outcomes even in the absence of traditional high-risk factors. This study aimed to examine the clinical characteristics, prognosis and factors affecting survival of patients who did not respond adequately to induction therapy. **Methods:** Between January 2015 and December 2022, a total of 176 patients had been diagnosed MM and initially treated with bortezomib and 52 of them had a partial (PR) or worse response to first-line induction therapy containing bortezomib and were included in the study. Information on demographics, laboratory results, imaging, pathology, response and survival was recorded and analysed retrospectively. **Results:** Fifty two patients with PR or worse (34 male and 18 female) had a median age of 60. The overall response rate (ORR) to induction therapy was 84.6%; PR and worse response rate was 29.6% and primary refractory disease rate was 7.3%. The mean overall survival (OS) from start of therapy was 67.4 months (95% CI: 56.5–78.3) and the mean progression-free survival time (PFS) was 27 months (95% CI: 19.5–34.6). The mean OS was shorter in patients who progressed under first-line induction therapy (76.1, 76.9, 58.7 and 30.6 months for PR, MR, SD and PD, respectively; $p = 0.005$). The mean OS of patients who achieved worse than PR and ≥PR after lenalidomide containing therapy was 43 months and 79 months, respectively ($p = 0.012$) and the mean PFS was 10 months and 33 months, respectively ($p = 0.001$). Overall and progression-free survival (OS-2 and PFS-2) after autologous stem cell transplantation (ASCT) were also found to be shorter in lenalidomide-refractory patients ($p = 0.015$ and $p = 0.042$, respectively). The presence of secondary extramedullary disease (EMD) and high risk cytogenetic abnormalities were associated with decreased overall survival ($p = 0.052$ and $p = 0.006$, respectively). Age over 65 years and secondary extraosseous EMD were independently associated with mortality (HR: 5.2; 95% CI: 1.7–16.4; $p = 0.004$ and HR: 12.4; 95% CI: 3.3–46.6; $p < 0.001$, respectively). Increased complete response rates ($p = 0.016$) and improvement in overall survival were demonstrated in the ASCT group ($p = 0.007$). **Conclusions:** Fifty two patients (29.6% of patients) had ≤ PR and 7.3% of patients had refractory disease under bortezomib based induction therapy. Failure to respond to induction therapy negatively affected survival. ASCT is an effective treatment option in this group.

PA-420

Real-World (RW) Outcomes of Newly Diagnosed Multiple Myeloma (NDMM) Patients (pts) Treated with Front-Line Daratumumab (dara) Lenalidomide (len) and Dexamethasone (dex) (DRd)

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Introduction: The phase III MAIA trial evaluated DRd vs. Rd in NDMM pts that were transplant ineligible (TI). Little is known about the efficacy of DRd in RW practice including modifications of DRd treatment and subsequent treatment after progression on DRd. We aim to evaluate the RW efficacy of NDMM pts treated with DRd

across the tri-site Mayo Clinic Comprehensive Cancer (MCCC). **Methods:** We retrospectively analyzed the medical records of pts treated with DRd between January 2016 and July 2023 at the MCCC. Outcomes were estimated using the Kaplan-Meier method. **Results:** 202 pts were included; 128 pts were male, and the median age of MM diagnosis was 75.42 pts had ISS III, 37 pts had R-ISS III, 87 pts had high risk FISH, 20 pts had extramedullary disease, 33 pts had ultra high-risk disease, 18 pts had renal insufficiency (RI) with creatinine >2 mg/dL.Starting len dose was 25 mg in 97 pts, 15 mg in 51 pts and ≤10 mg in 52 pts. 20 pts received dara IV, 179 received dara SQ. 51 pts received 1–2 cycles of a different regimen prior to DRd due to hospitalization (n = 5), RI (n = 12), poor performance status (n = 17), other (n = 18). The ORR was 91% with 130 achieving ≥VGPR and 32 (of 63 evaluable) achieving minimal residual disease negativity in the bone marrow to at least 10-5. 129 pts were considered TI and 72 pts were considered transplant eligible (TE). At a median follow-up (f/u) time of 27 mo, the median PFS of pts who did not undergo transplant (ASCT) was 43 mo, 4 yr PFS rate was 41.7%, and 4 yr OS rate was 43.9%. 28 TE pts underwent ASCT (26/28 received melphalan 200 mg/m2) and the median PFS was NR; at 47.1 mo of f/u, the PFS rate was 64.6%. 27 pts received post-ASCT maintenance therapy (tx); len (n = 12), dara (n = 1), len+ dara (n = 11), other (n = 3). 135 pts had modification (mod) of DRd. The median time from start of DRd to mod was 6 mo. DRd mod included len dose stopped/dropped (S/D) (n = 35), dex dose S/D (n = 23), both len and dex S/D (n = 62), dara and/or dex S/D, len continued (n = 19). Reasons for DRd mod included len toxicity (tox) (n = 47), dex tox (n = 10), len and dex tox (n = 9), other (n = 71). The median PFS for TI pts with DRd mod was 48 mo and was 14 mo for pts who did not have DRd mod, $p < 0.001$. Pts with DRd mod stayed on DRd 3x as long (15.7 mo) compared to those w/o mod (5.7mo). The median PFS for TI DRd treated pts with RI was 37 mo compared to 43 mo for pts without RI, $p = 0.70$. 45 pts relapsed after DRd tx. Median f/u time since relapse after DRd was 13 mo and the most common subsequent therapies included bortezomib (V)-DRd (n = 5), Dara-Vd, DRd, V-pomalidomide (P)-dex, and carfilzomib-P-dex in 4 pts each. PFS rate at 12 mo with post-DRd tx was 74%. **Conclusions:** In this RW analysis, the efficacy and survival outcomes of TI NDMM pts treated with DRd was comparable to that reported in the MAIA trial.

PA-421

Treatment Accessibility, Availability, and Healthcare Costs for Multiple Myeloma in South Asian Countries

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Introduction: Regional disparities in multiple myeloma (MM) care is leading to variable outcomes in South Asia. This study assesses the availability, accessibility, and cost of MM treatments in South Asian countries to identify gaps in care and inform healthcare policy. **Methods:** A cross-sectional, descriptive study was conducted through a web-based survey targeting physicians managing MM patients in Bangladesh, Bhutan, India, Maldives, Myanmar, Nepal, Pakistan and Sri Lanka. The survey covered institutional healthcare structures, drug availability, treatment regimens, diagnostic access, and patient out-of-pocket expenditures (OOPE). Data were analyzed to evaluate disparities in MM care across public and private healthcare sectors. **Results:** Public and private healthcare institutions coexist in all studied countries except Bhutan, where MM care is primarily public. Physicians reported a high OOPE for MM treatment, with patients covering an average of 70% of total medical costs. Key diagnostic investigations such as serum protein electrophoresis, immunofixation, and free light chain assays, were unavailable in public hospitals in 62.5% of the countries, while minimal residual disease estimation via flow cytometry was available publicly only in India. PET scans were available in public hospitals in India, Bangladesh, Sri Lanka and Pakistan but remained cost prohibitive. Lenalidomide and bortezomib were available in public institutions in 75% of the countries, while advanced therapies like daratumumab were largely restricted to private institutions in 62.5% of the countries. IV melphalan was unavailable in public institutions in 62.5% of the countries. Autologous stem cell transplant (ASCT) centers were reported in 75% of the studied countries; however, cryopreservation facilities were limited to 25% of the countries, and mobilization agents like plerixafor were accessible in 62.5% countries. The most commonly used first-line therapy for transplant-eligible patients in public institutions was VRd (bortezomib, lenalidomide, dexamethasone) in 50% of the countries, while private institutions more frequently incorporated daratumumab (VRd-D). Only India had a dedicated myeloma patient support group, whereas general oncology support groups were reported in 62.5% of the countries. **Conclusions:** There are significant disparities in MM treatment accessibility across South Asia. Public sector institutions often lack essential diagnostic tools and advanced therapies, forcing patients to rely on private healthcare at high OPE. Improved government policies, financial assistance programs, and public-private partnerships are needed to enhance drug accessibility, diagnostic infrastructure, and transplant availability.

PA-422

Frontline Bortezomib-Based Therapy and Autologous Hematopoietic Stem Cell Transplantation in Latin American Multiple Myeloma Patients: Insights from a Real-World Multinational Cohort

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Introduction: Anti-CD38 monoclonal antibodies have become a cornerstone in the management of newly diagnosed multiple myeloma (NDMM). However, due to limited access to novel agents in Latin America (LATAM), bortezomib-based triplets (BBT), followed by autologous stem cell transplantation (ASCT), remain the standard of care. This study aimed to evaluate real-world outcomes in NDMM patients across LATAM who received BBT and ASCT as frontline treatment. **Methods:** This was a retrospective, international, multicenter cohort study of patients with NDMM diagnosed between 2010 and 2023 and treated with BBT followed by ASCT. Responses were assessed according to the International Myeloma Working Group (IMWG) criteria. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier curves, and differences between groups were assessed using the log-rank test. Cox regression analysis was used to evaluate prognostic variables. **Results:** A total of 766 patients from 10 Latin American countries were included. The median age was 56 years, with 59% being male. The IgG subtype was predominant (59%). ISS and R-ISS stage II/III were observed in 62% and 68% of patients, respectively. The most common myeloma-defining events were bone lesions (79%), anemia (48%), hypercalcemia (18%) and renal failure (17%). Extramedullary disease was reported in 13% of cases. FISH testing was performed in 50% of patients, with high-risk cytogenetic features detected in 24% —the most common being del(17p) (13%), followed by t(4;14) (6%) and t(14;16) (2%). The regimens used were CyBorD (42%), VTd (30%), and VRd (28%). The use of VRd increased from 1.5% during 2010–2014 to 54% during 2020–2023. A very good partial response (VGPR) or better was achieved in 78% of patients treated with VRd and VTd, and in 61% of those treated with CyBorD ($p < 0.001$). The median time from diagnosis to ASCT was 274 days. Maintenance therapy was administered in 87% of patients, most commonly with lenalidomide (74%). With a median follow-up of 62 months, the median PFS and OS were not reached. The 5-year PFS was 53% (95% CI, 50–57%), and the 5-year OS was 82% (95% CI, 79–86%). No significant differences in OS ($p = 0.125$) or PFS ($p = 0.699$) were observed among the three induction regimens. In multivariate analysis, dialysis dependance ($p = 0.03$) and extramedullary disease ($p = 0.008$) were independently associated with inferior OS. **Conclusions:** To the best of our knowledge, this study represents one of the largest real-world evaluations of NDMM patients undergoing ASCT in LATAM. Treatment with BBT followed by ASCT yielded survival outcomes comparable to international benchmarks. The lack of survival differences among the three triplet regimens, despite showing different response rates, merits further investigation. In conclusion, this approach remains effective and represents a valid option for patients with NDMM in LATAM, especially when anti-CD38 monoclonal antibodies are not available.

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HIV and Multiple Myeloma: Do Patients Present at a Younger Age? A Perspective From a South African Orthopaedic Oncology Unit

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Introduction: Multiple Myeloma (MM) is the third most common haematological malignancy and the most common malignancy affecting the skeletal systems of the elderly. Skeletal-related events (SREs) such as hypercalcaemia, bone pain, spinal cord compression, and pathological fracture are common sequelae of Multiple Myeloma Bone Disease (MMBD) and are the reasons patients may consult an orthopaedic surgeon. It has been established that infection with the human immunodeficiency virus (HIV) increases one's risk of developing haematological malignancies. However, there is scant literature on how HIV infection affects MMBD, particularly from a South African perspective. We hypothesised that MMBD presents at a younger age and with more advanced disease in HIV-positive individuals. **Methods:** A retrospective single-centre descriptive study of patients with newly-diagnosed MM presenting with SREs to an orthopaedic oncology unit between 01 January 2016 and 31 December 2020. Patient demographic data (e.g., age, race and sex), biochemical and

histopathological results, and whole-body X-rays (WBXR) were collected for each participant. **Results:** Twenty-seven patients were included. The median age at presentation was 56 years (inter-quartile range, IQR: 49 − 47). Regarding HIV infection, 19% (n = 5) were HIV-positive, 45% (n = 12) were HIV-negative, and 37% (n = 10) had an unknown status due to absent screening. The age at presentation in HIV-positive patients was 44 years (IQR: 41–51); in HIV-negative patients, it was 58 years (IQR: 48–66). The difference in age at presentation between HIV-positive and HIV-negative patients was statistically significant, with a Kruskal-Wallis p-value of 0.041. Among HIV-positive patients, 60% (n = 3) presented with ISS stage III disease, while 50% (n = 10) of HIV-negative patients presented with ISS stage II disease, Fisher's exact p-value = 0.836; an insignificant difference. The presenting complaint was mainly a pathological fracture at 67% (n = 20), predominantly affecting the femur in 50% (n = 10). **Conclusions:** The majority of MM patients present to the orthopaedic surgeon with pathological fractures and commonly have more advanced disease. In the Sub-Saharan Africa setting, when treating a young HIV-infected individual with a pathological fracture, one should always consider MM as a likely diagnosis. Further research is needed to understand the real impact of HIV on MM, especially considering the small sample size (n = 27) and the significant percentage of patients with an unknown HIV status (37%) in our study.

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Daratumumab(Dara) Lenalidomide(R) Maintenance Following Dara-Carfilzomib(K)R Dexamethasone with Tandem Transplant in High-Risk Newly Diagnosed Myeloma Patients: Update of the Phase 2 Study IFM 2018-04

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Introduction: High-risk (HR) cytogenetic is associated with poor outcome in transplant eligible (TE) newly diagnosed multiple myeloma (NDMM). Quadruplet combination including carfilzomib lenalidomide and dexamethasone (KRd) with anti-CD38 plus transplantation demonstrated high efficacy in high-risk TE-NDMM patients (CONCEPT, Leypoldt et al. JCO 2023; IFM2018-04, Touzeau et al. Blood 2024). We present here the update of the phase 2 trial IFM 2018-04, including data from the maintenance phase (NCT03606577). **Methods:** HR MM was defined by the presence of del17p, t(4;14) and/or t(14;16). Treatment strategy included Dara-KRd induction (6 cycles), autologous stem cell transplantation (ASCT), Dara-KRd consolidation (4 cycles), second ASCT, Dara-lenalidomide (Dara-R) maintenance for 2 years. The primary endpoint was the feasibility of this intensive strategy. **Results:** Fifty patients with previously untreated NDMM were included from july 2019 to march 2021 in 11 IFM centers. Median age was 57 (range 38–65). Based on inclusion criteria, all patients had HR cytogenetic, including 17p deletion (n = 20, 40%), t(4;14) (n = 26, 52%) or t(14;16) (n = 10, 20%). Four (8%) patients had extramedullary disease. Efficacy and safety profile of induction, transplant and consolidation were previously reported (Touzeau et al. Blood 2024). With a median follow-up of 49 months, twenty patients (40%) discontinued treatment, due to stem-cell collection failure (n = 8), disease progression (n = 7), adverse event (n = 4), consent withdrawal (n = 1). Among the 36 patients who entered the maintenance phase, 6 patients discontinued treatment (disease progression, n = 5; grade 5 adverse event, n = 1). Most common treatment related adverse events (>15% of patients) during Dara-R maintenance were infections (86%), diarrhea (58%), asthenia (30%), peripheral neuropathy (19%) and neutropenia (19%). Grade 3–4 Dara-R maintenance related adverse events (>5% of patients) were neutropenia (14%) and infections (16%). One patient discontinued maintenance due to severe adverse event (grade 5 JC virus related encephalopathy). At data cut-off, the 4-year progression free survival was 72% (61–86) and the 4-year overall survival was 81% (70–93). Among the 5 patients with disease progression during maintenance, 4 had negative pre-maintenance Minimal Residual Disease (MRD) (NGS, 10-6), suggesting that MRD negativity might not prevent early relapse at the individual level for patients with HR disease. **Conclusions:** Dara-KRd induction/consolidation with tandem transplant and Dara-R maintenance continue to demonstrate high progression free survival in patients with high-risk NDMM.

PA-425

Enhancing GAH Score to Optimize Tolerance to Quadruplet Therapies in Multiple Myeloma: A Subanalysis of the GEM2017FIT Trial

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Introduction: The Geriatric Assessment in Hematology (GAH) scale, using a 42-point threshold, predicts treatment-related toxicity in hematologic neoplasms and helps guide frailty-adapted therapy. In the GEM2017FIT trial, transplant-ineligible multiple myeloma (MM) patients with GAH score of ≤42, received 18 induction cycles of either VMP/Rd (control), DKRd, or KRd (experimental). DKRd and KRd showed higher minimal residual disease negative after induction compared with VMP/Rd, meeting the primary endpoint. However, DKRd was associated with higher toxicity and toxicity-related mortality, particularly in patients with GAH >20. In contrast, KRd was better tolerated across all GAH scores. This finding raised the question of whether optimizing the GAH score could improve quadruplet tolerability and allow more patients to receive them. This analysis focused on the DKRd and KRd arms. **Methods:** We conducted a post hoc analysis of patients treated with DKRd or KRd in the GEM2017FIT trial. Patients were stratified as fit (GAH >20) or ultra-fit (GAH < 20). We analyzed GAH components contributing to fitness classification and assessed their modifiability. **Results:** Of 307 patients (153 DKRd, 154 KRd), 151 (49.3%) were fit and 155 (50.7%) ultra-fit, and were balanced across arms (DKRd: 75 fit, and 78 ultra-fit; and KRd: 77 fit, and 77 ultra-fit). No baseline differences were observed between groups. The main contributors to being classified as fit were abnormal mini nutritional assessment short form (MNA-SF, 48.7%) and any dependence on activities of daily living (ADL, 46.7%). Other GAH components (polypharmacy, gait speed, mental and physiological status, comorbidities) did not significantly differ. In the DKRd arm, fit patients more often had abnormal MNA-SF (47.3% vs. 0.0%, $P < 0.001$) and ADL dependence (51.4% vs. 0.0%; $P < 0.001$) as compared with ultra-fit patients. KRd arm showed similar results (abnormal MNA-SF: 49.4% vs. 0.0%, $P < 0.001$; ADL dependence: 44.2% vs. 0.0%, $P < 0.001$). Notably, certain items of MNA-SF and ADL dependence (GAH score: 40 and 22 points, respectively) are potentially modifiable, offering an opportunity to optimize the overall GAH score. With target interventions, 75/151 fit patients (49.7%) could become ultra-fit: 42/75 (56.0%) in the DKRd arm and 33/77 (42.9%) in the KRd arm. Nutritional improvement could reclassify 47/151 fit patients (31.1%, 26 in DKRd and 21 in KRd), while ADL-focused physical interventions could benefit 28/151 fit patients (18.6%, 16 in DKRd and 12 in KRd). **Conclusions:** Nutritional status and ADL dependence were the key GAH domains driving fitness classification in MM patients treated with DKRd or KRd. Both are potentially modifiable and, if addressed, could reclassify nearly half of fit patients as ultra-fit, thereby optimizing their ability to tolerate and benefit from quadruplet therapies. A multidisciplinary approach is essential to target these domains, improving treatment eligibility and outcomes in older patients.

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Geriatric Assessment in Hematology-Guided Selection for Quadruplet Therapy in Transplant-Ineligible Myeloma. A Post Hoc Analysis from GEM2017FIT Trial

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Introduction: The Geriatric Assessment in Hematology (GAH) scale, using a 42-point cutoff, predicts toxicity and helps guide frailty-adapted therapy in hematologic malignancies. Its role had not been evaluated in the context of novel agents for multiple myeloma (MM). The GEM2017FIT trial included transplant-ineligible MM patients with GAH score ≤42, treated with 18 induction cycles of VMP/Rd (control) or DKRd and KRd (experimental). The trial met its primary endpoint, showing significantly higher minimal residual disease (MRD) negativity rates with DKRd and KRd compared to VMP/Rd. Also, a GAH score < 20 could represent a clinically relevant threshold to identify patients with better tolerability to quadruplet combinations (Mateos, Lancet Haematol 2025). **Methods:** Patients in the GEM2017FIT trial were classified as ultra-fit (GAH <20) or fit (GAH >20). A post hoc analysis was conducted to assess toxicity and efficacy. **Results:** Of 461 patients, 240 were ultra-fit (52.1%) and 221 fit (47.9%), evenly distributed across arms (VMP/Rd: 85 ultra-fit and 69 fit; DKRd: 78 ultra-fit and 75 fit; KRd: 77 ultra-fit and 77 fit). Baseline characteristics were comparable among groups. Overall, 11.9% of patients experienced toxicity leading to discontinuation or toxicity-related death, with no differences by fitness group. Notably, in the DKRd arm, ultra-fit had lower rates of severe toxicity/toxicity-related death than fit patients (7.7% vs. 18.7%, P = 0.037). No differences were seen in other arms. In the intention to treat population, MRD negativity was similar in ultra-fit and fit patients (47.9% vs. 46.6%, P = 0.331). Among ultra-fit patients, DKRd attained superior MRD negativity (69.2%) than VMP/Rd (28.2%) (P < 0.001) and KRd (44.6%) (P = 0.007). In fit patients, DKRd showed improved MRD negativity (53.3%) over VMP/Rd (24.6%) (P < 0.001) but comparable to KRd (55.4%) (P = 0.426). In the DKRd arm, ultra-fit patients achieved higher MRD negativity than fit patients (P = 0.043). These differences were not shown with VMP/Rd (P = 0.615) or KRd (P = 0.146) Progression-free survival (PFS) was similar between ultra-fit and fit patients (not reached (NR) vs. 53.9 months, P = 0.195). In ultra-fit patients, DKRd resulted in prolonged PFS (NR) compared to VMP/Rd (NR, P = 0.051) or KRd (NR, P = 0.045), whereas no differences were shown in fit patients. In the DKRd arm, ultra-fit patients had significantly longer PFS than fit patients (NR in both, P = 0.038). A similar benefit was seen with VMP/Rd (NR vs. 41.0 months, P = 0.046), but not with KRd (NR vs. 53.9 months, P = 0.077). **Conclusions:** The GAH scale effectively identified patients eligible for triplet and quadruplets combinations. A GAH score <20 further defined a subset of patient suitable for quadruplets, which led to higher MRD negativity and longer PFS with acceptable toxicity. These results suggest that addressing modifiable GAH dimensions may enhance patient fitness, broaden access to intensive therapies and improve clinical outcomes.

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Optimizing The Alcyone Trial: Efficacy Of Daratumumab And Bortezomib Maintenance In Transplant-Ineligible Newly Diagnosed Multiple Myeloma Patients Post Dvmp Induction, 2 Year Analysis

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Introduction: Daratumumab (D) has represented a paradigm shift in the treatment of transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM), as shown in the ALCYONE and MAIA trials. Although no head-to-head comparison between daratumumab, bortezomib, melphalan and prednisone (DVMP) and daratumumab, lenalidomide and dexamethasone (DRd) exists, both achieved comparable rates of minimal residual disease (MRD) negativity. However, median progression-free survival (PFS) with DVMP is shorter than DRd (≈3 vs. ≈5 years), possibly due to differences in maintenance strategies: D monotherapy in ALCYONE vs. continuous DRd in MAIA. In this context, the Spanish Myeloma Group investigated whether continuous double maintenance with D and bortezomib (DV) after DVMP induction could improve outcomes. Here, we present the updated results after 2 years of DV maintenance. **Methods:** In this prospective, multicenter observational study, TIE NDMM patients received DV maintenance (D 1800 mg SC monthly + bortezomib 1.3 mg/m² SC biweekly) after 9 cycles of Dara-VMP, until progression or unacceptable toxicity. The data cut-off was April 30, 2025. **Results:** A total of 118 patients were enrolled (Nov 2021–May 2023). Median age was 77 years (range, 65–90), 78% were ≥75 years. Twenty-six percent had an International Staging System (ISS) 3 and 34% high-risk cytogenetics. Notably, 33 patients (27.9%) would have been excluded from the ALCYONE trial, mainly due to an estimated glomerular filtration rate < 40 ml/min (27/33, 81.8%). The rate of a very good partial response or better after induction was 62%, increasing to 78% after 1 year of maintenance and 81% after 2 years. In the MRD-evaluable population (n = 53), 45% achieved MRD negativity. After a median follow-up of 32 months (range, 7–55), the 2-year PFS and overall survival (OS) were 73% and 90%. No significant differences in response or survival were seen by ISS or cytogenetics risk. Comparative data with the ALCYONE trial will be presented at the meeting. During maintenance, 87 (74%) patients experienced adverse events (AE), and 32 (27%) serious adverse events (SAE). A total of 304 AEs and 51 SAEs were reported. Infections, especially respiratory tract, were the most common (AEs: n = 117, 39%; and SAE: n = 23, 45%). Hematologic, cardiac or neurologic toxicity and secondary malignancies were uncommon (<5%). Only 3 patients were discontinued due to toxicity (1 DV; 2V), with no toxicity-related deaths. **Conclusions:** After 2 years of DV maintenance following DVMP in TIE NDMM patients showed sustained efficacy with manageable safety profile, even in an older and challenging population. While longer follow-up is needed, this strategy may represent a valuable option for patients who are ineligible for quadruplet therapies and/or intolerant to lenalidomide.

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Clinico-Hematological and Cytogenetic Profile of Multiple Myeloma Patients in a North Indian Tertiary Care Hospital

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Introduction: Multiple myeloma (MM) is the 2nd most common hematological malignancy, relapsing and remitting in nature. Although treatments are evolving, MM remains incurable, with rapidly increasing incidence. Clinical presentation, molecular variability, and geographical and ethnic factors impact outcomes. This study aims to provide a clinico-hematological profile of MM patients at presentation in a tertiary care hospital in North India. **Methods:** This retrospective cross-sectional study included 99 MM patients diagnosed between 2020 and 2024 at a North Indian tertiary care hospital. Data was collected from electronic medical records and analyzed using SPSSV20.2. **Results:** Among the 99 patients, 58 were male. The median age was 64 years (range 41–98). Symptoms at presentation included bone pain/fractures (38.4%), weakness (34.3%), and renal dysfunction (23.2%). Major comorbidities were hypertension (40.4%) and diabetes (25.3%). The median hemoglobin level was 9 g/dL (range 5–15.8 g/dL), with 86.8% having anemia. Hypercalcemia (>10.3 g/dL) and hypocalcemia (< 8.4 g/dL) were noted in 10.2% and 25.3%, respectively. Lytic lesions were observed in 53.4% of 88 patients. Elevated LDH (>246 IU/L) occurred in 21.5% of 65 patients. Peripheral blood smears predominantly showed normochromic normocytic anemia (59.6%). Bone marrow aspirates revealed >60% plasma cells in 28 patients. Elevated serum free light chain ratios (>1.65) were observed in 56/84 patients. IgG κ was the most common M protein type (62.9%). FISH analysis (n = 83) identified IGH rearrangements in 44.6%, monosomy in 45.8%, and any trisomy in 65.1% of patients. Translocations included t(11;14) (20.5%), t(4;14) (13.3%), and t(14;16) (3.6%). TP53 and RB1 deletions were observed in 12.0% and 7.2%, respectively. **Conclusions:** MM presents with diffuse symptomatology, necessitating a high level of suspicion for timely diagnosis. This study correlates clinical, laboratory, radiological, and cytogenetic findings, emphasizing bone pain, renal dysfunction, and high-risk genetic aberrations like TP53 deletion. Increased awareness of these features is crucial for early detection, enabling timely intervention to improve outcomes.

PA-429

Effectiveness of Daratumumab plus Bortezomib, Lenalidomide, and Dexamethasone (DVRd) Versus VRd as Frontline Treatment for Transplant-Eligible Newly Diagnosed Multiple Myeloma: A Chart Review Study

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Introduction: Recently, a shift in the frontline (FL) treatment strategy for transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM) patients (pts) from a triplet (e.g., bortezomib [V], lenalidomide [R], and dexamethasone [d]) to a quadruplet regimen (e.g., daratumumab in combination with VRd [DVRd]) has been observed, driven by the pivotal PERSEUS and GRIFFIN trial data. While improved efficacy with DVRd over VRd has been established in these trials, there is a need to assess the comparative effectiveness in the real-world (RW) setting. The goal of this RW study was to compare the progression-free survival (PFS) among TE NDMM pts receiving DVRd plus DR or R maintenance (DVRd-DR/R) versus VRd plus R maintenance (VRd-R). **Methods:** A retrospective, multi-center, chart review study was conducted at 10 clinical sites in the United States. Eligible TE adult pts with NDMM who initiated FL DVRd-DR/R or VRd-R between 1/1/2020 and 6/30/2022, were included. Pts were excluded if they previously received any multiple myeloma treatment for ≥30 days, participated in a multiple myeloma-related clinical trial, were treated for another invasive malignancy < 12 months prior to induction, or had amyloidosis at induction. Comparability of baseline characteristics between cohorts was assessed using standardized differences (< 10% = balanced). PFS was assessed from time of FL therapy initiation until disease progression or death. Inverse probability of treatment weighting (IPTW) was used to balance difference in baseline characteristics between cohorts. A doubly-robust Cox proportional hazards model, additionally adjusting for baseline characteristics that remained imbalanced after IPTW, was used to estimate the hazard ratio (HR) of PFS in pts treated with DVRd-DR/R versus VRd-R. **Results:** A total of 137 DVRd-DR/R (DR: 67 pts; R: 70 pts; median age: 63 years; female: 42%) and 86 VRd-R (median age: 65 years; female: 51%) pts were included. After IPTW, age, sex, race, ethnicity, disease stage, performance status, frailty, cytogenetic risk status (including 1q21 gain/amplification) were balanced. Remaining imbalanced characteristics, including region of residence, type of insurance, extramedullary disease, plasmacytomas, comorbidity score, and selected comorbidities, were included as covariates to the weighted regression. Median follow-up was 26.7 months for DVRd-DR/R cohort and 39.8 months for VRd-R cohort. Median PFS was not reached in either cohort. FL treatment with DVRd-DR/R led to a 63% reduction in risk of disease progression or death compared to VRd-R (HR = 0.37, 95% confidence interval = 0.17 to

0.80, p = 0.006) as progression/death was observed in 11 (9%) DVRd-DR/R pts, and 32 (30%) VRd-R pts. **Conclusions:** Consistent with the findings from the pivotal clinical trials, RW FL use of the daratumumab-based quadruplet regimen DVRd was associated with a significant PFS benefit compared to VRd among TE pts with NDMM, underscoring the superiority of DVRd as FL treatment for these pts.

PA-430

Recent Trends in Real-World Frontline Treatment Patterns and Outcomes for Patients with Multiple Myeloma in the United States

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Introduction: The treatment landscape for multiple myeloma (MM) has rapidly evolved since the approval of daratumumab (DARA) in frontline (1L). While the efficacy of DARA was established in clinical trials, evidence on its real-world effectiveness is still emerging. This study describes the trends of 1L DARA utilization in recent years and its impact on outcomes among patients (pts) with MM in the real world. **Methods:** A retrospective cohort study of adults initiating 1L for MM between 1/1/2015 and 5/31/2024 was conducted using the Flatiron Health Research Database. Time to next treatment (TTNT) was evaluated using Kaplan-Meier analyses. Results were reported separately for pts who received stem cell transplant (SCT cohort) and pts who did not receive transplant (non-SCT cohort). Results were stratified by use of DARA, race (Black or non-Black) and cytogenetic risk (standard or high risk, among pts with known risk). **Results:** In the SCT cohort (n = 1,757), median age at 1L initiation was 63 years and 44% of pts were female; in the non-SCT cohort (n = 6,559), median age was 72 years and 47% were female. Use of DARA increased steadily since its approval, both in the SCT cohort (2019: 4%; 2020: 11%; 2021: 31%; 2022: 58%; 2023–24: 70%) and the non-SCT cohort (4%; 11%; 22%; 38%; 55%). Use of quadruplet regimens also increased between 2019 and 2023–24 (SCT cohort: 4%; 11%; 30%; 56%; 69%, non-SCT cohort: 2%; 8%; 14%; 25%; 41%). In the SCT cohort, median TTNT was not reached for DARA users (n = 332) compared to 47 months (mos) for DARA non-users (n = 1,425). Proportions of pts still on 1L at 48 mos were 58% and 49%, respectively. In the non-SCT cohort, median TTNT was 23 mos for DARA users (n = 1,059, 35% on 1L at 48 mos) and 12 mos for non-users (n = 5,500, 19% on 1L at 48 mos). Approximately 21% (62/289) of Black pts in the SCT cohort and 16% (197/1,248) of Black pts in the non-SCT cohort received DARA. In the SCT cohort, the proportion of Black pts still on 1L at 48 mos was higher among DARA users than non-users (70% vs. 49%, respectively). This was also observed in the non-SCT cohort (DARA users: 30%, non-users: 24%). In pts with standard cytogenetic risk, the proportion of pts still on 1L at 48 mos was higher in DARA users than non-users in the SCT cohort (65% [n = 218] vs. 53% [n = 919], respectively) and the non-SCT cohort (DARA users: 40% [n = 613], non-users: 21% [n = 3,165]). In pts with high cytogenetic risk, the proportion of pts still on 1L at 48 mos was higher in DARA users than non-users in the SCT cohort (31% [n = 60] vs. 27% [n = 244], respectively) and the non-SCT cohort (DARA users: 20% [n = 155], non-users: 10% [n = 671]). **Conclusions:** Use of DARA as 1L treatment for MM steadily increased since its approval, which resulted in real-world improvements in TTNT. The TTNT benefit was higher among DARA users than non-users, regardless of SCT status and cytogenetic risk. These findings confirm the translation of clinical trial findings in the real-world practice and supports the use of DARA in 1L.

PA-431

Global Research Trends and Inequities in Clinical Trials in Multiple Myeloma: A Focus on South and Southeast Asia

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Introduction: Despite advances in research and treatment modalities, disparities persist in research priorities and the geographical distribution of clinical trials in multiple myeloma (MM). This scoping review aims to classify clinical trials in MM and identify research gaps present in the South and Southeast Asia region. **Methods:** The scoping review included all clinical trials in MM undertaken in 15 South and Southeast Asian countries, from 1 Jan 2008 to 1 May 2025 as registered on ClinicalTrials.gov and relevant national registries, which were our primary sources of data. Trials were classified based on their country, epidemiological characteristics, patient population involved (newly diagnosed MM [NDMM] vs. relapsed/refractory MM [RRMM]) and type of intervention. The data was presented using choropleths and hierarchical charts. **Results:** 746 trials across 15 countries were classified based on their characteristics. China was found to have the highest number of trials (345) followed by Japan (142), South Korea (131), India (83), Singapore (32), Thailand (6), Malaysia (5), and the Philippines (2) while seven South and Southeast Asian countries, i.e., Sri Lanka, Nepal, Indonesia, Bhutan, Pakistan, Myanmar and Bangladesh had no registered trials in the last 17 years. Interventional trials comprised 90.1% (n = 672) of all the trials, with the majority focusing on pharmacotherapy (55.9%, n = 376), followed by cellular therapies (31.5%, n = 212), while a smaller proportion (4.5%, n = 30) employed both cellular and pharmacotherapy and a few concerned supportive therapy (8.03%, n = 54). 22.4% (n = 167) of all interventional trials were comparative

in their design and trials involving RRMM patients dominated the landscape. In NDMM patients 20.9% (n = 9) of the comparative trials assessed a single agent while the remaining comparative trials involved a combination of drugs. In RRMM patients 7.69% (n = 8) of the comparative trials assessed a single agent while 92.3% (n = 96) involved a combination of drugs. Observational trials formed 9.9% (n = 74) of all registered trials and focused on the prevalence (n = 12), diagnosis (n = 11), risk factors (n = 5), and outcomes (n = 41) of the disease. There was also a consistent increase in the number of trials from this region over the years with 6 trials registered in 2008, 12 in 2010, 27 in 2012, 28 in 2014, 30 in 2016, 46 in 2018, 57 in 2020, 89 in 2022 and 91 in 2024. **Conclusions:** There is a marked disparity that exists in the regional distribution of clinical trials in MM, with only a limited number conducted in resource constrained settings involving novel therapeutic agents. This scoping review can serve as a guiding tool for future research to bridge these gaps, thereby championing equity in MM research and improving patient outcomes.

PA-432

Exploratory Analyses of Progression-Free Survival (PFS) with Lenalidomide-Bortezomib-Dexamethasone (RVd) Alone/RVd+ASCT by Duffy genotype in Patients (pts) with Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: In the DETERMINATION phase 3 trial, relative PFS with RVd-alone vs RVd+ASCT differed between White (n = 540/722, 74.8%; median 44.3 vs 67.2 months [mos]; hazard ratio [HR] 1.67, 95%CI 1.29–2.15) and African American (AA) pts (n = 132/722, 18.3%; median not reached [NR] vs 61.4 mos; HR 1.07, 95%CI 0.61–1.89). Given that access to care was enhanced in DETERMINATION and race is a social construct, a pathobiological explanation was sought; high prevalence of Duffy null phenotype among AA pts and its known impact on the inflammasome was proposed as an alternative hypothesis for the observed differential treatment effect by race. **Methods:** Genomics analysis of baseline peripheral blood samples for SNP rs2814778 classified pts as C/C (Duffy null) or non-C/C (Duffy non-null). Duffy status is currently available for 295 pts (40.9% of intent-to-treat [ITT] population); this cohort is broadly representative but contains fewer AA pts, pts with ECOG PS >0, and pts with elevated LDH, and also had longer treatment duration. Impact of Duffy status on PFS was evaluated with Cox proportional hazards regression in univariate and multivariable models. Heterogeneity of treatment effect was assessed by a test for interaction. **Results:** Of 295 pts, 37 (12.5%) were AA, of whom 27 (73.0%) were Duffy null; 256 (86.8%) were White/other race, of whom 1 (0.4%) was Duffy null. In all pts in our cohort, PFS with RVd-alone vs RVd+ASCT (median 52.2 vs 82.3 mos; HR 1.41, 95% CI 1.01–1.96) was consistent with the ITT population; PFS data in AA pts (median NR vs NR; HR 0.76, 95%CI 0.23–2.50) and White/other race pts (median 49.4 vs 66.5 mos; HR 1.52, 95%CI 1.06–2.17) (interaction p-value 0.130) were similar to ITT findings in AA and White pts. PFS (pooled across treatment) was similar in Duffy null vs Duffy non-null pts (12/29 vs 132/266 events/pts; median NR vs 61.9 mos; HR 0.78, 95%CI 0.43–1.41). PFS with RVd-alone vs RVd+ASCT was substantially different in Duffy null pts (2/13 vs 10/16 events/pts; median NR vs 44.0 mos; HR 0.21, 95%CI 0.04–1.02) compared to Duffy non-null pts (73/121 vs 59/145 events/pts; median 48.4 mos vs NR; HR 1.73, 95%CI 1.21–2.46) (interaction p-value 0.002). On multivariable analysis, PFS was significantly longer in Duffy null vs Duffy non-null pts with RVd-alone (HR 0.15, 95%CI 0.04–0.63), but PFS HR was 1.69 (95%CI 0.85–3.37) with RVd+ASCT. **Conclusions:** Treatment effect was substantially different according to Duffy status and more pronounced than that observed by race. The Duffy antigen has a key role in cytokine/chemokine homeostasis, potentially affecting MM pathobiology and inflammatory stressor responses, thereby providing a biologically plausible rationale for differential treatment effect. Current analyses are limited by sample size, near-complete concordance of Duffy status with race, and absence of Duffy null White/other race patients, with additional analysis therefore ongoing. Encore abstract, previously presented at EBMT 2025, poster A352.

PA-433

Frontline Anti-CD38 Monoclonal Antibodies in Patients with High-Risk, Newly Diagnosed Multiple Myeloma: A Meta Analysis

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Introduction: The anti-CD38 monoclonal antibodies daratumumab and isatuximab are both approved for use in patients with newly diagnosed multiple myeloma (NDMM) in both the transplant-eligible and transplant-ineligible settings. However, the degree to which high risk patients in particular benefit from the addition of an anti-CD38 monoclonal antibody to NDMM regimens is not clear. We conducted a meta-analysis to evaluate the effect of anti-CD38 monoclonal antibodies on progression free survival (PFS) across the NDMM space. **Methods:** Criteria for inclusion of a study were defined as any randomized, controlled trial (RCT) in NDMM examining standard of care myeloma therapy with or without daratumumab or isatuximab. The primary endpoint was PFS. Only studies stratifying PFS data by cytogenetic risk were included. Notably, classification of cytogenetic risk status was not equivalent across trials (for example, with respect to whether 1q gains are considered high risk), but for the purposes of this analysis all high risk subgroups were combined into one category. The pooled effect of frontline anti-CD38 monoclonal antibodies across studies was quantified using a PFS hazard ratio, separately in standard-risk and high-risk subgroups, with 95% confidence intervals calculated using theDerSimonian-Laird random effects model. For analysis, trials were divided into transplant trials and nontransplant trials. Hazard ratios and confidence intervals were derived from reported trial data. The "Meta" package (version 6.5–0), R version 4.3, was used. **Results:** A total of 9 trials (MAIA, ALCYONE, CEPHEUS, IMROZ, OCTANS, CASSIOPEIA, GRIFFIN, PERSEUS, and GMMG-HD7) were identified and included in the analysis. Frontline receipt of an anti-CD38 monoclonal antibody was associated with improved PFS both in patients with standard-risk NDMM (HR 0.51; 95% CI 0.46–0.58, p(heterogeneity) 0.44) and high-risk NDMM (HR 0.64, 95% CI 0.49–0.84, p(heterogeneity) 0.13). Subgroups of patients with standard risk disease derived similar benefit from frontline anti-CD38 monoclonal antibody receipt whether on a nontransplant study (HR 0.49, 95% CI 0.43–0.57, p(heterogeneity) 0.52) or a transplant study (HR 0.52, 95% CI 0.40–0.67 p(heterogeneity) 0.26). Subgroups of patients with high-risk disease also benefitted, both if treated on transplant studies (HR 0.57, 95% CI 0.35–0.94, p(heterogeneity) 0.56) and on nontransplant studies (HR 0.71, 95% CI 0.53–0.97, p(heterogeneity) 0.04). **Conclusions:** Patients with high-risk NDMM and standard-risk NDMM treated on frontline myeloma trials experienced improved PFS with anti-CD38 monoclonal antibody-based regimens, although the effect was less pronounced in high-risk patients treated on nontransplant studies. The myeloma community continues to refine clinical risk classification systems. Further comparison of NDMM therapeutic strategies in more refined cytogenetic subgroups should be a focus of future work.

PA-434

Renal Histopathologic Spectrum and Factors Associated with Reversibility of Renal Injury in Newly Diagnosed Patients of Multiple Myeloma

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Introduction: Myriad of etiologic factors underlie renal impairment in patients of multiple myeloma(MM). Renal involvement portends a poor prognosis in MM and renal injury is reversible only in 30%-50% of cases. We studied the renal histopathologic spectrum, renal recovery and survival of patients of newly diagnosed MM with renal impairment. **Methods:** This was a prospective, single-centre study, conducted at a tertiary care centre in North India. All patients with newly diagnosed MM with renal impairment (defined as serum creatinine >2 mg/dl or an eGFR < 60 ml/min/1.73 m2) were included. Renal biopsy was performed in all patients after obtaining a written informed consent. Patients received Bortezomib-based triplet or quadruplet (with Daratumumab) induction. Renal and hematologic responses were assessed as per IMWG 2016 criteria. **Results:** A total of 52 patients of MM with renal impairment underwent renal biopsy and were included in this study. Median age of the cohort was 54 years (IQR 49–64). Thirty-seven(71%) were male. Median creatinine and eGFR was 3.8 mg/dl and 17 ml/min/1.73 m2, respectively. Nineteen(36.5%) required dialysis at presentation. Cast nephropathy(n = 22, 42.3%) followed by MIDD(n = 8, 15.4%) were the most common finding on renal biopsy. Five(10%) patients had diabetic nephropathy on renal histology. Majority (n = 43, 83%) received bortezomib/cyclophosphamide/dexamethasone (VCD) induction. Best hematologic response (>VGPR) occurred in 70.5%. Thirty-one(59.6%) achieved a renal response. Median time to best renal response was 16 weeks. Out of 19, 10(53%) became dialysis independent at a median of 3 weeks. Hypercalcemia at presentation was associated with improved renal recovery(p = 0.01). Lambda light-chain isotype had higher renal recovery compared to kappa isotype (OR = 3.46, 95% CI1.05–11.32, p = 0.04). Out of 5 patients with diabetic-nephropathy, none achieved renal response (p = 0.008). Presence of severe interstitial-fibrosis and tubular-atrophy(IFTA)(n = 5) was associated with lack of renal-response

(p = 0.016). Median overall survival was not reached in patients with renal response (72% at 22 months), compared to 8 months in non-renal responders (95% CI 0–28, p = 0.006). At a median follow-up of 16 months, out of 52 patients, 8(15.3%) died, while 11(21%) were lost to follow up. **Conclusions:** Our study underscores the value of renal biopsy in MM and also identifies important clinical, hematologic and histopathologic factors associated with renal response and survival. Our study underscores the value of renal biopsy in MM and also identifies important clinical, hematologic and histopathologic factors associated with renal response and survival.

PA-435

Survival Impact of Anti-CD38-Based Quadruplet Regimens in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: A Network Meta-Analysis and Reconstructed Individual Patient Data Meta-Analysis

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Introduction: Frontline therapy for transplant-ineligible newly diagnosed multiple myeloma (TI-NDMM) has evolved significantly. Although triplet regimens have long constituted the standard of care, recent quadruplet combinations incorporating anti-CD38 monoclonal antibodies (mAb), daratumumab and isatuximab, have demonstrated improved response rates and progression-free survival (PFS). However, the impact on long-term outcomes, particularly overall survival (OS), remains uncertain. **Methods:** We conducted a systematic review, network meta-analysis (NMA), and reconstructed individual patient data meta-analysis to evaluate survival outcomes of quadruplet versus triplet lenalidomide-containing regimens in TI-NDMM. This study adhered to Cochrane and PRISMA guidelines and was registered on PROSPERO (CRD420251033401). A comprehensive literature search through April 2025 identified randomized clinical trials (RCT) evaluating quadruplet and triplet regimens involving daratumumab, isatuximab, bortezomib, lenalidomide, and dexamethasone in any combination, compared to their backbone regimens, reporting OS and PFS. The NMA employed a frequentist random-effects model with P-scores for treatment ranking. Individual patient data were reconstructed from published Kaplan-Meier curves using the IPDfromKM method to enable pooled survival analyses. **Results:** Four RCT (CEPHEUS, IMROZ, MAIA, SWOG S0777) comprising 2,038 patients were included: D-VRd (n = 197), I-VRd (n = 265), D-Rd (n = 368), VRd (n = 614), and Rd (n = 598). Median follow-up ranged from 58.7 to 89.3 months. Estimated 60-month PFS rates were: D-VRd (66.4%), I-VRd (63.3%), D-Rd (51.9%), and VRd (42.6%). Both D-VRd and I-VRd significantly improved PFS vs. D-Rd (HR 0.65, 95% CI 0.48–0.87, P = 0.003; and HR 0.68, 95% CI 0.52–0.89, P = 0.004) and vs. VRd (HR 0.51, 95% CI 0.39–0.67, P < 0.0001; and HR 0.53, 95% CI 0.41–0.67, P < 0.0001). D-Rd also showed superior PFS over VRd (HR 0.77, 95% CI 0.64–0.93; P = 0.007). At 60 months, OS rates were: D-VRd (72.8%), I-VRd (72.2%), D-Rd (67.1%), and VRd (66.2%). When analyzed as grouped strategies, quadruplets (D-VRd, I-VRd) achieved significantly superior outcomes at 60 months compared with triplets (D-Rd, VRd), with higher PFS (64.7% vs. 46.3%) and OS (72.5% vs. 66.7%). Pooled analysis confirmed improved PFS (HR 0.57, 95% CI 0.47–0.69, P < 0.0001) and OS (HR 0.78, 95% CI 0.63–0.96, P = 0.02) for quadruplets. The OS benefit of quadruplets was consistent in comparisons against both D-Rd (HR 0.77; 95% CI: 0.60–0.98; P = 0.04) and VRd (HR 0.77; 95% CI: 0.62–0.97; P = 0.02). In the NMA, D-VRd and I-VRd ranked highest in probability of achieving complete response or better (P-scores: 0.9876 and 0.7318), PFS (0.8668 and 0.8114), and OS (0.7043 and 0.8328). **Conclusions:** This meta-analysis provides the first comprehensive comparative assessment of anti-CD38-mAb based quadruplet versus triplet regimens in TI-NDMM, demonstrating a significant overall survival advantage and supporting quadruplet regimens as the most effective frontline treatment.

PA-436

A Network Meta-Analysis of Randomized Clinical Trials Comparing the Efficacy of Daratumumab Versus Isatuximab in the Treatment of Multiple Myeloma

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Introduction: The introduction of anti-CD38 monoclonal antibodies (mAb) has significantly advanced treatment of multiple myeloma (MM). Both daratumumab (D) and isatuximab (I) have demonstrated substantial efficacy and improved outcomes in newly diagnosed and relapsed/refractory MM. Although widely evaluated with similar backbone regimens, direct comparative evidence between these agents remains unavailable. In the absence of head-to-head trials, network meta-analysis (NMA) provides a rigorous framework for indirect comparisons to support evidence-based selection of CD38-targeted strategies. **Methods:** We conducted a systematic review (SR) and NMA of randomized clinical trials (RCT) to compare efficacy and survival outcomes of daratumumab- versus isatuximab-based regimens in MM. A structured search of Cochrane Library, Embase, Google Scholar, Medline, PubMed, Scopus, Web of Science, clinical trial registries, and major conference abstracts (2022–2025) was performed in January 2025. Eligible phase II/III RCT evaluated either antibody in combination with a shared therapeutic backbone and reporting progression-free survival (PFS)

as endpoint. Two authors extracted and quality-checked data. We estimated hazard ratios (HR) for PFS and overall survival (OS) using a frequentist NMA model based on aggregate-level data, for each indirect comparison between regimens sharing a common backbone. Subsequently, we pooled the results using a random-effect model to summarize the overall treatment effect. Heterogeneity was assessed using Cochran's Q and I^2 statistics. **Results:** Six phase III trials comprising 2,587 patients met inclusion criteria. To enable an indirect comparison between D and I, studies were grouped into three networks based on identical backbone regimens: carfilzomib and dexamethasone (Kd), pomalidomide and dexamethasone (Pd), and bortezomib, lenalidomide and dexamethasone (VRd). No significant differences in PFS were observed across regimens: D-Kd vs. I-Kd (HR 1.10, 95% CI: 0.73–1.66), D-Pd vs. I-Pd (HR 1.11, 95% CI: 0.75–1.63), and D-VRd vs. I-VRd (HR 0.95, 95% CI: 0.60–1.49). Similarly, no differences in OS were detected: D-Kd vs. I-Kd (HR 0.91, 95% CI: 0.59–1.40), D-Pd vs. I-Pd (HR 1.05, 95% CI: 0.70–1.58), and D-VRd vs. I-VRd (HR 1.09, 95% CI: 0.65–1.82). In the pooled analysis, no significant differences were found between daratumumab- and isatuximab-based regimens for either PFS (HR 1.06, 95% CI: 0.86–1.30; P = 0.36) or OS (HR 1.01, 95% CI: 0.79–1.28; P = 0.91). Heterogeneity was low in both analyses (PFS: Cochran's Q, P = 0.86; I^2 = 0%; and OS: Cochran's Q, P = 0.84; I^2 = 0%). Risk of bias was low across all studies, and effect modifiers were sufficiently balanced to support transitivity. **Conclusions:** This is the first NMA to indirectly compare daratumumab and isatuximab in MM using RCT-level evidence. In absence of significant differences in PFS or OS between these two anti-CD38 mAbs, therapeutic choice should be based on factors other than efficacy. Protocol Registration: CRD420250618823.

PA-437

Real-World Evaluation of Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone (D-VRd) Induction Followed by Daratumumab and Lenalidomide (DR) Maintenance in Transplant-Eligible Multiple Myeloma

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Introduction: The introduction of novel therapeutic agents has significantly improved outcomes in multiple myeloma (MM). The phase 2 GRIFFIN and phase 3 PERSEUS trials demonstrated that adding daratumumab to VRd induction and consolidation, as well as to lenalidomide maintenance, significantly enhances response depth and prolongs progression-free survival. However, long-term real-world follow-up data on this regimen remain limited. This study evaluates the real-world experience of D-VRd induction followed by autologous stem cell transplantation (ASCT) and daratumumab plus lenalidomide (DR) maintenance as frontline therapy for transplant-eligible newly diagnosed multiple myeloma (TE-NDMM) patients. **Methods:** We conducted a retrospective analysis of TE-NDMM patients who received D-VRd induction between January 2021 and March 2025. Patient demographics, disease characteristics, response rates, and clinical outcomes were assessed using descriptive statistics. A swimmer plot was utilized to visualize treatment timelines, duration, and response evolution. **Results:** A total of 22 patients received D-VRd induction between April 2021 and February 2025. The median age was 60 years (range, 36–73), with 59% female, 72% White, and 28% Black. At diagnosis, 45% had an ECOG performance status of 0–1, and ISS staging was I in 59%, II in 27%, and III in 14%. Clinical characteristics included hemoglobin < 10 g/dL in 40%, lytic bone lesions in 77%, and creatinine >2 mg/dL in 5%. The IgG isotype was present in 82%. Cytogenetic data were available for five patients. At a median follow-up of 26 months (range, 9–45), 17 patients had undergone ASCT. The overall response rate (ORR) was 100%, with 76% achieving a complete response (CR) or better, 18% a very good partial response (VGPR), and 6% a partial response (PR). No cases of primary refractory disease, progression, or relapse were observed. One patient in CR died from COVID-19. Among the 94% of patients who initiated DR maintenance, one discontinued daratumumab due to a skin reaction, and two discontinued lenalidomide due to diarrhea and neutropenia. Post-ASCT, the ORR remained 100%, with CR in 30%, VGPR in 53%, and PR in 17%. Responses deepened during maintenance: 78% of patients with VGPR post-ASCT converted to CR, while among those with PR post-ASCT, 33% improved to CR and 33% to VGPR. **Conclusions:** D-VRd induction followed by DR maintenance demonstrated high efficacy in this real-world cohort, with an ORR of 100% and 94% of patients achieving VGPR or better. These findings reinforce the effectiveness of this regimen as a frontline option for TE-NDMM patients and support its broader implementation in clinical practice.

PA-438

Pan-Pacific Multiple Myeloma (MM) Working Group Guidelines and Recommendations for CD38 Monoclonal Antibody-Based Quadruplet Therapy and Management in Clinical Practice for Newly Diagnosed MM

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Aichi Medical University; [9]Department of Hematology, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine; [10]National Taiwan University Hospital; [11]Japanese Red Cross Medical Center; [12]Myeloma Research Center of Beijing, Beijing Chaoyang Hospital, Capital Medical University; [13]Botkin Moscow City Clinical Hospital; [14]Russian Cancer Research Center named after N.N. Blokhin RAMS; [15]Nerima Hikarigaoka Hospital; [16]Prince of Wales Hospital, The Chinese University of Hong Kong

Introduction: Incorporating anti-CD38 monoclonal antibodies (mAbs), including isatuximab and daratumumab, into the bortezomib/lenalidomide/dexamethasone (VRd) therapy backbone as first-line (1L) treatment for newly diagnosed MM (NDMM) has demonstrated improved efficacies and no additional safety concerns. Based on these results, the National Comprehensive Cancer Network Guidelines Version 1.2025 was updated to incorporate anti-CD38 mAbs with VRd-based therapies as primary therapy for both transplantation-eligible (Te) and transplantation-ineligible (Ti) NDMM patients (pts). A panel of hematology and oncology experts with experience in NDMM convened in 2024 to develop consensus recommendations based on evidence from pivotal clinical trials and real-world practices, providing clear guidance for optimizing treatment strategies in Te and Ti pts. **Methods:** A modified Delphi consensus process was employed to generate statements regarding the use of anti-CD38 mAb quadruplet (quad) therapy in NDMM, using anonymous online voting and in-person meetings. A steering committee formulated 8 statements for online voting and a meeting was held to discuss and finalize the statements. The main topics identified for discussion for quad therapy in NDMM were: benefits and indications; optimization strategies; management and monitoring of potential adverse events (AEs), and the impact on tandem stem cell transplantation and maintenance treatment. **Results:** Of 14 voters, 85.7% agreed that anti-CD38-based quad therapy is suitable for Ti NDMM pts and 92.9% agreed it was suitable as 1L treatment for Te pts. Quad therapy is preferred for pts < 80 years old who are not frail (78.6% consensus) and for those with mild renal impairment (92.9% consensus). All voters agree that hematologic toxicities are among the most common AEs in pts undergoing quad therapy, and management supports are recommended. There was 85.7% agreement that quad regimens may increase infection susceptibility; therefore, prophylactic antiviral and antibacterial agents and vaccinations are advised prior to initiating therapy. For high-risk pts receiving tandem autologous stem cell transplant (ASCT), 71.4% agreed that stem cell collection should be planned before the fourth cycle. Following induction and ASCT, 85.7% agreed that lenalidomide remains the cornerstone of maintenance therapy and a more aggressive strategy may be considered in pts with high-risk cytogenetic abnormalities or those who achieved minimal residual disease negativity. **Conclusions:** The use of anti-CD38 mAb quad therapies represents a significant advancement in the treatment of NDMM. The addition of anti-CD38 mAbs to VRd-based regimens has the potential to become the new standard of care. By incorporating evidence from clinical trials and expert opinions, this consensus provided clear, evidence-based guidance on the integration of quad regimens into clinical practice for NDMM, particularly for Ti pts. **Funding:** Sanofi. Recently published: Chen W, et al. Clin Hematol Int 2025;7(2):1–19.

PA-439

Model-Based Assessment of Monthly Isatuximab Dosing Performance in Newly Diagnosed Multiple Myeloma Patients Using IMROZ Phase 3 Data

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Introduction: Isatuximab (Isa) with bortezomib, lenalidomide and dexamethasone (VRd) is associated with a significant benefit in progression-free survival (PFS) in patients (pts) with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (IMROZ, NCT03319667). As approximately 70% of Isa-VRd pts achieved very good partial response (VGPR) within the first 3 mo and maintained it, an earlier switch to monthly Isa dosing than the current 18-mo may reduce treatment burden without compromising efficacy. The current study evaluates alternative dosing strategies via simulation, using joint modeling of serum M-protein dynamics and PFS within the IMROZ trial framework. **Methods:** Data from IMROZ comparing Isa 10 mg/kg QW for 4 wk then Q2W, then Q4W at cycle 18 onwards in combination with VRd vs VRd in 357 evaluable NDMM pts were used. Longitudinal data of serum M-protein and PFS data were analyzed separately then in a joint model to describe their association using Monolix 2024R1. A tumor growth inhibition model was developed to describe serum M-protein dynamics, accounting for tumor growth, isatuximab-induced anti-tumor effect, combined with VRd, along with drug resistance effect. A covariate analysis assessed baseline pts characteristics' influence on serum M-protein kinetics and PFS. Trial simulations evaluated if efficacy is maintained upon switching to a Q4W dosing after 6 or 12 mo versus approved 18 mo, including a targeted approach for pts achieving 3 mo-stable ≥VGPR status (≥90% reduction of M-protein from baseline with ≥5 g/L and disease stability over the last 3 mo). **Results:** Isa and VRd individual drug exposures (average daily AUC) were used to predict treatment effect on serum M-protein. The dynamic difference in M-protein relative to its current lowest value was the best on-treatment predictor of PFS. Pts with high β-microglobulin tended to have higher serum M-protein at baseline and higher risk of progression; non-IgG pts were likely to have faster M-protein shrinkage rate induced by VRd, causing faster M-protein decrease during first 6 mo but similar PFS vs IgG pts. Simulation results showed switching to monthly regimen after 12 mo instead of

18 minimally impacted efficacy: 60-mo PFS rate (76.2 vs 77.7%), HR (0.543 vs 0.518), 12.4% of pts expected to have shorter time to progression (TTP) by an average 4 mo. Earlier switch after 6 mo instead of 18 mo slightly reduced efficacy (60-mo PFS rate: 74.9% vs 77.7%; HR: 0.563 vs 0.518). However when restricted to pts with 3 mo-stable ≥VGPR status at 6 mo (78.6% of pts), outcomes were comparable vs 12-mo switch at population level (60-mo PFS rate: 75.4 vs 76.2%; HR: 0.55 vs 0.543), though 5% of individual pts could experience ≥8 mo shorter TTP, possibly due to poorer prognostic factors with higher proportion of R-ISS stage 3 pts. **Conclusions:** Simulations suggest that Q4W Isa dosing after 12 mo in all NDMM pts or after 6 mo in pts achieving stable ≥VGPR status did not compromise treatment efficacy vs switching after 18 mo.

PA-440

Infusional Chemotherapy Regimens for Multiple Myeloma: Characterization of Current-Day Use at a Single Center

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Introduction: Despite the rapidly evolving treatment landscape for multiple myeloma (MM) with the advent of novel therapies such as proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and CAR T-cell therapies, infusional chemotherapy regimens like DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) and VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) remain crucial anti-myeloma therapies. They play a vital role in rapid debulking of high disease burden, as salvage therapy in relapsed/refractory cases, as well as bridge to definitive therapies. Few studies have directly compared outcomes between these regimens or comprehensively characterized their use in the era of novel agents. In this single-center study, we look at outcomes of infusional chemotherapy regimens in the current era of MM therapy. **Methods:** Patients with biopsy-confirmed MM or plasma cell leukemia treated at a university cancer center between January 2020 and April 2025 were included for total of 63 records. Among these, infusional chemotherapy regimens were identified and used as data points. Regimens were characterized by disease status and ISS/RISS prior to treatment, line of therapy (LOT), purpose of therapy, timing of autologous stem cell transplantation (ASCT), CAR-T or BiTE, best response to therapy, and patient demographics. **Results:** Review revealed 20 LOT among 8 regimens: 3 CED, 5 (V)DCEP, 6V(T)D-PACE, 1 Hyper-CVAD, 1 Hyper CDT and 4 HD CY. Of these 20 LOT, 13 (65%) were administered to males; 17 (85%) to Caucasians. Mean age was 60 years (range 39–70). Patients with ISS/RISS III disease received 6 LOT (30%), and 9 (45%) for those with ISS/RISS II disease. 14 (70%) were administered to patients with high-risk cytogenetics; 9 (45%) were administered to patients with extramedullary involvement. 12 (60%) were administered in refractory/relapsed cases as fourth-line or greater therapy. 3 (15%) were used for salvage therapy, 7 (35%) were used for rapid debulking, 6 (30%) were used for bridge to CAR-T or BiTE, and 4 (20%) were used as bridge to ASCT. 7 lines (35%) were administered prior to ASCT, 7 (35%) were administered in patients who had previously undergone ASCT, and 6 (30%) were administered in patients who had not received any ASCT to date. Of 10 LOT administered as a bridge, 5 resulted in partial response or better, 1 resulted in stable disease, and 4 resulted in progressive disease. **Conclusions:** Infusional chemotherapies were utilized as bridge to alternate therapy such as CAR-T, BiTE or ASCT in one-half of cases and resulted in adequate response in about half. Our results reflect ongoing utility of these regimens. Further investigation is required into duration of response and comparative efficacies of infusional chemotherapies. Future directions will involve expansion of the data set with overall response rate, progression free survival, overall survival, and adverse effects with statistical analysis with larger sample size.

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Early Treatment with Daratumumab in Patients with Multiple Myeloma and Kidney Impairment: A Real-World Analysis

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Introduction: Renal failure is common in patients with newly diagnosed multiple myeloma (NDMM) and is associated with unfavorable outcomes. Daratumumab (Dara) is associated with rapid light chain reduction and may improve patient outcomes. We hypothesized that, among patients with kidney impairment who started treatment within 15 days of NDMM diagnosis, early Dara initiation would be associated with improved outcomes. **Methods:** A retrospective study was performed on all patients with NDMM diagnosed from January 2014 to January 2024 in the US Flatiron Health electronic health record-derived, de-identified database. We identified patients with a creatinine clearance (CrCl) of less than 45 mL/min and received at least one dose of Dara or other treatment within 14 days of NDMM diagnosis. Real world progression-free survival (rwPFS) and overall survival (rwOS) were analyzed using Cox proportional hazards model adjusting for age, race, ECOG status, transplant status, ISS Stage, practice type, and first-line treatment received. **Results:** Of 1946 patients with NDMM and initial CrCl< 45 mL/min, 175 (9.0%) received at least one dose Dara within 15

days of NDMM diagnosis. The mean (SD) age at diagnosis was 72.5 (10.1) years, with 762 (72.8%) presenting with ISS Stage III disease and 61 (3.1%) eventually able to receive stem cell transplantation. Among the 1771 patients who did not receive Dara, treatments included CYBorD (21.0%), RVD (30.1%), VD (18.6%), KRD (0.7%), RD (7.8%), and dexamethasone alone (3.8%). Among the 175 patients who received Dara, adjunct regimens included CYBorD (17.7%), RVD (19.4%), VD (19.4%), KRD (0.6%), RD (18.3%), and dexamethasone (2.9%). Patients with baseline CrCl < 45 mL/min receiving Dara had improved rwPFS (log-rank p = 0.03) compared to non-Dara recipients; there was no difference in rwOS (log-rank p = 0.3). The median rwOS and rwPFS were 37.1 and 20.4 months, respectively. After adjusting for confounders, the association between Dara with rwPFS was attenuated (p = 0.1). In contrast, lower ECOG status and younger age were associated with improved rwPFS and rwOS. In total, 1020 (52.4%) patients presented with CrCl < 30 mL/min, of which 92 (9.0%) received Dara. In patients with baseline CrCl < 30 mL/min, there were no apparent differences in rwPFS (p = 0.8) or rwOS (p = 0.9) between Dara and non-Dara recipients. The median rwOS and rwPFS were 35.2 and 19.2 months, respectively. After adjusting for confounders, treatment with Dara was associated with improved rwPFS (p = 0.04) and rwOS (p = 0.08). Lower ECOG status was also associated with improved rwPFS and rwOS. **Conclusions:** In this large real-world analysis, rapid initiation of Dara as a component of frontline induction was associated with improved rwPFS among patients with CrCl < 30 mL/min. This finding may support the early initiation of Dara regimens in renal failure. Further investigation is needed to fully characterize if Dara improves outcomes compared to standard induction therapies.

PA-442

Outcomes and Maintenance Strategies for Transplant-Eligible Newly Diagnosed Multiple Myeloma Among Patients Age 40 and Younger

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Introduction: The median age at diagnosis for multiple myeloma is approximately 70 years old, and < 2% of patients are age ≤40 at diagnosis. Although younger patients may have better tolerance to therapies, there may be greater impacts on quality of life (QoL) and late toxicities of therapies. Disease characteristics and outcomes are also less well-described in this group. We explored outcomes and maintenance strategies for patients age ≤40 with transplant-eligible newly diagnosed multiple myeloma (NDMM). **Methods:** We conducted a single center retrospective analysis of patients who underwent autologous stem cell transplantation (ASCT) for NDMM between 2004 and 24 and identified patients who were diagnosed and underwent ASCT at age ≤40. Demographic and disease features were analyzed using descriptive statistics. Survival outcomes were analyzed using the Kaplan-Meier method. Univariate and multivariate analysis was conducted using a Cox regression model to identify predictors of survival. **Results:** We identified 54 out of 1512 patients (3.6%) who underwent ASCT for NDMM at age ≤40, with a median age of 37 years (range 28–40). 44.4% of patients were male and 22.2% identified as Hispanic/Latino. 44.4% of patients identified as white, 13% as Asian, and 11.1% as Black. 68.5% had heavy chain disease and 22.7% had ISS stage 3 disease. 27.1% had ≥1 high-risk cytogenetic abnormality and 16.7% met 2024 IMWG high-risk criteria. Two patients received a tandem ASCT. At a median follow-up duration of 106 months, the median progression-free survival (PFS) after ASCT was 53 months (range 28–117). Median overall survival (OS) was not reached with an estimated 5-year OS of 85.1% and 10-year OS of 71.5%. Eight patients received consolidation after ASCT and 45 received maintenance therapy with a median duration of 15 months (range 0–148). On univariate analysis, longer duration of maintenance therapy had a minimal impact on PFS (HR 0.99, p = 0.04), while multi-drug maintenance was associated with improved PFS (HR 0.30, p = 0.01) and OS (HR 0.11, p < 0.005). Patients not started on any maintenance therapy had worse PFS (HR 3.34, p = 0.006) and OS (HR 9.33, p < 0.001). Presence of high-risk cytogenetics had a trend toward worse PFS (HR 1.74, p = 0.19). On multivariate analysis, depth of response after ASCT was associated with improved PFS but only the number of maintenance drugs was associated with improved OS (HR 0.23, p = 0.03). Three patients developed secondary malignancies, 1 with T-cell lymphoma and 2 with t-AML. **Conclusions:** Among patients with NDMM age ≤40, depth of response after ASCT and number of maintenance drugs had the strongest association with PFS and OS. PFS and OS were comparable to previously published studies. Outcomes did not differ based on duration of maintenance therapy, suggesting that risk-adapted maintenance strategies may be possible to reduce overall treatment duration and benefit QoL. Additional studies are warranted to determine ideal choice and duration of maintenance strategies in this population.

PA-443

Lenalidomide Duration during Induction Does Not Affect Stem Cell Mobilisation, A Real-World Study with G-CSF and Pre-Emptive Plerixafor

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Introduction: Stem cell collection is typically recommended within 4 months of lenalidomide-based induction in multiple myeloma due to concerns over impaired mobilisation with prolonged lenalidomide exposure. However, in resource-limited settings, delays in ASCT are common due to financial constraints and limited access to cryopreservation. In this context, it becomes imperative to determine whether extended lenalidomide exposure impact stem cell mobilisation when G-CSF and pre-emptive plerixafor are used. **Methods:** We retrospectively reviewed records of 81 multiple myeloma patients who underwent ASCT between January 2015 and December 2024. Mobilisation was performed with G-CSF (10 mcg/kg), and plerixafor was added if Day-4 peripheral blood CD34+ count was < 10 cells/μL. A Day-5 yield target of $>2 \times 10^6$ CD34+ cells/kg was set. Patients were grouped based on lenalidomide exposure: ≤4 months (short-exposure, SE) and >4 months (long-exposure, LE). **Results:** Median age was 55 years (IQR: 47.5–60), with younger patients in the LE group (median: 54 vs. 60 years; p = 0.01). Median induction duration was 11 months (IQR: 4–14), with a median lenalidomide exposure of 6 months (IQR: 4–8.25). Fifty-eight patients (72%) were in the LE group. Median Day-4 peripheral blood (PB)CD34+ cell counts were similar between groups (LE = 4.64/μL vs. SE = 5.45/μL; p = 0.27). Day-4 subcategories showed comparable proportions with <5 cells/μL (48% vs. 55%), 5–10 cells/μL (15.5% vs. 23%), and >10 cells/μL (36.2% vs. 22%; p = 0.59). Plerixafor use was comparable (59% LE vs. 59% SE; p = 0.99). Day-5 median CD34+ yields were similar (LE = 5.12×10^6/kg vs. SE = 3.88×10^6/kg; p = 0.14), and the need for >1 apheresis session was not significantly different (LE = 13.8% vs. SE = 27.3%; p = 0.13). In the LE group, 2 patients failed to achieve $>2 \times 10^6$/kg yield; none failed in the SE group. Among LE patients, 60% achieved $>4 \times 10^6$/kg compared to 36% in the SE group (p = 0.39). Lenalidomide dose, analyzed both as nominal (10 mg, 15 mg, 25 mg) and binary (≤15 mg vs. >15 mg), was not significantly associated with impaired stem cell mobilisation. Patients receiving higher doses (>15 mg) had comparable Day-4 CD34+ counts and Day-5 yields. Patients < 50 years had higher median CD34+ yield (5.99 vs. 3.83×10^6/kg; p = 0.02), and the association remained significant after adjusting for exposure duration and dose (p = 0.03). Pre-transplant disease status also predicted stem cell mobilisation; those with ≥PR had higher median yield (5.2 vs. 3.1×10^6/kg; p = 0.04). Among patients receiving Dara-VRD, there was no significant difference in mobilisation kinetics; however, two-thirds required plerixafor. **Conclusions:** Prolonged lenalidomide exposure (>4 months) and variation in lenalidomide dose did not adversely affect stem cell mobilisation outcomes when G-CSF with pre-emptive plerixafor was used.

PA-444

Evaluation of Haematopoietic Second Primary Malignancies in Multiple Myeloma: A Single Centre Australian Experience

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Introduction: Novel myeloma therapies have led to increased life expectancy. Long-term risk of second primary malignancies (SPM) has become increasingly relevant. Increased risk has been seen in the context of alkylating agents, such as melphalan, and lenalidomide. Data on SPM in myeloma patients in Australia is lacking. This study describes the local experience of haematopoietic SPM in treated myeloma patients at Royal Prince Alfred Hospital in Sydney, Australia. **Methods:** Electronic medical records from 346 myeloma patients, diagnosed from April 2012 to March 2025, were reviewed to identify patients with haematopoietic SPM. Patient and disease characteristics were analysed, including prior treatment lines and autograft(s), genetic risks, duration of lenalidomide and survival outcomes. **Results:** 13 patients were identified with haematopoietic SPM: B-cell acute lymphoblastic leukaemia (n = 2), acute myeloid leukaemia (n = 4), myelodysplastic neoplasm (n = 7). Of 7 patients with MDS, 1 developed AML. 5 patients had mutated TP53 at the time of SPM diagnosis. In myeloma FISH analysis, 2 patients had gain of 1q with no other high-risk cytogenetic abnormalities. 11 patients did not have high-risk cytogenetic features, or results were unavailable. All patients underwent autologous stem cell transplantation for myeloma; 4 patients had a second autograft at the time of disease progression. 11 patients received lenalidomide, of whom 9 received lenalidomide as the most recent line of treatment prior to SPM diagnosis. Median duration of lenalidomide was 33 months and longest duration was 72 months. All patients had standard risk myeloma and were at risk of SPM from prolonged lenalidomide. Median time to SPM diagnosis was 6.25 years. 4 patients are currently alive. 1 patient had non-SPM-related death. Median survival time is 9.6 months. **Conclusions:** This review highlights the experience of haematopoietic SPM at our centre, with diagnoses including B-ALL, AML and MDS. This review will form the basis of the first nationwide observational study of haematopoietic SPM in Australia, to evaluate incidence over time and with the introduction of novel myeloma therapies.

Table 1 (abstract PA-444) Summary of patient and disease characteristics for myeloma patients with haematopoietic SPM

Age	Sex	SPM diagnosis	FISH/Cytogenetics (myeloma)	R-ISS	No. prior treatment lines	No. auto-grafts	Duration of lenalidomide (months)	Myeloid NGS
54	F	B-ALL	No high-risk features	I	1	1	35	N/A
54	F	AML	Gain 1q	II	1	1	31	No variants
46	M	AML	No high-risk features	I	1	1	23	Not available
76	M	MDS	No high-risk features	II	3	2	N/A	ASXL1, TP53, U2AF1
59	F	AML	No FISH available	I	2	1	31	RUNX1, DNMT3A
69	M	B-ALL	Gain 1q	I	1	1	55	N/A
57	M	MDS	t(11;14) - No high-risk features	II	5	2	72	TP53
67	F	MDS	No FISH available	I	2	2	47	Biallelic TP53
65	M	AML	No FISH available	I	2	2	56	TP53
65	M	MDS	No high-risk features	I	2	1	23	DNMT3A
64	M	MDS	Unknown	I	1	1	Unknown	ASXL1
52	F	MDS	No high-risk features	II	1	1	N/A	Not available
54	M	MDS	No high-risk features	II	4	1	12	RUNX1, TP53

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DKRD vs. DVRD Induction Prior to Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma

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Introduction: There are limited real-world data on the outcomes of newly-diagnosed multiple myeloma (MM) patients treated with quadruplet induction followed by upfront autologous transplant (autoHCT). **Methods:** This is a single-center retrospective chart review of consecutive adult MM patients that received upfront autoHCT after standard of care daratumumab, carfilzomib, lenalidomide (Len) and dexamethasone (DKRD) or daratumumab, bortezomib, Len, and dexamethasone (DVRD) between 2021 and 2024. Primary outcomes were progression-free (PFS) and overall survival (OS). **Results:** 140 patients were included: 15 (11%) received DKRD induction and 125 (89%) received DVRD. Median age at autoHCT was 58 years for the DKRD cohort and 62 years for the DVRD cohort (p = 0.09). 10 (67%) patients in the DKRD cohort had R2-ISS III/IV and 4 (27%) patients had high-risk cytogenetic abnormalities, compared to 58 (46%; p = 0.18) and 64 (51%; p = 0.10) in the DVRD cohort, respectively. Most patients in both groups received post-transplant maintenance (93% in the DKRD group and 82% in the DVRD group; p = 0.47), mostly Len alone (57% and 70%, respectively). Median time to neutrophil engraftment (ANC >500) after transplant was 12 days in both groups (p = 0.75), and median time to platelet engraftment (plt >20 K) was 12 days in the DKRD group and 13 days in the DVRD group (p = 0.35). The pre- and post-transplant response rates in the DKRD and DVRD groups were: ≥CR and ≥VGPR pre-transplant 40% and 100% vs. 26% (p = 0.24) and 78% (p = 0.08); at day 100 post-transplant: 60% and 100% vs. 52% (p = 0.60) and 94% (p = 1.00); at best post-transplant response: 73% and 100% vs. 77% (p = 0.75) and 99% (p = 1.00), respectively. Prior to transplant, 67% of the patients in the DKRD group achieved MRD negativity compared to 48% in the DVRD group (p = 0.18); at best-post transplant response, 60% and 71% had MRD negativity, respectively (p = 0.48). After a median follow up of 18.7 (3.6–47.4) months, median PFS and OS were not reached for either the DKRD or DVRD groups. 1-year and 2-year PFS rates were both 100% for DKRD; 93% and 86% for DVRD. 1-year and 2-year OS rates were both 100% for DKRD; 98% and 93% for DVRD. There was no significant difference in either PFS (hazard ratio [95% CI] 1.62 [0.16–16.33], p = 0.68) or OS (0.68 [0.03–16.35], p = 0.81) between the two induction groups, using stabilized inverse probability weights. Day100 and 1-year non-relapse mortality rates were 0% for both induction groups. All deaths were due to progression of MM. Three patients developed second primary malignancies, all in the DVRD group. **Conclusions:** To the best of our knowledge, this is the first study comparing the outcomes of MM patients receiving standard of care DKRD and DVRD induction followed by autoHCT. With the limitation that only 11% patients received DKRD, response rates and post-transplant survival outcomes

were highly encouraging, and comparable, with both quadruplet regimens.

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DVRD Induction Followed by Autologous Hematopoietic Stem Cell Transplantation for Older Patients with Multiple Myeloma

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Introduction: There are limited data on the outcome of older patients with newly-diagnosed multiple myeloma (MM) receiving daratumumab, bortezomib, lenalidomide (Len), and dexamethasone (DVRD) followed by upfront autologous transplant (autoHCT). In both the GRIFFIN (Voorhees et al. Blood 2020) and PERSEUS (Sonneveld et al. NEJM 2024) trials the upper age limit for inclusion was 70 years. **Methods:** This is a single-center, retrospective chart review of consecutive adult MM patients that received upfront autoHCT after standard of care DVRD between 2021 and 2024. Primary outcomes were progression-free (PFS) and overall survival. We used stabilized inverse probability weights (IPW) to compare outcomes between the older group (age ≥70) and the younger group (age < 70). **Results:** 125 patients were included: 27 (22%) in the older group and 98 (78%) in the younger age group. Median age at autoHCT was 74 (range 70–78) years for the older group and 59 (40–69) years for the younger group. 16 (64%) patients in the older group had R2-ISS III/IV and 12 (44%) had high-risk cytogenetic abnormalities, compared to 42 (49%; p = 0.26) and 52 (53%; p = 0.52) in the younger group, respectively. Most patients received post-transplant maintenance (85% in the older group and 82% in the younger group; p = 0.78), mostly Len alone (65% and 71%, respectively). Median time to neutrophil engraftment (ANC >500) after transplant was 12 days (range 10–15) in the older group and 12 days (range 10–13) in the younger age group (p = 0.06), and median time to platelet engraftment (plt >20 K) was 14 days (range 10–18) and 13 days (range 9–20), respectively (p = 0.09). The pre-and post-transplant response rates in the older and younger groups were ≥CR and ≥VGPR: pre-transplant 30% and 81% vs. 24% (p = 0.62) and 78% (p = 0.79); at best post-transplant response 78% and 100% vs. 77% and 99% (both p = 1.00), respectively. Prior to transplant, 42% of the patients in the older group achieved MRD negativity compared to 49% in the younger group (p = 0.66); at best-post transplant response, 50% and 75% had MRD negativity, respectively (p = 0.10). After a median follow up of 19.1 (range 3.6–47.4) months, 1-year and 2-year PFS rates were 91% and 78% for the older age group vs. 93% and 89% in the younger group (p = 0.41). The median OS was not reached for both age groups. 1-year and 2-year OS rates were 100% and 92% in the older age group vs. 98% and 93% in the younger group. There was no significant difference in either PFS (hazard ratio [95% CI] 1.23 [0.34–4.42], p = 0.75) or OS (0.49 [0.02–14.29], p = 0.68) between the two age groups, using stabilized inverse probability weights. There were no non-relapse mortality (NRM) events in both age groups. Four patients developed second primary malignancies, all in the younger age group. **Conclusions:** MM patients aged ≥70 years, who received DVRD induction followed by autoHCT had similar response rates, PFS and OS as younger patients, without any treatment-related deaths.

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Outcomes of Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplant Following VRD or KRD Induction Therapy

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Introduction: The optimal induction regimen for patients with newly diagnosed multiple myeloma (NDMM) remains an area of ongoing investigation. Real-world comparative data on outcomes following bortezomib, lenalidomide, and dexamethasone (VRD) versus carfilzomib, lenalidomide, and dexamethasone (KRD) induction prior to autologous hematopoietic cell transplantation (autoHCT) is limited. **Methods:** We conducted a single-center retrospective analysis of patients with NDMM who received VRD or KRD induction followed by upfront autoHCT between 2006–2021. All cytogenetic risk groups were included. High-risk cytogenetic abnormalities (HRCA) were defined as del(17p), t (4;14), t (14;16) or 1q21 gain or amplification (1q+) by FISH. **Results:** 1129 patients were included in the analysis, 364 received KRD induction and 765 received VRD. The median age was 61.9 years (range 25.4–82.6). Baseline characteristics were mostly balanced between the two groups,

though the KRD group had a higher proportion of patients with HRCA (43% vs. 32%; p < 0.001), Second Revision of the International Staging System (R2-ISS) stage III/IV disease (38%/9% vs. 34%/5%; p = 0.008), creatinine ≤2 mg/dL (95% vs. 90%; p = 0.007) and more often received busulfan-melphalan conditioning (22% vs. 15%; p = 0.005). KRD was associated with higher response rates compared to VRD across all timepoints: ≥CR and ≥VGPR] pre-transplant 23% and 71% vs. 16% (p = 0.006) and 61% (p < 0.001); at day 100 post-transplant: 47% and 85% vs. 38% (p = 0.003) and 80% (p = 0.050); at best post-transplant response:71% and 93% vs. 60% (p < 0.001) and 89% (p = 0.07), respectively. A higher proportion of patients treated with KRD achieved MRD negativity prior to transplant (49% vs. 42%, p = 0.027). With a median follow-up of 38.6 months (range 0.3–172.8), median PFS was significantly longer in the KRD group compared to VRD (62.2 months vs. 48.7 months; p = 0.009). 5-year PFS rate was 52% with KRD compared to 44% with VRD. Median OS was not reached with KRD vs. 122.7 months with VRD (HR 1.16, 95% CI 0.80–1.68, p = 0.43). KRD induction was associated with improved PFS in a weighted multivariable analysis (hazard ratio [95% CI] 0.76 [0.60–0.97], p = 0.026). Subgroup analysis showed PFS benefit for KRD in patients with standard-risk cytogenetics (0.51 [0.35–0.74]), patients aged < 65 years (0.74 [0.55–0.99]) and male patients (0.61 [0.44–0.84]), whereas there was no significant advantage for KRD in patients with HRCA (0.82 [0.60–1.12]), patients aged ≥65 years (0.75 [0.52–1.07]) and female patients (0.91 [0.66–1.26]). **Conclusions:** In a large real-world study, KRD induction was associated with higher response rates and longer PFS compared to VRD in NDMM patients who received upfront autoHCT. Subgroup analysis showed significant PFS advantage for KRD in patients with standard-risk cytogenetics, those aged < 65 years and male patients.

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Survival of Light-Chain Multiple Myeloma at the National Cancer Institute of Peru

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Introduction: Light-chain multiple myeloma (LCMM) is a specific subtype of MM accounting for 15% of all MM cases. In LCMM abnormal plasma cells only produce light-chain proteins (kappa or lambda) instead of both heavy and light chains, leading to unique clinical challenges and manifestations. Data on this specific type of MM was not reported in LATAM. Our aim was to describe the clinical characteristics and the progression-free and overall survival of LCCM patients. **Methods:** This is a retrospective study, the information was abstracted from medical records (MR) for all newly diagnosed light-chain multiple myeloma patients >18 years treated at the Instituto Nacional de Enfermedades Neoplasicas (INEN) from 2017 to 2023. The patients must have received bortezomib thalidomide dexamethasone (VTd) as first-line treatment regardless of their eligibility for autologous transplants to be included in the study. The estimate of the survival curves was performed by the Kaplan-Meier method, and the difference was computed by the log-rank test. **Results:** A total of fifteen patients were included, mostly were male (80%). The median age was 55 years (range 44–76). The clinical stage was reported as I and II in 60% and 40% of cases, respectively. Two-third were kappa light chains. All patients received VTd. Fourteen patients had enough information to evaluate the treatment response: the overall response rate was 87% (complete response: 47%, very good partial response: 27%, and partial response: 13%). 80% were eligible for autologous transplant (AT), only 66% of this population finally proceed to AT. The median follow-up time was 27 months (range 5–76). The median overall survival was not reached. The 5-year overall survival was 64.6% (CI, 34.4–83.6). The median progression-free survival was 58 months (IQR 55m-76 m). The 5-year PFS was 26.3% (CI, 1–67). **Conclusions:** The overall response rate was high in our LCMM cohort. Overall survival was higher than reported in the literature. However, the progression-free survival was low, which is consistent with international reports. Only two-thirds of the eligible patients proceed to autologous transplant. The most common light chain was kappa.

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Survival of IgA Multiple Myeloma at the National Cancer Institute of Peru

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Introduction: IgA myeloma is a subtype of multiple myeloma, representing approximately 20% of all myeloma cases. It's the second most common type, after IgG myeloma, which accounts for about 52% of cases. IgA myeloma is generally considered more aggressive than IgG myeloma. Survival has improved significantly with modern treatment. In Peru, bortezomib-based triple therapy is used as first-line treatment. Our aim was to describe the clinical characteristics and the progression-free and overall survival of IgA multiple Myeloma patients. **Methods:** This is a retrospective study, the information was abstracted from medical records (MR) for all newly diagnosed IgA multiple myeloma patients >18 years treated at the Instituto Nacional de Enfermedades Neoplasicas (INEN) from 2017 to 2023. The patients must have received bortezomib thalidomide dexamethasone (VTd) as first-line treatment regardless of their eligibility for autologous transplants to be included in the study. The estimate of the survival curves was performed by the Kaplan-Meier method, and the difference was computed by the log-rank test. **Results:** A total of

34 patients were included, mostly were male (74%). The median age was 60 years (range 38–83). The clinical stage was reported as I, II and III in 29%, 41% and 24% of cases, respectively. 59% had kappa light chains. All patients received VTd. Thirty patients had enough information to evaluate the treatment response: the overall response rate was 73% (stringent complete response + complete response: 53%, very good partial response: 10%: and partial response: 10%). 65% were eligible for autologous transplant (AT), only 55% of this population finally proceed to AT. The median follow-up time was 30.5 months (range 3–96). The median overall survival was not reached. The 5-year overall survival was 73.6% (CI, 53.5–86). The median progression-free survival was 27 months (IQR 12m-NR). The 5-year PFS was 34.2% (CI, 1.5–53.9). **Conclusions:** The overall response rate was slightly below what was reported in the literature. Overall survival was similar to international reports. However, the progression-free survival was lower than previous clinical studies. Almost two-thirds of the eligible patients proceed to autologous transplant. The most common light chain was kappa.

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Survival of Non-Transplanted Newly Diagnosed Multiple Myeloma Patients at the National Cancer Institute of Peru

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Introduction: Approximately 70% of newly diagnosed multiple myeloma (NDMM) patients are ineligible for a stem cell transplant according to the literature. However, a group of patients eligible for transplant ultimately do not proceed with it. At our institution, we treat patients, whether or not they are eligible for transplant, with bortezomib-based triple therapy. The aim of this study was to evaluate the progression-free and overall survival in the cohort of non-transplanted patients. **Methods:** A retrospective study was conducted by retrieving information from medical records for all newly diagnosed multiple myeloma patients >18 years who were treated at the Instituto Nacional de Enfermedades Neoplasicas (INEN) from 2017 to 2023. The patients must have received bortezomib thalidomide dexamethasone (VTd) as first-line treatment. Only patients who did not receive autologous transplant regardless of the initial eligibility for transplant were included in the study. The estimate of the survival curves was performed by the Kaplan-Meier method, and the difference was computed by the log-rank test. **Results:** A total of 82 patients were included, mostly were male (65%). The median age was 62 years (range 30–83). Ig G myeloma was the most common subtype with 63% followed by Ig A in 27% and and light chains in 10% of the cases. The clinical stage was reported as I, II and III in 33%, 31% and 33% of cases, respectively. Kappa light chains account for 68%. All patients received VTd. 64% of the patients were initially classified as eligible for transplant, however none of them were transplanted. Sixty-nine patients had enough information to evaluate the treatment response: the overall response rate was 71% (stringent complete response + complete response: 24%, very good partial response: 22%: and partial response: 24%). The median follow-up time was 22.5 months (range 1–91). The median overall survival was not reached. The 5-year overall survival for the entire cohort was 63.3% (CI, 50.8–73.5). The 5-year overall survival for transplant eligible group was 58.8% (CI, 42.9–71.6) and for the transplant ineligible group was 72.5% (CI, 50.6–85.8), p = 0.99. The median progression-free survival was 18 months (IQR 10 m–29 m). The 5-year PFS was 10.9% (CI, 2.4–26.6). **Conclusions:** In this cohort of non-transplant patients, there were many young patients. Patients eligible for transplants accounted for more than 50% of cases. The overall response rate was slightly lower than reported in the literature; however, a marked decrease in the complete response rate was observed. This group of patients had poor overall survival and ever worse progression-free survival. New strategies and novel treatments are needed in this group of patients with poor prognosis.

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Evaluating Racial and Ethnic Disparities in Progression Assessment Patterns in Routine Clinical Practice Among Patients with Newly Diagnosed Multiple Myeloma

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Introduction: Globally, multiple myeloma (MM) is the second most common hematologic malignancy. Underrepresented minorities (URM) may lack access to care, resulting in disparities. Disease progression in MM is based on assay results specified in the International Myeloma Working Group (IMWG) Uniform Response Criteria. This research aimed to understand differences in progression assessment patterns in routine clinical practice among URM to elucidate potential disparities in care. **Methods:** We included newly diagnosed multiple myeloma (NDMM) patients starting on first line

of therapy (1L) from the Flatiron Health Research Database (2011–2023). Recommended assays as per consensus guidelines to evaluate disease progression include serum protein electrophoresis (SPEP), 24 hr urine protein electrophoresis (UPEP), and free light chains (FLC). Patterns and cadence of assays collected at each progression assessments were characterized for racial and ethnic (R&E) groups: Non-Hispanic White (NHW; N = 7,178), Hispanic (N = 904), Non-Hispanic Black (NHB; N = 2,159), Non-Hispanic Asian (NHA, N = 226), and Non-Hispanic Other Races (NHO, N = 749). Testing patterns were characterized at baseline (90 days prior to 7 days post 1L initiation) and on-treatment (8 days post 1L initiation through the end of 1L) periods. Stratified analysis by factors such as age and socioeconomic status (SES) were explored to understand their impact on the assessment pattern and cadence in URMs. **Results:** The most common assessment pattern was combined SPEP + FLC, conducted across R&E groups during baseline (33–48%) and similarly on-treatment period among all assessment episodes (41–52%). This was followed by individual assessments during baseline (FLC:15–24%, SPEP:10–13%) and on-treatment period (SPEP: 20–29%, FLC:18–29%), respectively. UPEP was infrequently utilized during baseline (6–11%) and on-treatment period (1–3%). Patterns remained consistent in analyses stratifying on age, transplant reception and SES. The Hispanic and NHO groups appeared to have slightly lower rates of having any IMWG tests recorded during on-treatment period when compared with other groups, in the full cohort (80%–83% compared to 85%–89%) and in stratified analyses. The median time between IMWG assays was 28 days across all patients, irrespective of R&E group. This was consistent when stratified by age, transplant reception, SES, and treatment start year, except in transplant recipients, where median time was 21 days. **Conclusions:** Assay collection patterns and cadence were consistent during baseline and on-treatment periods among NDMM patients in 1L, suggesting no observed disparities in progression assessment in URMs. Further evaluation of real-world progression endpoints is needed to understand if there are meaningful differences in MM assay collection across URM in later lines of treatment or other real-world populations.

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Interim Analysis of DARA VRD in the Treatment of TE-NDMM Patients with Standard Risk Who Refused to Accept ASCT as First Line in China

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Introduction: In China, ASCT as front-line therapy is merely 10%. Studies, such as GRIFFIN (D-VRd) and CASSIOPEIA (D-VTd), have shown promising results in TE-NDMM patients receiving ASCT as initial therapy. These findings have prompted us to investigate the potential efficacy of D-VRd in standard-risk patients. This interim analysis presents the first open-label, single-arm study evaluating the efficacy and safety of D-VRd in TE-NDMM patients with standard risk who declined ASCT in China (NCT 05088330). **Methods:** We enrolled IMWG-defined NDMM patients,who were TE but voluntarily declined ASCT,excluding those with t(4;14), Del(17p), t(14;16), R-ISS stage III. The D-VRd regimen consisted:Daratumumab:16 mg/kg I.V. weekly for 2 cycles, then every 3 weeks for 6 more cycles,bortezomib:1.3 mg/m2 SC,Days 1, 4, 8, 11,lenalidomide:25 mg P.O., Days 1–14,dexamethasone:20 mg P.O., Days 1, 2, 4, 5, 8, 9, 11, 12.All for 8 cycles, followed by daratumumab maintenance:16 mg/kg q4w × 12mo. The primary endpoint was NGS MRD negativity at 10-5 after 8 cycles of D-VRd. Secondary objectives included ORR,sCR,≥CR,≥VGPR, AEs,TTR, and DOR. Stem cell collection advised post-Cycle 4. **Results:** By June 30, 2024, 46 pts were enrolled. The median age was 62 years, with 23 male pts. Cytogenetic analysis revealed 27 patients with 1q gain and 4 pts with t(11;14). Additionally, 8 pts presented with renal insufficiency, and 6 had EMD. The ORR was 97.4%, with 89.7% of pts achieving VGPR or better. Notably, 64.1% of patients attained CR or sCR. The median treatment duration was 10 months and median treatment cycles was 9.19 pts successfully underwent autologous stem cell collection and storage. With a median follow-up of 12 months, 72.7% of pts achieved NGS MRD negativity after 8 cycles. Subgroup analysis comparing pts with 1q gain versus those without showed ORR, CR+sCR, and 1-year progression-free survival rates of 95.8%, 58.3%, and 88.2% versus 100%, 73.3%, and 100%, respectively ($p > 0.01$). Treatment-related adverse events primarily consisted of hematological toxicities, occurring in all 46 pts. These included thrombocytopenia in 80.4% (n = 37; 22 Grade 1–2, 15 Grade 3–4), lymphopenia in 58.7% (n = 27; 17 Grade 1–2, 10 Grade 3–4), and neutropenia in 43.4% (n = 20;9 Grade 1–2, 11Grade 3–4) of pts. Other adverse events included ALT/AST elevation in 43.4% (n = 20; 19 Grade 1–2, 1 Grade 3–4) and peripheral neuropathy in 45.7% (n = 21;12 Grade 1–2, 9 Grade 3–4) of pts. Infusion-related reactions were reported in 23.9% of pts (n = 11, all Grade 1–2). Pneumonia occurred in 13.0% of pts (n = 6, all Grade 3),with all cases resolving. One patient discontinued lenalidomide due to pulmonary embolism. **Conclusions:** Interim analysis shows D-VRd induces rapid, deep responses in Chinese TE-NDMM patients declining ASCT (including1q gain). High NGS MRD negativity (72.7%) pre-maintenance underscores efficacy. Hematological toxicities (most common AEs) were manageable after cycle 2, supporting acceptable safety. These results warrant further long-term evaluation.

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Efficacy of Daratumumab-Bortezomib-Lenalidomide-Dexamethasone (DVRd) vs Daratumumab-Lenalidomide-Dexamethasone (DRd) in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: The CEPHEUS trial was a phase 3 study in transplant-ineligible (TIE) patients with NDMM and patients for whom transplant was not planned as initial therapy. DVRd demonstrated superiority with respect to the overall minimal residual disease-negative complete response or better (MRD-negative CR) rate and progression-free survival (PFS) over bortezomib-lenalidomide-dexamethasone (VRd) in CEPHEUS. The current standard of care for the treatment of TIE patients with NDMM is DRd, based on data from the MAIA trial; however, the comparative efficacy of DVRd vs DRd has not been assessed. **Methods:** An unanchored, indirect treatment comparison (ITC) of DVRd vs DRd was performed based on individual patient-level data (IPD) from the CEPHEUS and MAIA trials. As MAIA enrolled only TIE patients and CEPHEUS excluded patients aged >80 years, only TIE patients aged ≤80 years at enrollment in CEPHEUS and MAIA were included in this ITC. Inverse probability of treatment weighting (IPTW) was used to balance the DVRd and DRd treatment cohorts on the following baseline patient characteristics: International Staging System stage, cytogenetic risk, age, Eastern Cooperative Oncology Group performance status, multiple myeloma immunoglobulin isotype, extramedullary disease, frailty status (per the simplified International Myeloma Working Group frailty score), sex, estimated glomerular filtration rate, anemia, and lactate dehydrogenase. To assess the relative efficacy of DVRd and DRd with respect to MRD-negative CR rate, PFS, and overall survival (OS), weighted logistic regression, Cox regression, and Kaplan-Meier estimates were used. Because the COVID-19 pandemic impacted CEPHEUS more than MAIA, an OS sensitivity analysis was performed, in which deaths attributed to COVID-19 in both studies were censored. **Results:** In total, 144 CEPHEUS DVRd patients (TIE subgroup) and 313 MAIA DRd patients (age ≤80 years subgroup) were included in the analysis. After IPTW, baseline patient characteristics were well balanced across the 2 treatment cohorts. For the MRD-negative CR rate, the adjusted odds ratio for DVRd vs DRd was 3.04 (95% CI, 2.01–4.61; 61.2% vs 34.2%). For PFS, the adjusted hazard ratio (HR) for DVRd vs DRd was 0.62 (95% CI, 0.44–0.88). For OS, the adjusted HR for DVRd vs DRd was 0.80 (95% CI, 0.53–1.19). When censoring the COVID-19 deaths, the adjusted OS HR for DVRd vs DRd was 0.63 (95% CI, 0.41–0.98). **Conclusions:** Results from this ITC using IPD from the CEPHEUS and MAIA trials show that treatment with DVRd leads to a statistically significant improvement in the MRD-negative CR rate and PFS as well as an improved OS trend compared with DRd in TIE patients with NDMM ≤80 years. When COVID-19 deaths were censored, treatment with DVRd led to a statistically significant improvement in OS. In the absence of a head-to-head trial, this ITC may inform and guide appropriate treatment selection for maximum benefit in TIE patients with NDMM aged ≤80 years.

PA-454

Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone for Newly Diagnosed Multiple Myeloma: Outcome and Safety Profile from a Multi-Center Real-World Experience

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Introduction: The lenalidomide-bortezomib and dexamethasone (RVD) regimen was once the first-line treatment for multiple myeloma, and achieved favorable outcomes. The addition of daratumumab to the RVD regimen (D-VRD) has been shown to improve response rates and depth of response. Currently, the D-VRD regimen has been recommended by the NCCN as a first-line treatment for newly diagnosed multiple myeloma (NDMM). **Methods:** A retrospective study was conducted with medical review of all patients diagnosed with multiple myeloma and treated with D-VRD at Peking University People's Hospital-Sheng Jing Hospital of China Medical University and Fu Xing Hospital, Capital Medical University-from June 2021 to February 2025-response rate and safety profile were evaluated. The results were compared with the outcomes of NDMM patients treated with the RVD regimen in the Peking University People's Hospital from August 2016 to September 2020. **Results:** A total of 96 patients were enrolled (median age 60, range 35–70 years), including 34 with high-risk cytogenetic abnormalities. Among all 93 evaluable patients, the overall response rate (ORR), ≥very good partial response (≥VGPR), and complete response (CR) rates were 93.5% (87/93), 82.8% (77/93), and 50.5% (47/93), respectively, including 21 cases of stringent complete response (sCR). The median time to response was 1.0 cycle (range 1.0–4.0). There

were no significant differences in ORR or CR rate between patients with high-risk and standard-risk cytogenetics. Compared to historical data from NDMM patients treated with RVD regimen, the D-VRD regimen demonstrated significantly higher rates of ORR, ≥ VGPR and CR rate ($p = 0.042$, $p < 0.001$ and $p < 0.001$, respectively). In patients with high-risk cytogenetics, ORR rate and ≥VGPR rate were higher in D-VRD group ($p = 0.027$, $p = 0.004$, respectively). There was no significant difference in 1-year progression-free survival (PFS) rates between the two regimens (96.6% vs 96.0%-$p = 0.658$). Autologous hematopoietic stem cell collection was completed in 46 patients, with median MNC 14.16 (2.5–39.72) × 10^8/kg and median CD34+ cells 3.97 (1.04–16.4) × 10^6/kg. The most common adverse events (AEs) were hematological toxicities-grade 3/4 neutropenia was detected in 27 patients (28.1%), thrombocytopenia in 2 patients (2.1%). The most common non-hematological AEs were infection, in 34 patients, including 2 cases of septic shock-peripheral neuropathy in 14 patients, hepatotoxicity in 6 patients. None of the patients experienced grade 3/4 infusion reactions. Treatment discontinued in 4 patients due to transient ischemic attack (TIA), cerebral infarction, pulmonary embolism and peripheral neuropathy, respectively.

Table 1 Efficacy of RVD and D-VRD Regimen.

	RVD	D-VRD	*P* value
ORR (%)	84.2	97.0	0.027
≥VGPR (%)	55.8	78.8	0.004
≥CR (%)	24.2	42.4	0.077

Conclusions: The D-VRD regimen demonstrates safety and efficacy in NDMM patients, facilitating deeper disease remission and counteracting the poor prognostic impact of high-risk cytogenetic abnormalities.

PA-455

Dara-VCd in Newly Diagnosed Multiple Myeloma with Severe Renal Impairment: A Prospective Multicenter Single-Arm Study

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Introduction: Renal impairment (RI) is one of the most common complications of multiple myeloma (MM). The combination of bortezomib, cyclophosphamide, and dexamethasone (VCd) has significantly improved treatment outcomes and overall survival (OS) in MM patients. However, persistent RI after treatment remains a poor prognostic factor. Recent studies have demonstrated that Daratumumab not only deepens hematologic responses but also promotes renal recovery. Nevertheless, patients with severe RI are frequently excluded from clinical trials. Therefore, we conducted a prospective study to evaluate the efficacy and safety of the DVCd regimen (daratumumab + VCd) in newly diagnosed MM (NDMM) patients with severe RI. **Methods:** This is an ongoing prospective multicenter single-arm study. NDMM patients with myeloma-related RI (eGFR< = 40 ml/min/1.73 m2) were enrolled. Patients received one initial cycle of VCd (1.3 mg/m2 bortezomib at day 1,4,8,11 of 28-day cycle, Cyclophosphamide 200 mg/m2 at day 1,4,8,11, and dexamethasone 20 mg on the day of and after bortezomib). Thereafter Daratumumab was added to VCd regimen (16 mg/kg weekly for 2 cycles, bi-weekly for next 4 cycles, monthly up to 24 does, and subsequently every 8 weeks until disease progression or unacceptable toxicity). Autologous stem cell transplantation (ASCT) was administered to transplant-eligible patients following induction therapy. During the maintenance phase, a Daratumumab-based doublet regimen (daratumumab with bortezomib) was recommended. The primary endpoint was the renal overall response rate (ORR) after 4 cycles of induction therapy. Secondary endpoints included hematological ORR, progression-free survival (PFS), and OS. **Results:** A total of 51 patients were enrolled across five centers between September 25, 2023, and March 31, 2025. Three patients discontinued after one cycle and were lost to follow-up. At data cutoff, 43 had completed four induction cycles, and five remained on treatment. The median age was 63 years (range, 47–79), and 25.0% (n = 12) required dialysis at baseline. High-risk cytogenetics (del[1p32], del[17p], t[4;14], or +1q21) were present in 58.3% (n = 28). Based on R2-ISS, 27.1% and 37.5% of patients were stage III and IV, respectively. Forty-three patients were evaluable for efficacy. Median follow-up was 10.8 months (range, 5.1–18.2). Five (11.6%) underwent ASCT after induction. Renal ORR was 76.7%, including 18.6% CR, 20.9% PR, and 37.2% MR. Hematologic ORR was 95.1%, comprising 26.8% ≥CR, 51.2% VGPR, and 17.0% PR. The most common grade 3/4 adverse events were neutropenia (18.6%) and infections (20.9%). Two patients progressed during follow-up, including one with double-hit cytogenetics who died. Median PFS and OS were not reached; estimated 12-month PFS and OS were both 95.2%. **Conclusions:** DVCd combination regimen could deepen both renal and hematologic responses in NDMM patients with severe RI.

PA-456

Treatment Outcomes in Isolated Gain1q Multiple Myeloma Patients

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Introduction: Risk-adaptive treatment for newly diagnosed multiple myeloma (MM) is crucial for optimizing outcomes. High-risk disease is heterogenous across a variety of cytogenetic

abnormalities (CA), of which extra copies of 1q is the most prevent. While the presence of >3 copies (amp1q) has worse outcomes than 3 copies (gain1q), gain1q is itself an independent high-risk factor incorporated into R2-ISS. Gain1q can occur in combination with other high-risk CA or in isolation, but the majority of phase III RCTs do not specify these nuances, impeding understanding of therapy-related outcomes for this subgroup. To better tailor therapies in patients with isolated gain1q, evaluating different components to frontline treatment is paramount. We performed a retrospective analysis of treatment characteristics and outcomes for patients with an isolated gain1q and amp1q. This is the first study in isolated gain1q that includes daratumumab (dara)-based regimens and will provide insights into managing such patients. **Methods:** This is a single-center, retrospective cohort study at the Yale Cancer Center from January 1, 2017 to November 1, 2024. Patients (pts) with a new diagnosis of MM and copy number change in chromosome arm 1q were included. Patients were excluded if they had other high-risk CA. The primary endpoint was progression free and overall survival within the gain1q cohort stratified by induction regimen, use of autologous stem cell transplant (ASCT), and doublet verses single agent in maintenance. The secondary endpoints are PFS and OS comparison between gain1q and amp1q cohorts. **Results:** A total of 72 pts were identified with isolated gain1q and 16 pts with isolated amp1q. Median follow-up was 3.42 years for gain1q and 3.52 years for amp1q cohorts. Within the gain1q cohort, 24% received dara as quadruple and 11% as triplet therapy, 38% received VRd, 18% KRd, and 10% CyBorD. Of the entire cohort, 43% of pts received an ASCT and 40% had doublet maintenance. Within the dara-treated cohort, 52% of pts received an ASCT and 100% continued maintenance therapy with two agents, of which 72% were dara and lenalidomide. The use of dara-based induction regimens significantly prolonged PFS with a 5-year PFS of 85% compared to 44% for all others ($p = 0.044$). In addition, the use of ASCT resulted in a 5-year OS of 100% compared to 64% without ($p = 0.0022$). Secondary endpoints demonstrated that amp1q was associated with shortened PFS ($p = 0.04$) and OS ($p = 0.015$) compared to gain1q. **Conclusions:** Our study demonstrates treatment characteristics associated with improved outcomes in isolated gain1q. The use of dara-based therapy is shown to improve PFS within this specific cohort, which is aligned with subgroup analyses from both isatuximab-based phase III trials and dara-based phase II GRIFFIN trial. We also demonstrate an OS benefit with ASCT. Further analysis is needed to evaluate long-term outcomes of dara with and without transplant, and duration of dara in maintenance.

PA-457

Early Identification of Patients with Multiple Myeloma Progressing within a Short-Term following Tandem Transplantation

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Introduction: High-dose chemotherapy followed by autologous stem cell transplant (ASCT) remains the standard treatment for transplant-eligible patients with newly diagnosed multiple myeloma (MM), significantly improving long-term outcomes. Tandem ASCT, defined as a second ASCT within six months of the initial procedure, has been proposed to further optimize therapeutic efficacy. However, early disease progression following tandem ASCT remains a significant challenge, reflecting the inherent biological heterogeneity of MM. In this study, we identified that patients progressing within 12 months post-tandem ASCT demonstrated markedly inferior progression-free survival (PFS) and overall survival (OS) compared to who did not progress within 12 months. In this study, we aim to explore risk factors associated with clinical features to identify these high-risk patients and construct a prognostic model. This model may facilitate early risk stratification and therapeutic optimization for high-risk patients in clinical practice. **Methods:** This retrospective cohort study analyzed consecutively enrolled patients with newly diagnosed MM undergoing tandem ASCT between July 1, 2017, and March 31, 2025, with a second transplantation follow-up duration ≥12 months. The cohort was randomly allocated into training (n = 23, 70%) and validation (n = 11, 30%) sets. Univariate and multivariate analyses were performed to identify independent risk factors for patients progressing within 12 months post-tandem ASCT. A prognostic nomogram was developed using logistic regression algorithms and internally validated. **Results:** The study cohort comprised 34 MM patients undergoing tandem ASCT, stratified into early progression (≤12 months post-transplant, n = 9, 26.5%) and non-early progression (>12 months post-transplant, n = 25, 73.5%) subgroups. With a median follow-up of 26.2 months, the early progression cohort demonstrated significantly inferior outcomes: median PFS of 18.3 months versus unreached in the non-early progression group ($P < 0.0001$), while OS remained immature in both cohorts. Multivariate regression identified serum creatinine ≥ 96.8 μmol/L (OR 47.0, 95% CI 1.64–1345.14; $P = 0.024$) and hypercalcemia (OR 27.0, 95% CI 1.34–545.71; $P = 0.032$) as independent predictors of early progression, contrasting with M-protein decline Pattern B exhibiting protective effects (OR 0.04, 95% CI 0.00–0.88; $P = 0.041$). The composite prognostic model achieved exceptional discrimination (training cohort AUC 0.951; validation cohort AUC 1.0). **Conclusions:** This study establishes a validated predictive nomogram incorporating serum creatinine, hypercalcemia, and M-protein decline Pattern B that accurately stratifies early progression risk following tandem ASCT.

PA-458

Autologous Peripheral Blood Hematopoietic Stem Cell Transplantation on the Treatment of Multiple Myeloma: A Single-Center Clinical Analysis on PFS

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Introduction: Since the launch of intravenous melphalan (Mel) in China in 2019, our transplantation center has adopted high-dose intravenous Mel as a conditioning regimen, treating 50 consecutive newly diagnosed MM patients receiving ASCT, achieving good clinical efficacy. This study retrospectively analyzed the clinical characteristics and PFS of these 50 MM patients after HDM-ASCT, and preliminarily discussed the impact of different risk levels, response degrees, and minimal residual disease (MRD) on PFS. Our findings may provide more clinical evidence for MM patients before and after ASCT about the importance of MRD monitoring and the impact of the degree of remission on PFS **Methods:** A retrospective study was conducted on 50 consecutive MM patients who underwent HDM-ASCT. The PFS was the primary outcome, while the treatment efficacy and MRD status after ASCT served as the secondary outcomes. **Results:** All 50 patients with MM achieved hematopoietic reconstruction, with no transplant-related deaths. The effective remission rate of the 50 MM patients (≥very VGPR)increased from 54% before HDM-ASCT to 82% after HDM-ASCT, with the CR rate increasing from 30% before HDM-ASCT to 62% after HDM-ASCT. The MRD negativity rate after HDM-ASCT was 64.4%, a significant improvement from 44.4% before HDM-ASCT. As of October 31, 2023, the median follow-up time was 25 months (7.5–49.5 months), with 12 patients experiencing relapse, 5 deaths, and an expected 3-year PFS and overall survival rate of 70.5% and 88.4%, respectively. Patients with CR and VGPR after HDM-ASCT had a significantly longer expected 3-year PFS compared to patients with PR. The expected 3-year PFS of MRD-negative patients before (84.7% vs 62.8%) and after HDM-ASCT (80.5% vs 57.6%) was longer than MRD-positive patients,without significant difference. Among 18 patients who never achieved MRD negativity or sustained negativity for more than 1 year, 12 experienced relapse, with an expected 3-year PFS of only 32.6%. In contrast, among 26 patients with sustained MRD negativity for 1 year or longer, no relapse cases occurred. The 3-year PFS rates of patients with standard-risk and high-risk cytogenetic abnormalities were 71.9% and 66.0%, respectively, without significant difference. **Conclusions:** HDM-ASCT can significantly improve the CR and MRD negativity rates in MM patients. Patients need to strive for CR and MRD negativity before undergoing HDM-ASCT to optimize PFS benefits post-transplantation. Patients who remain in PR after ASCT have a poor prognosis. Regular monitoring of MRD is needed after ASCT, and sustained MRD negativity for one year is crucial for the long-term PFS of MM.

PA-459

Efficacy and Safety of Ixazomib-Based Maintenance Therapy after Autologous Hematopoietic Stem Cell Transplantation in Multiple Myeloma Patients: A Retrospective Analysis

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Introduction: Multiple myeloma (MM) is the second most prevalent hematologic malignancy, and autologous hematopoietic stem cell transplantation (ASCT) remains the standard treatment for transplant-eligible patients. The use of Ixazomib as maintenance therapy has shown promise in extending survival outcomes post-ASCT. This study investigates the efficacy and safety of maintenance therapy with Ixazomib in MM patients after ASCT. **Methods:** A retrospective analysis was conducted on 28 MM patients who received Ixazomib-based maintenance therapy out of 64 MM patients who underwent ASCT at the Hematology Center of the First Affiliated Hospital of Xinjiang Medical University from August 2019 to August 2023. The primary outcome was progression-free survival (PFS). The treatment efficacy and minimal residual disease (MRD) status served as secondary outcomes. **Results:** The median age of 28 patients who received Ixazomib-based maintenance therapy after ASCT was 57 years (range: 48–69 years). Before ASCT, 9 patients (32.1%) achieved complete response (CR), 7 patients (25.0%) achieved very good partial response (VGPR), and 12 patients (42.9%) achieved partial response (PR). After ASCT, the responses improved significantly, with 17 patients (60.7%) achieving CR, 6 patients (21.4%) achieving VGPR, and 5 patients (17.9%) remaining at PR. After the Ixazomib maintenance therapy, 15 patients (53.5%) achieved CR, 8 patients (28.6%) achieved VGPR, and 5 patients (17.9%) retained a PR. However, 4 patients experienced disease progression during the analysis period, including a decline from CR to PR in 2 cases, from CR to VGPR in 1 case, and from VGPR to PR in 1 case. The incidence of grade ≥3 adverse reactions was 3.6%. For survival outcomes, the 3-year expected PFS for 28 patients was 70.8% (95% CI, 52.18%–89.42%), and the 3-year expected OS was 87.4% (95% CI, 73.88%–100.92%). Notably, patients who maintained MRD negativity for more than one year had a favorable expected 3-year PFS rate of 100%, significantly higher than that of MRD-positive patients. **Conclusions:** Ixazomib-based maintenance therapy demonstrates good efficacy and safety for MM patients after ASCT. The sustained negative MRD status is crucial for the long-term survival of these patients.

PA-460

Efficacy and Safety of Biweekly/Weekly Ixazomib-Dexamethasone Maintenance Therapy in Chinese Patients with Newly Diagnosed Multiple Myeloma: A Multi-Center Study

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Introduction: Ixazomib, the first oral proteasome inhibitor, has shown efficacy as maintenance therapy in newly diagnosed multiple myeloma (NDMM) patients in clinical trials. However, real-world data on ixazomib-dexamethasone (Id) maintenance in this population, particularly comparing weekly and biweekly dosing, remain limited. We conducted a multicenter real-world study to evaluate the efficacy and safety of Id maintenance in Chinese NDMM patients, including those on a biweekly ixazomib schedule. **Methods:** This retrospective study included NDMM patients from 11 tertiary centers who received ≥3 cycles of Id maintenance, from Nov 1, 2018, to Dec 1, 2022. All had achieved at least partial response (PR) after 6–8 cycles of primarily bortezomib-based induction. The primary end-point was progression-free survival (PFS). The dosing schedule of ixazomib (4 mg on days 1, 8, and 15 of a 28-day cycle [I1d] or 4 mg on days 1 and 15 of a 28-day cycle [I2d]) was determined by the treating physician based on baseline physical condition and toxicity. **Results:** A total of 168 patients were analyzed. Median age was 63 (IQR 59–73). Sixty-one of 112 (54.5%) patients had gain/amp(1q) and 35 (20.8%) had renal insufficiency. A majority of patients (111, 66.1%) had not undergone ASCT. At a median follow-up of 29.5 months, the median PFS was 24.4 (95% CI 19.2–38) months. Twenty-five (14.9%) were deceased and the median overall survival was 59 (95% CI 59-NA) months. In subgroups with amp/gain(1q), renal insufficiency, and ASCT, the median PFS was 19.2, 19.6, and 29.9 months, respectively; differences were not statistically significant (all P > 0.05). Notably, patients with MRD+ before maintenance had a significantly inferior PFS compared with those with MRD- (10.8 vs. 24.4 months, P = 0.002). MRD status remained an independent predictor of PFS in the multivariate analysis (HR 2.28 [1.19–4.36], P = 0.01). The I1d cohort (n = 118) had more frequent prior exposure to lenalidomide versus the I2d cohort (n = 47) (54.2% vs. 21.3%, P < 0.001). Median PFS was comparable between I2d and I1d (25.5 vs. 21.7 months, P = 0.4), and remained so after sIPTW adjustment (25.5 vs. 19.5 months, P = 0.45). In the elderly, amp/gain(1q), and ASCT subgroups, there was no significant difference in PFS between the two regimens (all P > 0.05). Common adverse events (AEs) included thrombocytopenia (33.3%) and gastrointestinal symptoms (23.8%). The I2d group had fewer GI AEs than I1d (10.6% vs. 28.9%, P = 0.02). **Conclusions:** In the real-world setting, Id maintenance therapy provides sustained survival benefits for NDMM patients. The biweekly ixazomib schedule achieves similar PFS with reduced toxicity, supporting its feasibility. MRD status remains a critical prognostic marker during maintenance therapy.

PA-461

Selinexor Combined Bortezomib, Lenalidomide, and Dexamethasone for Newly Diagnosed Multiple Myeloma with High-Risk Cytogenetics Abnormalities: A Single-Arm, Multi-Center, Observational Clinical Study

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Introduction: Over the past 20 years, survival of multiple myeloma (MM) has significantly improved-however certain cytogenetic abnormalities are associated with poor prognosis. Cytogenetic abnormalities are the core indicators in the risk stratification system of MM. To date, no standardized treatment approach for NDMM with high risk (HR)CAs. Selinexor(X) is a first-in-class Selective Inhibitor of Nuclear Export (SINE) small molecule compound that selectively binds and inactivates XPO1. Previous studies have demonstrated its clinical activity in patients with HRCAs. **Methods:** This prospective study enrolled patients aged ≥18 with NDMM and at least 1 HRCAs. The treatment regimen is induction/consolidation therapy with 8 cycles of XVRd (X 60 mg PO weekly, bortezomib 1.3 mg/m2 SC days1, 4, 8, 11, Lenalidomide 25 mg PO days 1–14, and Dexamethasone 40 mg PO weekly)over 21-day cycles. Maintenance therapy with XR continued for at least 2 years until disease progression, death or withdrawal over 28-day cycles. The primary endpoint was overall response rates (ORR) at the end of induction. Secondary endpoints included complete response (CR), duration of response (DOR), progression free survival (PFS), overall survival (OS)

and toxicity. This trial was registered ChiCTR2200062860. **Results:** Between August 2022 to December 2024, 26 pts with NDMM and at least one CAs were enrolled in 4 hospitals. The median age was 61.5 (R 47–73). R-ISS stage III was present in 11 pts, CAs are including del (17p) (n = 9), 1q21 gain(n = 18),t(4,14)(n = 9) and t(14;16)(n = 5). 17 pts had double-hit or triple-hit and 15 had both 1q21 amplification and others. Among the 26 pts, 10 had completed at least 8 courses of treatment, 25 at least 4 courses and 18 remained treatment. The median follow-up time was 15.7 months(range 4.3–34.8). with a median time remission of 1 month(range 0.5–2). According to IMWG criteria,the ORR was 92.3%, including 5 sCR, 9 CR, 4 VGPR and 10 PR, MRD negativity was sutstained in 5 pts after achieving CR. For CAs pts (n = 26), the m PFS was 16.2 months (95%CI: 14.6-NA) with a 1-y PFS rate of 91% (95%CI: 0.8–1). For CAs pts with DH/TH (n = 17), the mPFS was 16 months (95%CI: 14.1-NA) with a 1-y PFS rate was 93% (95%CI: 0.8–1). TRAEs were mostly observed in the first 2 cycles. Grade 3–4 hematological AEs included thrombocytopenia (3.3%), neutropenia (3.3%), and anemia (3.3%). Grade 1–2 hematological AEs included leukopenia (26.7%), thrombocytopenia(30%) and anemia (13.3%). Grade 1–2 non-hematological AEs included including nausea (33.3%), vomiting (16.7%) and anorexia (16.7%),which improved with antiemetics and GI agents. Other Grade 1–2 AEs are fatigue (30%) and limb numbness (13.3%). Overall toxic effects were manageable. **Conclusions:** The XVRd regimen as induction therapy prior to ASCT is safe and effective in achieving deep responses in NDMM pts with CAs. These preliminary results warrant further investigation. Long-term outcomes will be assessed as more patients are enrolled and followed up.

PA-462

Real-World (RW) Burden of Infection Among Triple-Class–Exposed (TCE) Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Pts with RRMM often require multiple lines of therapy (LOTs); a cumulative immunosuppressive effect of these multiple lines of therapy may contribute to an increased infection risk. Bispecific antibodies (BsAbs) have become key treatment options in later LOTs. While studies of BsAbs have investigated infection rates, RW data on the burden of infection with conventional (non-T-cell–redirecting) therapies is limited. This retrospective, observational study aimed to identify infection risk in pts with TCE (≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 monoclonal antibody) RRMM receiving conventional therapies. **Methods:** Pts with TCE RRMM and with ≥4 prior LOTs who had started a subsequent LOT (index LOT) during the study period (Jan 1, 2016–Oct 31, 2024) were identified from the Komodo Research Dataset (KMD) and the All-Payer Claims Data (APCD). Pts enrolled in a trial ≤6 mo prior to index (index LOT start date) or receiving T-cell–redirecting therapies on/post index were excluded. Pt characteristics were collected during the 6-mo baseline period. Pts were followed from the index date to end of continuous enrollment, death, data cut-off, or end of study period. An algorithm requiring a 30-day washout with no infections prior to index was developed to define infection episodes. Infections that led to hospitalization or emergency room visits were considered severe. Meta-analysis was used to synthesize data between KMD and APCD. **Results:** 2702 KMD and 1755 APCD pts were included (median follow-up, 9.5 and 14.9 mo, respectively). Mean (SD) age was 67.2 (10.6) y for KMD and 69.3 (9.5) y for APCD. Of KMD/APCD pts, 54.0%/52.4% were male and 53.2%/64.2% were White; 29.3%/17.4% had a commercial payer, 9.0%/6.6% had Medicaid, and 61.5%/75.0% had Medicare. Mean (SD) Quan-Charlson Comorbidity Index was 3.2 (3.1)/2.3 (2.8). Pts were heavily pre-treated, with a median index LOT number of 5 in both databases. The most common prior therapies in the TCE classes for KMD/APCD pts were daratumumab (D; 99.3%/99.1%), lenalidomide (83.8%/89.9%), and bortezomib (79.5%/81.6%). The most frequent index LOTs in KMD pts were elotuzumab+pomalidomide (P) ± dexamethasone (d; 5.1%), DP ± d (6.3%), carfilzomib (K) ± d (5.2%), DK ± d (4.4%), and KP ± d (3.9%). Across KMD and APCD pts, the weighted average (wavg) infection rate for any infection was 63.5% (58.2%, bacterial; 27.4%, viral; 8.2%, fungal); at 26 and 52 wks, the wavg cumulative infection rates for any infection were 49.5% and 66.4%, respectively. The wavg rate of severe infection was 46.1% for any infection (42.5%, bacterial; 17.1%, viral; 4.9%, fungal); at 26 and 52 wks, these wavg cumulative rates for severe infection were 31.5% and 44.9%, respectively. **Conclusions:** These RW data highlight the substantial burden of infection in TCE pts with RRMM receiving conventional (non-T-cell–redirecting) therapies after ³4 prior LOTs, with a high risk of any infection (>60%) and severe infection (>45%).

PA-463

Poor Outcomes in Extramedullary Multiple Myeloma Persist Despite Novel Therapies

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Introduction: Extramedullary disease (EMD) arises in 10–30% of multiple myeloma (MM) patients, and is associated with poor survival. EMD arising via haematogenous spread is particularly

aggressive yet remains poorly characterised due to limited cohort sizes. We conducted a retrospective cohort study to define clinical presentation, treatments and outcomes. **Methods:** 85 patients with EMD arising by haematogenous spread were included, diagnosed between June 2009 and September 2024. Clinical features, treatment exposures and survival outcomes were obtained. **Results:** Twelve patients (14%) had primary EMD. The median age of the cohort was 58 years, and 61% were male. Notably, 48.2% (n = 41) demonstrated lambda light chain restriction, increased relative to BM-restricted MM. The most frequent anatomical sites at diagnosis were muscle (30.6%), liver, pleura and lymph nodes (all 26%), with a median of 2 anatomical sites (range 1–8). Secondary EMD occurred a median of 36 months (range 1–159) after MM diagnosis, following a median of 3 prior lines of therapy (range 1–11). 80% were proteasome inhibitor exposed, 83% immunomodulatory agent exposed and 70% had undergone autologous transplantation. Median overall survival (mOS) from EMD diagnosis was 11 months and 26 months for secondary and primary EMD, respectively. From initial MM diagnosis, mOS in secondary EMD was 4.5 years. There was no improvement in survival over three eras of therapy (2009–2013, 2014–2018, 2019–2024) despite increasing use of novel and immunotherapies with mOS 16, 11 and 11 months, respectively ($p = 0.7608$). Interpretation of therapy outcomes is limited by the treatment landscape and drug reimbursement in the Australian setting. The median time to next therapy (TTNT) after first line EMD treatment was 17 weeks; (22 and 16 weeks in primary and secondary EMD respectively). There was no significant shortening of TTNT with second and subsequent lines ($p = 0.544$). The use of anti-CD38 monoclonal antibodies was associated with shorter TTNT (HR 2.83, $p = 0.035$). Regimens including radiotherapy were associated with longer TTNT (HR 0.096, $p = 0.007$); this may reflect bias towards low disease burden. 25% of patients died before second line therapy, and < 25% of patients reached fifth-line therapy. There was no improvement in TTNT with the use of novel therapies including bispecific antibodies and drug antibody conjugates (21 weeks, $p = 0.416$). **Conclusions:** This is one of the largest EMD cohorts reported to date. The high rate of lambda restriction suggests distinct biology and warrants further investigation. Secondary EMD is preceded by rapid progression through therapies, suggesting innate resistance in patients destined for EMD development. Despite major improvements in outcomes in bone marrow restricted MM with newer agents, the outcomes in EMD remain dismal. This underscores the need for better understanding of EMD biology and the development of targeted therapeutic strategies.

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APOBEC3B-Driven Metabolic Adaptation Contributes to Bortezomib Resistance in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is characterized by profound genomic instability, with APOBEC3 enzymes serving as major drivers of mutagenesis during disease progression. Recent studies have shown that APOBEC3-driven mutations are enriched in high-risk MM patients and may influence metabolic pathways, particularly oxidative phosphorylation (OXPHOS). However, the functional role of APOBEC3B in MM metabolism remains poorly defined. This study investigates how APOBEC3B expression modulates mitochondrial metabolism and metabolic rewiring under proteasome inhibition in MM cells. **Methods:** We established APOBEC3B knockdown (KD), knockout (KO), and overexpression (OE) models in MM cell lines using CRISPR/Cas9 (NCI-H929) and lentiviral transduction (OPM-2). APOBEC3B expression was validated by qRT-PCR and western blot (WB). DNA double-strand breaks (DSBs) were assessed by γH2AX via flow cytometry and WB. Mitochondrial function was evaluated using Seahorse XF Analyzer (OCR/ECAR). Cell viability was measured with an ATP-based luminescence assay. Cells were treated with bortezomib (BTZ, 3–12 nM) alone or with dexamethasone (Dex), and metabolic and viability changes were assessed. **Results:** CRISPR-mediated KO of APOBEC3B in NCI-H929 (high endogenous A3B) and OE in OPM-2 (no endogenous A3B) was successfully established and validated. APOBEC3B OE significantly increased γH2AX, while KO reduced DSBs. BTZ treatment induced DNA damage and increased APOBEC3B expression regardless of baseline APOBEC3B levels. Seahorse analysis revealed that APOBEC3B OE in OPM-2 significantly enhanced mitochondrial respiration (basal, coupled, maximal OCR, and respiratory reserve) compared to EV controls under both untreated and BTZ-treated (10–12 nM) conditions. In contrast, APOBEC3B KO in NCI-H929 led to reduced mitochondrial function under both untreated and 3 nM BTZ-treated conditions. Notably, across all treatment conditions, mitochondrial activity decreased compared to untreated controls, reflecting the metabolic suppressive effect of BTZ. Despite APOBEC3B's role in metabolic rewiring, ATP-based viability assays showed no significant survival difference between OE and KO cells under BTZ, suggesting that elevated mitochondrial activity provides metabolic flexibility but does not directly confer survival advantage under proteasome inhibition. **Conclusions:** APOBEC3B promotes mitochondrial rewiring and enhanced respiration under proteasome inhibitor stress but does not significantly alter viability in MM cells treated with bortezomib. These findings suggest that APOBEC3B contributes to

metabolic adaptation without directly promoting resistance and highlight potential metabolic vulnerabilities that could be exploited for therapeutic targeting in MM.

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Factors Influencing CAR T-Cell vs. Bispecific Antibody Preferences in Relapsed/Refractory Multiple Myeloma

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Introduction: Treating relapsed or refractory multiple myeloma (RRMM) is increasingly complex with the rise of Chimeric Antigen Receptor T-cell Therapy (CAR T-cell) and Bispecific Antibodies (BsAbs) therapies, each offering distinct benefits and burdens. Understanding patient perspectives is essential to guide personalized treatment. This study assessed patient preferences and factors influencing the choice between CAR T-cell and BsAbs. **Methods:** A retrospective survey conducted via HealthTree Cure Hub registry (Feb 14, 2023–Jan 1, 2024) gathered data on patient-reported treatment preferences, relapse experiences, and influential decision-making factors rated from 1 (Not influential) to 5 (Extremely influential). Responses were analyzed based on drug class preference and relapse timing (initial and most recent treatment changes). Data were anonymized and analyzed using descriptive statistics. **Results:** Of 784 respondents, 333 experienced relapse (RRMM), and 201 indicated a drug class preference. CAR T-cell therapy was preferred by 66% (n = 132), while BsAbs were favored by 34% (n = 69). Patients favoring CAR T-cell rated higher influence for treatment efficacy (4.6 ± 0.7 vs. 4.2 ± 1.1, $p < 0.05$), genetic-based high-risk status (2.0 ± 1.7 vs. 1.3 ± 1.5, $p < 0.05$), and prior treatment response duration (2.7 ± 1.2 vs. 2.1 ± 1.5, $p < 0.05$). Additionally, the importance of care team explanations increased over time for this group (initial: 4.0 ± 1.2; recent: 4.3 ± 0.9, $p < 0.05$). In contrast, patients favoring bispecifics were less accepting of side effects requiring hospitalization (4.2 ± 1.7 v. 5.0 ± 1.8, $p < 0.05$), higher family care burden (3.1 ± 1.7 v. 3.7 ± 1.6, $p < 0.05$), or a one-time therapy involving relocation costs for several weeks (4.4 ± 1.7 v. 5.5 ± 1.6, $p < 0.05$). Furthermore, these patients rated out-of-pocket costs and economic status as less influential over time (initial: 2.5 ± 1.4; recent: 2.0 ± 1.4, $p < 0.05$), and similarly, decreased the influence rating of previous response duration (initial: 2.6 ± 1.4; recent: 2.1 ± 1.5, $p < 0.05$). **Conclusions:** Our study reveals that perceived efficacy is the most influential factor in initial treatment decisions due to its direct impact on expected outcomes and patient satisfaction. Financial considerations also play a crucial role, particularly for long-term adherence and quality of life, with importance varying based on individual patient circumstances. Patients who prefer CAR T-cell therapy prioritize treatment efficacy, high-risk status, and response duration to previous treatments, focusing on effectiveness and personalized care. In contrast, patients favoring BsAbs are less accepting of factors such as hospitalization, relocation, and caregiving burdens. While they initially weigh prior response to therapies and financial factors, over time their influence diminishes. This shift, prioritizing autonomy and stability within the chronicity of RRMM, may reflect the need for an adaptive reevaluation of what constitutes a tolerable quality of life after multiple lines of therapies.

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Survival Outcomes of KRD vs. IRD as Second-Line Therapy in Relapsed/Refractory Multiple Myeloma: A Multicenter Retrospective Study with Propensity Score Matching

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Introduction: The treatment landscape for multiple myeloma (MM) has evolved with the introduction of novel proteasome inhibitors. Carfilzomib and ixazomib, both combined with lenalidomide and dexamethasone (KRD and IRD, respectively), are widely used in the setting of relapsed/refractory MM (RRMM). However, direct comparisons of efficacy between these regimens in real-world

settings remain limited. This study aimed to evaluate the clinical outcomes of RRMM patients treated with KRD versus IRD. **Methods:** We conducted a retrospective analysis of patients with RRMM who received either KRD or IRD as second-line therapy between 2015 and 2021 at 17 medical centers in South Korea. Baseline characteristics were compared between the two groups using chi-square tests. Survival outcomes were evaluated using Kaplan–Meier survival analysis and multivariate Cox proportional hazards models. To minimize selection bias, propensity score matching (PSM) was performed. **Results:** A total of 342 RRMM patients who received second-line KRD (n = 268) or IRD (n = 74) were analyzed. Baseline characteristics, including ASCT status, prior bortezomib use, gender, high-risk (HR) cytogenetics, ISS, and R-ISS stages, were well balanced between the two groups. However, patients treated with KRD were more likely to be younger (≤65 years: KRD 119/268 [44.4%] vs. IRD 48/74 [64.9%], p = 0.002) and to have experienced early relapse (ER) within 2 years after initiation of front-line therapy (KRD 172/268 [64.2%] vs. IRD 23/74 [31.1%], p < 0.001). In the entire cohort, there was no significant difference in second progression-free survival (2nd PFS) (2-year: KRD 59.6% vs. IRD 50.4%, p = 0.254), while patients receiving IRD showed superior overall survival (2nd OS) (2-year: 78.4% vs. 62.8%, p = 0.004). In multivariate Cox analysis including baseline characteristics, ER within 2 years was independently associated with worse outcomes (2nd PFS: HR 1.531, p = 0.044; 2nd OS: HR 2.050, p = 0.003), as was the presence of HR cytogenetics (2nd PFS: HR 1.589, p = 0.017; 2nd OS: HR 1.798, p = 0.003). The second-line treatment (KRD vs. IRD) was not significantly associated with survival outcomes. PSM was performed using the same clinical variables included in the multivariate Cox model. This resulted in a matched cohort of 104 patients (KRD n = 52; IRD n = 52) with well-balanced characteristics (SMD < 0.1 for most variables). In the matched cohort, no statistically significant differences were observed in either 2nd PFS (2-year: 60.1% vs. 47.1%, p = 0.254) or 2nd OS (2-year: 64.0% vs. 71.9%, p = 0.148) between the two treatment groups. **Conclusions:** Patients with high-risk features such as ER within 2-years were more likely to receive KRD. When adjusted for baseline characteristics, survival outcomes were comparable between KRD and IRD in patients with RRMM. These findings suggest that either regimen may be appropriate as a second-line option, and that treatment selection can be guided by practical considerations and patient preference.

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Weekly Carfilzomib in Combination with Cyclophosphamide and Dexamethasone in Relapsed/Refractory Multiple Myeloma after Bortezomib and Lenalidomide: A Real-World Study

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Introduction: Patients with relapsed or refractory multiple myeloma (RRMM) after exposure to both bortezomib and lenalidomide represent a population with poor prognosis and limited treatment options. Carfilzomib, a second-generation proteasome inhibitor, has demonstrated promising efficacy in combination therapies. The weekly carfilzomib, cyclophosphamide, and dexamethasone (KCd) regimen offers a potentially effective and convenient treatment strategy. However, real-world data, particularly from Asian populations, are lacking. **Methods:** We conducted a single-center retrospective analysis of 33 consecutive RRMM patients treated with weekly KCd between March 2020 and February 2024. All patients had prior exposure to both bortezomib and lenalidomide; 93.9% were lenalidomide-refractory. Carfilzomib was administered weekly (20 mg/m2 on day 1 of cycle 1, then 70 mg/m2 on days 8 and 15 of cycle 1 and on day 1, 8, and 15 of the subsequent cycles), with oral cyclophosphamide (300 mg/m², capped at 500 mg, on day 1, 8, and 15) and dexamethasone (40 mg weekly). Response was assessed using IMWG criteria, and survival outcomes were evaluated via Kaplan–Meier analysis. Adverse events were graded by CTCAE v4.3. **Results:** The overall response rate was 66.7%, including complete response or better in 15.1% and very good partial response or better in 42.4%. Median progression-free survival (PFS) was 13.5 months (95% CI, 11.47–15.53), and median overall survival (OS) was not reached at a median follow-up of 31.7 months. In patients with high-risk cytogenetics (n = 11), ORR was 63.6% with 45.5% achieving VGPR or better. Prior autologous stem cell transplantation and age < 65 years were associated with improved PFS. Grade ≥3 adverse events were mostly hematologic, with neutropenia being most common (15.2%). Non-hematologic toxicities ≥ grade 3 occurred infrequently. No treatment-related deaths or grade ≥3 cardiovascular events were reported. Dose reductions were implemented in 24.2% of patients, primarily for hematologic toxicities. **Conclusions:** The weekly KCd regimen demonstrated encouraging efficacy and manageable toxicity in pretreated, predominantly lenalidomide-refractory RRMM patients. These findings support the feasibility of KCd as a practical treatment option in real-world settings, particularly in populations with limited remaining therapies.

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Nanobody-Based Multifunctional Killer Engagers for Next-Gen BCMA-Directed Myeloma Therapy

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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. Among recent advances, immunotherapy leveraging natural killer (NK) cells is emerging as a promising approach due to their lack of MHC restriction and lower immunogenicity. NK cells express a variety of activating receptors that can be targeted to activate cell-mediated cytotoxicity, such as CD16, NKp30, NKp44, or NKp46 **Methods:** We developed a novel class of nanobody-based therapeutic molecules called Bi- and Tri-specific Killer Engagers (BiKEs and TriKEs) to harness NK cell activity against MM. Llamas were immunized with human BCMA, NKp-family cytotoxicity receptors, and human serum albumin (HSA) to generate high-affinity nanobody binders. We generated dual-nanobody BCMA-NKp30 nanobodies, and also explored triple-nanobody molecules integrating HSA-binding or IgG-like BiKE fused to a human Fc fragment (BiKE hFc), designed to enhance serum stability and effector function. Candidates were screened for antigen binding, NK cell activation, and cytotoxicity in vitro; followed by in vivo xenograft studies for anti-MM efficacy and pharmacokinetics. **Results:** All BiKE formats tested showed similar strong binding to BCMA and NK cell receptors, antigen-specific NK cell activation, and efficient tumor cell killing in vitro. In contrast, in vivo analysis revealed that molecular format significantly influenced therapeutic performance, with BiKE hFc showing much greater anti-MM effect compared to TriKE and non-Fc BiKE formats. Pharmacokinetic analysis indicated significantly higher plasma antibody concentration—approximately 200-fold greater than TriKE in mice—providing a potential mechanistic explanation of this greatly improved efficacy. **Conclusions:** This work provides strong proof of concept that BiKE hFc, among other nanobody-based formats, holds significant therapeutic potential for NK cell–based immunotherapy in MM. We are now exploring similar molecules which target alternative MM surface antigens such as TACI, FCRL5, and CD38. Future directions include manufacturing scale-up, preclinical safety/specificity evaluations, and progression toward clinical trials of BiKE hFc for the treatment of multiple myeloma.

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Updated Results From the Phase 3 DREAMM-8 Study of Belantamab Mafodotin Plus Pomalidomide and Dexamethasone vs Pomalidomide Plus Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma

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Introduction: In DREAMM-8 (NCT04484623), belantamab mafodotin + pomalidomide + dexamethasone (BPd) demonstrated statistically significant and clinically meaningful progression-free survival (PFS) benefit vs pomalidomide + bortezomib + dexamethasone (PVd; hazard ratio [HR], 0.52) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) who received ≥1 prior line of therapy (LOT), including lenalidomide. With 8 additional months of follow-up, we report updated post hoc efficacy and safety results. **Methods:** DREAMM-8 is a phase 3, open-label, randomized, multicenter trial evaluating the efficacy and safety of BPd vs PVd in pts with RRMM who received ≥1 prior LOT, including lenalidomide. Pts were randomized 1:1 to BPd (28-day cycles), which comprised belantamab mafodotin 2.5 mg/kg IV (C1 D1), then 1.9 mg/kg (C2+ D1), plus pomalidomide 4 mg (D1–21, all cycles) and dexamethasone 40 mg (D1, QW, all cycles), or PVd (21-day cycles), which comprised pomalidomide 4 mg (D1–14, all cycles) plus bortezomib 1.3 mg/m2 SC (C1–8 D1, 4, 8, and 11; C9+ D1 and D8) and dexamethasone 20 mg (day of and 1 day after bortezomib dose). Treatment continued until progressive disease, unacceptable toxicity, or death. Efficacy assessments occurred Q4W. **Results:** In the intention-to-treat population, 302 pts were randomized 1:1 to receive BPd (n = 155) or PVd (n = 147). At data cutoff (October 7, 2024), median follow-up was 28.01 mo (range, 0.03–47.74 mo); 55 pts (35%) in the BPd arm and 20 (14%) in the PVd arm had treatment ongoing. In the BPd arm, 68 pts (44%)

experienced a PFS event as did 89 (61%) in the PVd arm. PFS benefit was maintained and favored BPd. Median PFS was 32.6 mo (95% CI, 21.1 mo-not reached) with BPd vs 12.5 mo (95% CI, 9.1–17.6 mo) with PVd (HR, 0.49; 95% CI, 0.35–0.68). The estimated 18-month PFS rate was 63% (95% CI, 54%–70%) with BPd vs 41% (95% CI, 32%-50%) with PVd. PFS benefit was maintained across subgroups, including pts with high-risk cytogenetics (unadjusted HR, 0.55; 95% CI, 0.33–0.90), lenalidomide-refractory disease (unadjusted HR, 0.43; 95% CI, 0.30–0.60), anti-CD38–refractory disease (unadjusted HR, 0.64; 95% CI, 0.36–1.15), 1 prior LOT (unadjusted HR, 0.47; 95% CI, 0.29–0.77), and ≥2 prior LOTs (unadjusted HR, 0.51; 95% CI, 0.33–0.77). Updated safety results were consistent with the primary analysis as presented previously and did not change the safety profile of BPd. **Conclusions:** In DREAMM-8, BPd continued to demonstrate a clinically meaningful PFS benefit vs PVd in pts with RRMM with ≥1 prior LOT. This benefit was maintained across key subgroups, including pts with anti-CD38–and lenalidomide-refractory disease. No new safety signals were observed. These data further support BPd as a potential standard-of-care option in pts with RRMM. **Funding:** GSK. Drug-linker technology licensed from Seagen Inc; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

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Analysis of Infectious Risk in the Multiple Myeloma Patients Treated with Bispecific Antibodies. Real World experience

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Introduction: The addition of bispecific antibodies (BsAbs) to the treatment of multiple myeloma (MM) has significantly improved its prognosis. However, an increase in infectious complications due to post-treatment immunodeficiency is also observed. The risk of infection also varies depending on the target of each bispecific antibody, suggesting individualized infection prevention strategies. The aim is to analyze the infectious risk of patients treated with BsAbs according to the target, to evaluate the differences in the degree of hypogammaglobulinemia (HG) and the immunoglobulin replacement in our series **Methods:** A retrospective study was performed including patients treated with BsAbs in our center between July 2021 and April 2025. Three groups were considered according to the target received: 1) antiBCMA (teclistamab, elranatamab or linvoseltamab), 2) antiGPRc5d (talquetamab) and 3) antiFcRH5 (cevostamab). SPSS was used for the statistical analysis, the comparison of means was performed with Fisher's exact test due to the small sample size. **Results:** A total of 28 patients were included of which 13 received antiBCMA, 13 antiGPRC5d and 2 antiFcRH. 22 patients (76%) were treated within the trial and, of these, 14 received AcBs in combination with other drugs. 41.3% of patients received at least 3 prior lines. 50.6% of patients achieved Complete Remission (CR) and 61.7% Partial Response (PR) or better and 5 patients died in the setting of progression (Table 1). Regarding immune status, 52% had HG prior to treatment initiation. Patients with antiBCMA had lower IgG levels (not significant), the highest degree of HG was observed between the 2nd and 3rd treatment cycle. 67% of patients received IVIG replacement therapy. Patients with antiBCMA required IVIG more frequently (c 2/3 m), although significance was not reached. With respect to infectious risk, 64% of the patients presented some infectious event and 6 patients (21.4%) with 3 or more events. A total of 48% had severe infection, which required hospitalization. 78.6% of patients treated with antiBCMA presented infection vs 46.2% in the GPRC5d group (p 0.097). Serious infectious events were also more frequent with antiBCMA (50% vs. 30.8%, p 0.428). The frequency of respiratory infections was higher with antiBCMA (53.8 vs. 15.4, p 0.097); however, no differences were found between the two groups in the frequency or severity of pneumonia, diarrhea, UTI or other infections (Table 2). Only one patient discontinued treatment due to infectious cause in the antiBCMA group. **Conclusions:** The results of our series reproduce the infectious toxicity data reported in published pivotal trials. Sixty-seven percent of the patients in our series received IVIG prophylaxis; patients with antiBCMA required replacement more frequently than those with talquetamab.

PA-471

CYP3A4 Modulators do not Affect the Pharmacokinetics of Selinexor

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Introduction: Combination therapy for multiple myeloma (MM) is standard of care but could potentially increase adverse effects or reduce efficacy due to potential drug-drug interactions (DDI). Selinexor, approved for relapsed/refractory MM (RRMM) as a combination therapy with bortezomib and dexamethasone or dexamethasone, does not inhibit or induce drug metabolizing enzymes or transporters and does not affect the pharmacokinetics (PK) of other drugs. As selinexor metabolism involves cytochrome P450 3A4 (CYP3A4), inhibitors or inducers of CYP3A4 could potentially increase or decrease selinexor exposure, respectively, and the potential impact of strong CYP3A4 modulators was unknown. To understand the potential for CYP3A4-related DDI, we conducted 2 studies to evaluate the effect of clarithromycin (CAM; strong CYP3A4 inhibitor) and carbamazepine (CBZ; strong CYP3A4 inducer) on selinexor PK. **Methods:** The CYP3A4 inhibition study was nested in the Phase 1b/2 study KCP-330–017 (NCT02343042) in adult patients with MM (n = 11) with a 14-day PK run-in phase. Patients received selinexor 40 mg alone on day 1, CAM 500 mg twice-daily (BID) on days 2–8, and selinexor 40 mg on day 8 with the morning

CAM dose. The CYP3A4 induction study (XPORT-HV-045) was a stand-alone design in healthy adult volunteers (n = 16). Selinexor 10 mg was administered on day 1, followed by CBZ dose up-titration (days 3–5:100 mg BID, days 6–9: 200 mg BID, days 10–21: 300 mg BID) and 10 mg selinexor on day 21 with the morning CBZ dose. Serial blood samples for PK analyses were collected post selinexor dosing, alone and after CAM or CBZ. A statistical analysis was conducted to evaluate DDI by comparing selinexor PK exposure when co-administered with CAM or CBZ (test treatments) to selinexor alone (reference treatment) for PK exposure metrics AUC0-t, AUC0-inf, and Cmax. The geometric least square mean (GLSM), ratio of GLSM (GLSMR), and corresponding 90% confidence interval (CI) were calculated for each PK parameter. **Results:** The GLSMR (90% CI) for selinexor AUC0-t, AUC0-inf, and Cmax after co-administration with CAM vs selinexor alone was 0.99 (0.90, 1.08), 1.00 (0.92, 1.08), and 1.17 (1.03, 1.34), respectively. The GLSMR (90% CI) for selinexor AUC0-t, AUC0-inf, and Cmax after co-administration with CBZ vs selinexor alone was 0.90 (0.85, 0.95), 0.91 (0.87, 0.95), and 0.96 (0.86, 1.07), respectively. **Conclusions:** In both studies, GLSMR of AUC0-inf and AUC0-t (and Cmax in CBZ study) were within the no effect boundary of 0.80–1.25, indicating clearance of selinexor is not affected by either strong CYP3A4 inhibition or strong CYP3A4 induction. CAM increased selinexor Cmax 17% but this small increase is not considered clinically relevant. Selinexor was well tolerated, and no new safety signals emerged in the absence or presence of CAM or CBZ. Strong CYP3A4 inhibitors and inducers do not affect the PK of selinexor, and no dose adjustment is needed when such drugs are co-administered with selinexor.

PA-472

PomCyDex in Relapsed/Refractory Multiple Myeloma: Impact of Prior Refractoriness in a Real-World Setting

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Introduction: Despite recent advances, outcomes for patients with relapsed/refractory multiple myeloma (RRMM) who have been exposed to proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs) remain poor. Identifying effective and tolerable regimens for this heavily pretreated population is a clinical priority. The combination of pomalidomide, cyclophosphamide, and dexamethasone (PomCyDex) has shown synergistic activity. However, evidence on its effectiveness and safety, especially in double- and triple-refractory patients, remains limited. **Methods:** We conducted a retrospective, multicenter study across 13 centers in Catalonia, Spain, including RRMM patients treated with PomCyDex after at least one prior therapy. Patients previously treated with pomalidomide or cyclophosphamide, lacking response data, or lost to follow-up were excluded. Treatment included pomalidomide 4 mg daily (days 1–21), cyclophosphamide 50 mg daily (days 1–21), and weekly dexamethasone. Responses were assessed per 2016 IMWG criteria. Refractoriness was defined as progression during or within 60 days of treatment. Primary endpoints were ORR, PFS, and OS. Statistical analyses used Kaplan-Meier, Cox models, and comparative tests; significance was $p < 0.05$. Adverse events were recorded per CTCAE v6.0. **Results:** The cohort included 177 patients with a median age of 72 years and a median of 3 prior therapy lines. Double-refractory (lenalidomide and PIs) patients comprised 89.2%, while 64.4% were triple-refractory including lenalidomide and anti-CD38 mAbs. The ORR was 60.5%, which was significantly lower in lenalidomide-refractory patients with prior responses under 12 months (32.7% vs. 67.3%, $p < 0.001$) and in patients with high-risk cytogenetics (45.7% vs. 66.7%, $p = 0.03$). Median PFS was 7 months overall, with responders achieving ≥PR showing longer PFS (10 vs. 2 months, $p < 0.01$). Median OS was 13 months, poorer among patients with high-risk cytogenetics, prior lenalidomide refractoriness, or failure to respond to PomCyDex. In multivariate analysis, achievement of ≥PR (HR 0.11, 95% CI 0.52–0.24, $p < 0.01$) and prior anti-CD38 response < 12 months (HR 1.4, 95% CI 1.06–1.9, $p = 0.02$) were independent predictors of PFS, while response to PomCyDex (HR 0.25, 95% CI 0.13–0.46, $p < 0.01$) was the main predictor of OS. Grade ≥3 AEs included: neutropenia (57.6%), thrombocytopenia (29%), anemia (27.7%), and infections (29.4%). Dose reductions were required in 45.8%, and 12.9% discontinued due to AEs. **Conclusions:** PomCyDex showed manageable safety in heavily pretreated RRMM patients. Outcomes were determined by the duration of prior response to lenalidomide or anti-CD38 mAb treatments and by achieving at least a PR. PomCyDex is a treatment option for double- and triple-refractory RRMM patients, especially those with longer prior responses.

PA-473

Carfilzomib Use and Therapeutic Sequences in Patients with Relapsed/Refractory Multiple Myeloma in France: An Analysis from a Large-Scale Epidemiology of Multiple MYeloma (EmmY) Cohort

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Introduction: In the context of the rapidly evolving multiple myeloma (MM) treatment landscape, we aimed to explore carfilzomib (K) use and the therapeutic sequences in a French real-world cohort of K-treated patients (pts). **Methods:** In 73 MM care centres, pts initiating K in second line or later (2L+) between 2017 and 2023 and followed for ≥3 months were included. This analysis is purely descriptive and focuses on K-based regimens used in ≥10% of pts. **Results:** Overall, 1261 pts initiated K therapy in 2L (24.4%), 3L (25.2%), and 4L+ (50.4%). The most frequently used K-based regimens were K with dexamethasone (dex) alone (Kd; 32.5%), with pomalidomide (KPd [off-label use]; 15.9%), with lenalidomide (len) (KRd; 14.2%), with daratumumab (D-Kd; 13.9%), and with cyclophosphamide (KCd [off-label use]; 7.4%). Since 2018, Kd and KRd use declined in favor of D-Kd and KPd, and K once-weekly dosing increased over time with a majority of use since 2022. D-Kd (N = 175) was largely used in 2L (51%), 18% of pts were anti-CD38 refractory at D-Kd initiation. The main prior treatment was bortezomib (V) with len and dex (VRd; 37%). Where available (n = 76), treatments used after D-Kd included CPd (20% [n = 15]), teclistamab (17% [n = 13]) and isatixumab (Isa) with P and dex (8% [n = 6]). KRd (N = 179) was mainly used in 2L (39%) and 3L (20%). Among prior treatments, V-based triplets, mainly DVd (19% [n = 34]) and thalidomide (T) with Vd (VTd: 17% [n = 31]) were mostly used. After KRd, where available (n = 115), anti-CD38-Pd (35% [n = 40]) was the most used regimen. KPd (N = 201) was primarily used in 3L (47%) and 4L (22%) and most pts were refractory to len (91%) and to an anti-CD38 (76%). Since 2020, most KPd pts (90%) had been exposed to an anti-CD38 in a prior line of therapy, mainly DRd (35% [n = 71]) and DVd (22% [n = 44]). Where available (n = 116), the main treatment used after KPd was teclistamab (16% [n = 19]), especially since 2022. Kd (N = 410) was mostly (66%) used in 3L to 5L. Among prior treatments DRd (13% [n = 53]) and DVd (12% [n = 48]) were the most used. After Kd, where available (n = 253), bendamustine (12% [n = 31]), IsaPd (9% [n = 24]) and teclistamab (8% [n = 21]) were the most used regimens. Overall response rates (ORR) were high for D-Kd (84.5% in 2L), KRd (80.6% in 2L), and KPd (77.8% in 3L and 77.9% in 4L+); with long median overall survival (mOS): D-Kd and KRd, not reached in 2L; KPd, 16.7 months in 3L and 25.6 months in 4L+. Since 2022, the use of the new triplet Isa-Kd was very low (1.3% [n = 16]) and quadruplets (D-KPd, D-KRd, Isa-KPd) were used in 3.6% (n = 46) of pts, mainly in 2L 64% [n = 30]). **Conclusions:** Since 2018, use of KRd declined in favor of D-Kd (2L) and KPd (3L/4L), and K once-weekly is mainly used since 2022. After D-Kd, P-based regimens were preferably considered. In 3L and 4L, KPd was the most commonly used K-based regimen to treat patients largely refractory to anti-CD38 and len. K triplets resulted in long survivals. Kd was used in one third of patients, as an option for multi-refractory patients in 3L+.

PA-474

Intravenous Immunoglobulin 10% as Primary Versus Secondary Infection Prophylaxis in Adults with Multiple Myeloma Receiving B-Cell Maturation Antigen×CD3-Directed Bispecific Antibody: A Phase 3 Trial

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Introduction: Patients (pts) with multiple myeloma (MM) receiving B-cell maturation antigen (BCMA) × CD3-directed bispecific antibody (BsAb) therapy are at risk of severe infection, owing to both the underlying disease and its treatment. We aim to assess the efficacy, safety and tolerability of intravenous immunoglobulin (IVIG 10%) as primary vs secondary infection prophylaxis in pts with MM receiving BCMA × CD3-directed BsAb therapy. **Methods:** This multicenter, randomized, controlled, open-label phase 3 study is planned to be conducted in North America, South America, Europe and Asia Pacific. Eligible pts must be aged ≥18 years with a documented diagnosis of MM, have recently commenced teclistamab (within 8 weeks), have not received immunoglobulin treatment within 16 weeks before screening and have given informed consent. Exclusion criteria include an Eastern Cooperative Oncology Group performance status score of >2, documented polyclonal

immunoglobulin G < 150 mg/dL at the most recent assessment within 4 weeks before starting teclistamab, current serious infection or >1 serious infection within 3 months before screening. Pts who have demonstrated at least a minimal response to teclistamab (assessed during the 8-week screening period based on International Myeloma Working Group criteria) will be randomized 2:1 to receive IVIG 10% 400 mg/kg every 3–4 weeks as either primary infection (from randomization) or secondary infection (after experiencing ≥1 serious infection) prophylaxis and observed for up to 52 weeks. The primary endpoint is the time to first serious infection, defined as microbiologically/clinically documented viral/bacterial/fungal infection requiring ongoing treatment with intravenous anti-infectives (confirmed by an independent endpoint adjudication committee). Key secondary endpoints are the occurrence of ≥1 serious infection during the observational period, annualized rate of days on antibiotics for treatment of bacterial infections and annualized rate of bacterial infections. Safety endpoints include the occurrence of adverse events, treatment-emergent adverse events (TEAEs), TEAEs related to IVIG 10% and TEAEs temporally associated with IVIG 10% (within 72 hours). Tolerability assessments include the number of infusion withdrawals/interruptions/rate reductions owing to TEAEs. The impact of IVIG 10% treatment on health care resource utilization will also be evaluated. **Results:** In total, 183 pts are planned for enrollment (122 and 61 in the primary and secondary infection prophylaxis arms, respectively). **Conclusions:** This study will provide critical evidence on the efficacy, safety and tolerability of IVIG 10% as primary infection prophylaxis in pts with MM receiving BCMA × CD3-directed BsAb therapy. These results will support the development of appropriate strategies and guidance for infection prevention in this population who are at high risk of developing severe infections. Study/writing funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

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DREAMM-7 Study of Belantamab Mafodotin + Bortezumib (V) + Dexamethasone (d) vs Daratumumab + Vd in Relapsed/Refractory Multiple Myeloma: Efficacy in Patients by Subsequent Therapy

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Introduction: In the phase 3 DREAMM-7 trial (NCT04246047), belantamab mafodotin (belamaf) + bortezomib + dexamethasone (BVd) demonstrated significant progression-free survival (PFS) and overall survival (OS) benefits vs daratumumab + bortezomib + dexamethasone (DVd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) after ≥1 prior line of therapy. Analysis of PFS2, defined as the time from randomization to disease progression or death from any cause after initiation of the next antimyeloma therapy, showed that treatment benefit favoring BVd vs DVd was maintained following subsequent antimyeloma therapy (HR, 0.59; CI, 0.45–0.77). The purpose of this analysis was to understand efficacy in pts who received subsequent anti-CD38 monoclonal antibodies (mAb), pomalidomide, or carfilzomib following treatment with BVd in DREAMM-7. **Methods:** In DREAMM-7, pts were randomized 1:1 to 8 cycles of BVd (3-week cycles) or DVd (weekly in cycles 1–3, every 3 weeks in cycles 4–8), followed by belamaf or daratumumab monotherapy, respectively, in cycle 9+. In this post hoc analysis, time from start of subsequent therapy to progression/death and OS were evaluated in pts in the BVd arm who subsequently received an anti-CD38 mAb (daratumumab or isatuximab), pomalidomide, or carfilzomib as monotherapy or part of a combination regimen. **Results:** Of 494 pts (BVd, N = 243; DVd, N = 251), 60 (25%) and 38 (15%) were on treatment in the BVd and DVd arms, respectively, at this interim analysis 2 (data cutoff October 7, 2024). Overall, 87 pts (36%) in the BVd arm received subsequent antimyeloma therapies. Common first subsequent therapies after BVd included daratumumab (30/87 [34%]); isatuximab (16/87 [18%]); pomalidomide (26/87 [30%]); and carfilzomib (15/87 [17%]). Subsequent anti-CD38 mAbs were given at 3L+; the most common regimens included isatuximab + pomalidomide + dexamethasone (n = 12); daratumumab monotherapy (n = 8); daratumumab + lenalidomide + dexamethasone (n = 6); and daratumumab + pomalidomide + dexamethasone (n = 6). Median time from start of subsequent therapy to progression/death was 14.1, 15.1, and 14.9 months with an anti-CD38 mAb, pomalidomide, and carfilzomib,

respectively, after BVd. In the intention-to-treat population, median OS was not reached (NR); 36-month OS rates were 74% with BVd and 60% with DVd. Median OS was NR after any of the aforementioned subsequent therapies following BVd; OS rates at 36 months were 74%, 84%, and 86%, respectively. **Conclusions:** In pts who received anti-CD38 mAbs, pomalidomide, or carfilzomib as first subsequent therapy after BVd, median time from start of subsequent therapy to progression/death was approximately 15 months, showing that subsequent therapy with these agents in the 3L+ was effective post BVd and comparable to median PFS with DVd in the 2L+. **Funding:** GSK. Drug-linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

PA-476

What Matters to Patients on Bispecific Antibodies for Relapsed/Refractory Myeloma: Priorities, Symptom Burden, and Delivery Preferences

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Introduction: Despite expanding therapeutic options for relapsed/refractory multiple myeloma (RRMM), limited data exist on patient experiences and quality-of-life (QoL) in those starting treated with bispecific antibodies (bsAbs). These agents offer off-the-shelf, T-cell-redirecting alternatives to CAR T-cell therapy, yet their sustained impact from the patient perspective, including treatment burden, side effect tolerability, and care preferences, remains under-characterized. Understanding these factors is critical as bsAbs move earlier in treatment algorithms and transition to community-based delivery. **Methods:** This retrospective observational study analyzed patient-reported outcomes collected through HealthTree Cure Hub platform between June 2024 and May 2025. A total of 88 RRMM patients who had received bsAbs were surveyed, with subsets (n = 49) completing additional follow-up surveys ≥4 months after treatment initiation. Surveys captured treatment decision drivers, adverse events, QoL (pre/post initiation), and care delivery logistics. Paired t-tests and descriptive statistics were used to analyze changes in patient-reported outcomes. All data collection followed IRB-exempt protocols with informed consent. **Results:** Among 88 respondents, 26% ranked extended overall survival as the primary reason for selecting bsAbs, followed by delayed progression (25%) and tolerable side effects (24%). Of 77 patients who assessed clinical influence, 64% rated physician recommendation as "extremely influential." At the time of relapse prior to bsAbs (n = 75), 43% reported severe fatigue, 27% rated their quality of life as poor or fair, and 25% reported frequent emotional distress. Initial treatment was most often administered weekly (71% of 49), with later transitions to every-other-week (24%) or monthly dosing (31%). Among the same group, 61% preferred subcutaneous over intravenous delivery. Of 27 patients reporting adverse effects, weakened immunity (67%), cytopenias (41%), and hypogammaglobulinemia (26%) were most frequently cited. **Conclusions:** According to our study patients treated with bsAbs for RRMM often began treatment with significant fatigue, emotional strain, and limited functional well-being. Their choices were driven less by convenience or novelty and more by the belief that these therapies could extend survival and delay further progression, decisions shaped largely by input from their physicians. These patients weigh the practical and physical demands of ongoing care, with a high preference for subcutaneous delivery and less frequent dosing suggests that. As bsAbs move into broader clinical use, clinical trials that integrate efficacy with delivery adaptability and patient-defined acceptability may enhance therapy adoption in the real-world setting.

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Validation of a Rule-Based Algorithm for Line-of-Therapy Assignment in Multiple Myeloma Using Simulated Data

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Introduction: Advances in myeloma treatment have led to increasingly complex therapeutic sequences, often spanning multiple lines of therapy (LOTs). Labeling LOTs is essential for accurately tracking a patient's treatment history, guiding clinical decisions, ensuring eligibility for trials, and supporting reimbursement. Real-world data (RWD) enables the study of outcomes across these trajectories, but ambiguity in LOT transition criteria leads to variation in how electronic health records (EHRs) represent treatment history. This limits consistency in analyses. To address this challenge, we developed HEAL-MM, an algorithm vetted by MM specialists that converts EHR data into standardized LOTs and treatment phases. It segments therapies based on drug additions, treatment gaps, and procedural anchors (e.g., transplant, CAR-T), and assigns phase labels (e.g., induction, maintenance, bridging, consolidation) using clinical rules. We report results from initial testing to validate each decision path and rule implementation. **Methods:** We identified unique logic

paths in the algorithm and independently validated each through 100,000 randomized synthetic simulations. Each simulated case had 1–20 random treatment events, with 0–3 transplants, 0–2 CAR-T procedures, and myeloma-specific medications. These were all probabilistically weighted, randomly allocated, and spaced apart based on RWD frequencies observed in the HealthTree Cure Hub registry. HEAL-MM processed each sequence chronologically, applying LOT transition rules and assigning treatment phases. Precision was calculated based on the pass/fail status of the unique logic paths using the defined criteria (e.g., new LOT triggers, phase labeling, and structural output integrity). All tests were executed in Node.js v22.15.0 using Vitest for reproducibility and logic verification. **Results:** HEAL-MM processed all 2.6 million simulated patients without runtime errors or logic failures. The algorithm achieved a 100% precision rate on 26 unique logic paths. No unintended LOT transitions or misclassified phases were observed. **Conclusions:** HEAL-MM is the first algorithm to convert structured treatment data from standard EHR systems into clinically meaningful LOTs and phases. It demonstrated its ability to assign lines of therapy (LOTs) and treatment phases while adhering to expert-defined clinical rules. These promising results demonstrate its potential for integration into RWD pipelines, as it lets us identify treatment cohorts in real time on living databases, and compare outcomes across centers with confidence. While the present validation was limited to synthetic simulations, work is ongoing to evaluate the concordance of HEAL-MM with real-world LOTs. This represents an innovative approach in MM, and sets a template for similar advances in other hematologic diseases.

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Selinexor in Combination with Pomalidomide and Dexamethasone for Patients with Relapsed and/or Refractory Multiple Myeloma (SCOPE Trial)

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Introduction: Background: Although outcome of patients (pts) with multiple myeloma (MM) has improved over the past decade, the cancer eventually relapses, and more treatment options are needed. Patients typically prefer oral and limited duration therapies. Selinexor is an oral, selective exportin 1 inhibitor, with established synergistic activity in combination with other anti-MM therapies. **Methods:** In this investigator-initiated, single arm, phase 2 trial, we evaluated the efficacy and safety of fixed-duration (18, 28-day cycles) comprising weekly selinexor (S), 60 mg orally (PO), pomalidomide (P), 4 mg PO, days 1–21 and dexamethasone (d), 40 mg PO, weekly in pts exposed to 1–2 prior lines of therapy, at least one of which included both a proteasome inhibitor (PI) and lenalidomide (IMiD). Mandated antiemetic prophylaxis included 5HT3 antagonist and olanzapine. The primary endpoint was overall response rate, based on confirmed response, with progression free survival (PFS), duration of response (DOR) overall survival (OS) and safety of SPd regimen being the key secondary endpoints. **Results:** Among 29 enrolled pts with relapsed/refractory (RR) MM, 28 were evaluable at data cutoff date (May 28, 2025); median follow-up for was 23.9 (range: 2.9–38.8) months. Median age at study entry was 67.5 (range: 65–72) years. 79% of pts received 2 prior lines of therapy, while in the remaining pts (21%), SPd was used as the first salvage regimen. All pts were exposed to a PI and IMiD (32% dual-refractory); 64% and 11% were daratumumab-exposed and refractory, respectively. Median number of cycles administered was 9 (range 1–18), with 36% of pts completing all 18 cycles of therapy. The overall response rate was 61% (95% CI:41–78), with 21% pts achieving measurable residual disease (MRD)-negative complete response (CR), 11% CR, 18% very good partial response (VGPR), 11% PR (partial response) as best response. minimal response and stable disease were noted in an additional 7% and 25%, respectively. Median PFS was 24 (95%CI 7.1-NE) months, and the median DOR was not reached (NR). OS at 2 and 3 years was 93% and 86.7%, respectively. 7% of patients discontinued SPd due to toxicity. No grade (Gd) 5 events or unexpected toxicities were observed during treatment. CTCAE v5 Gd 3+ hematologic toxicity occurred in 43% [Gd 3/4 anemia (11%/0%), thrombocytopenia (14%/0%), neutropenia (25%/7%), lymphopenia (4%/4%)] and Gd 3+ non-hematologic toxicity occurred in 46% [Gd ¾ (%); infections (21%/0%), fatigue (4%/0%), nausea (7%/0%), vomiting (0%/0%), diarrhea (0%/0%), anorexia (0%/7%) and weight loss (0%/0%]. Additional data will be presented at the meeting. **Conclusions:** Low dose selinexor in combination with Pd is an effective and safe regimen for pts with RRMM, previously exposed to a PI and an IMiD. An ongoing Phase 3 trial of SPd versus elotuzumab-Pd is expected to shed more light on this value of this combination.

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First-in-Human, Open-Label, Phase 1 Trial Design of SAR446523, a Novel Anti-GPRC5D Antibody-Dependent Cellular Cytotoxicity (ADCC)-Enhanced Monoclonal Antibody for Multiple Myeloma

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Introduction: Despite significant therapeutic advancements, heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) continue to have poor prognoses. GPRC5D, an orphan G-protein-coupled receptor, is highly expressed on plasma cells. GPRC5D-targeting T cell-redirection therapies (i.e., chimeric antigen receptors (CAR)-T and T cell engagers) have shown promising efficacy in heavily pretreated and high-risk patients with multiple myeloma, thus validating the clinical relevance of targeting GPRC5D. SAR446523, an anti-GPCR5D antibody-dependent cellular cytotoxicity (ADCC)-enhanced monoclonal antibody engages natural killer (NK) cells via CD16a, facilitating NK cell-mediated tumor cell lysis. SAR446523 demonstrated potent antimyeloma activity in both in vitro and in vivo preclinical models with a favorable cytokine release profile, potentially reducing the toxicity associated with T cell-redirected therapies. Here, we present the design of the ongoing first-in-human, Phase 1 trial investigating SAR446523 in patients with RRMM. **Methods:** This Phase 1, open-label, dose-escalation (Part A) and dose-optimization (Part B) study is evaluating the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of SAR446523 in adults with RRMM (NCT06630806). SAR446523 will be administered subcutaneously at 6 dose levels, QW for Cycle 1 and Q2W for subsequent cycles with a cycle duration of 28 days. Eligible participants (N ~82) must have received ≥3 prior lines of therapy, including a proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody, and must be either relapsed and/or refractory to these therapies. Prior exposure to anti-GPRC5D or anti-BCMA therapy is allowed in Part A. There is a 90-day washout period for patients on prior NK cell-engaging therapy. Primary endpoints include dose-limiting toxicities (Part A) and overall response rate (Part B). Key secondary endpoints include the duration of response, progression-free survival, minimal residual disease negativity, patient-reported symptomatic adverse events, PK, and potential immunogenicity of SAR446523. The trial is currently recruiting across 3 countries. **Results:** N/A. **Conclusions:** N/A.

PA-480

BASECAMMP: An OBservational Retrospective Analysis of Treatment PatternS and Effectiveness of Standard of CAre for Multiple Myeloma Patients Exposed to Lenalidomide and a Proteasome Inhibitor

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Introduction: Most patients with relapsed or refractory multiple myeloma (RRMM) have been previously treated with combination therapies including lenalidomide (LEN) and proteasome inhibitors (PIs) in the front-line setting. This analysis explored real-world characteristics and clinical outcomes of patients with RRMM with 1–3 prior lines of therapy (LOTs) and previously treated with LEN and a PI from a large dataset in Germany. **Methods:** We analysed data from the Therapy Monitor Multiple Myeloma (TM MM) (Germany) electronic health record database. Patients who had previously received LEN and a PI with 1–3 prior LOTs were included if they initiated their next therapy (index therapy) between May 2016 and December 2023. To align with most ongoing randomized-controlled trials (RCTs) in this population, patients with an ECOG PS >2 were excluded, among other criteria. Patient characteristics, number of prior LOT, and treatment regimens were analyzed. Kaplan-Meier curves were calculated for progression-free survival (PFS) and overall survival (OS). In the TM MM dataset, biochemical progression was not available, therefore PFS was defined as time from index to death or start of a new LOT. **Results:** A total of 1834 patients were included in this analysis. The median age was 73 years and 41% of patients were female. Patients had received a median of 2 prior LOTs. Approximately a third of patients (30%) were double refractory with nearly half (48%) refractory to LEN and a third (36%) refractory to a PI. Index treatment regimens were heterogeneous. The 3 most common regimens were collectively used by < 50% of patients (daratumumab + bortezomib + dexamethasone [19.9%], pomalidomide + dexamethasone [14.7%], daratumumab monotherapy [11.0%]). The median PFS (95% CI) was 12.7 months (12.2–13.1) and median OS was 37.1 months (34.2–40.7). The results were very similar for the lenalidomide refractory population (n = 847) who had a median PFS of 11.3 months (10.3–12.1) and a median OS of 34.3 months (31.1–41.0). **Conclusions:** The median PFS was approximately one year, highlighting the poor outcomes and an unmet need for more effective therapies in this patient population. It should also be noted that there is a risk that the median PFS was overestimated due to the missing progression data.Further research is needed to optimize treatment strategies for this patient population as there is no clear

standard of care for patients with RRMM post-LEN and a PI with the most used regimen only being prescribed to less than 20% of patients.

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Socioeconomic Factors Affecting Health Equity in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

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Introduction: Socioeconomic factors impact health equity among patients (pts) with RRMM, often limiting access to advanced treatments (Tx) like CAR-T and bispecific antibodies (BsAbs). Identifying and addressing these determinants may ensure equitable care for all pts with RRMM. **Methods:** This prospective survey-based study (March-June 2024) included 1301 pts with RRMM and 983 oncologists from 7 countries. Data were analyzed using descriptive statistics and $\chi 2$ tests; only pt data are reported. $P < 0.01$ was used for all comparisons, unless specified. **Results:** Financial burden affected 52% of pts (62% among those with secondary education or lower). Pts with financial difficulties had worse physical burdens than those in better circumstances (77% vs 61%), and Tx outcomes for them were worse than expected for quality of life, side effects, and mental health. They prioritized limiting costs (40% vs 26%), whereas pts with good finances prioritized convenience (38% vs 21%) and limiting challenges for caregivers (32% vs 16%). Globally, there was greater awareness of CAR-T and BsAbs among employed vs unemployed pts (CAR-T, 44% vs 29%; BsAb, 41% vs 26%), educated above secondary level vs not (CAR-T, 37% vs 26%, statistically insignificant; BsAb, 34% vs 25%), and financially stable vs burdened (CAR-T, 52% vs 24%; BsAb, 53% vs 16%). Among pts who were aware of these therapies, those more likely to have discussed and been offered CAR-T and BsAbs were employed vs not employed (CAR-T, 24% vs 12%; BsAbs, 18% vs 9%), financially stable vs burdened (CAR-T, 25% vs 5%; BsAbs, 18% vs 8% P = .014), <65 vs ≥65 years (CAR-T, 28% vs 9%; BsAbs, 20% vs 8%), treated by an MM specialist vs not (CAR-T, 21% vs 10%; BsAbs, 15% vs 8%), and male vs female (CAR-T, 19% vs 12%, P = .019; BsAb, 14% vs 9%, stat insig). Younger and employed pts were more likely to accept BsAbs when offered (<65, 71% vs ≥65, 32%; employed, 72% vs not employed, 33%), with statistically insignificant differences for CAR-T acceptance. Expectations were better met for pts who discussed or were offered CAR-T and BsAbs. Pts who were older, female, with no dependents, unemployed, less educated, not treated by a specialist, or with financial burdens reported learning more than their counterparts from their healthcare providers (HCPs) about a range of Tx topics, including side effects and safety risks identified in clinical trials, clinical efficacy data, ongoing trials the pt may be eligible for, and how the pt's Tx choice may impact future Tx options. Such pts also reported having more support from their HCPs. **Conclusions:** Socioeconomic status impacts the chance of being offered CAR-T or BsAbs, and socioeconomically vulnerable pts relied more heavily on HCPs for education. Combined, these results highlight the need for appropriate pt education and support to improve equitable Tx (eg, through assistance programs). CAR-T and BsAb Tx could offer tailored approaches to time-limited, financially-burdened pts needs if socioeconomic barriers are addressed.

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Understanding Specific Treatment Sequences in Multiple Myeloma Dependent on the Treatment Received in Second Line: Survey Data from 141 International Clinicians

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Introduction: There are many treatment combinations for relapsed/refractory multiple myeloma (RRMM) comprising 7 classes: immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), anti-CD38 antibodies, exportin-1 inhibitors (XPO1), and agents targeting B-cell maturation antigen (BCMA), G protein-coupled receptor class C group 5 member D (GPRC5D), or Signaling Lymphocytic Activation Molecule F7 (SLAMF7). How to appropriately sequence the options in a clinician's armamentarium depends on many factors, including the previous treatments received by the patient. Guidelines exist to support treatment choice (ESMO/EHA, NCCN), but limited data exists on which sequences are most commonly being used in real-world practice. **Methods:** This cross-sectional survey (January to March 2025) included data from 141 hematologists, oncologists, and onco-hematologists across 5 countries: United States (US), United Kingdom (UK), Canada (CA), France (FR), and the Netherlands (NL). Physicians were recruited if they met the following criteria: 1) practiced medicine for 3–30 years 2) ≥60% of time spent in direct patient care 3) responsible for treating MM patients and 4) ≥10 MM patients treated per year. Respondents estimated the percentage of patients they prescribed each treatment regimen in 1L through 4L. Treatment regimens in 3L and 4L were reported separately based on treatments used in 2L and 3L, respectively. **Results:** N = 141 clinicians completed the survey (US: 49, UK: 28, CA: 29, FR: 24, NL: 11). Across countries, a total of 18,671 unique sequences from 2L to 4L were reported with the most unique sequences coming from the US (12,185 sequences) and least from the NL (837). The remaining number of sequences were as follows: CA = 2269, UK = 4757, and FR = 1737. In 2L, the number of different regimens was generally similar, from 24 in the NL to 39 in

the UK and FR. When filtering by regimens reported by ≥5% of respondents (to avoid infrequently used regimens), the number of 2L options ranged from 4 (UK) to 8 (FR/NL). Using the European countries as an example, the most common 2L regimen was CD38 +PI+dexamethasone (dex; 35%). These patients' 3L options included: PI+IMid+dex (30%), CD38+IMiD+dex (14%), PI +Dex (12%), BCMA bispecific antibodies (BsAb; 15%), BCMA CAR T (9%), IMiD+cyclophosphamide+dex (8%), IMid (6%), or SLAMF7 +IMiD+dex (6%). For patients on the most common 3L option (PI +IMiD+dex) in this sequence, their 4L options were a BCMA BsAb (37%), BCMA CAR T (10%), PI+dex (8%), CD38+IMiD+dex (15%), CD38+PI+dex (10%), IMiD+dex (9%), conventional chemotherapy (8%), and SLAMF7+dex (4%). **Conclusions:** There is significant variance in the approach to treating patients with 2L-4L MM across, and even within countries. This study extends existing literature by generating bespoke sequences dependent on prior treatments received. These can be used to identify the average sequence and understand how different regimens are being sequenced in real-world clinical practice.

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Understanding Different Treatment (Tx) Goals and Experiences According to Characteristics in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Tx choices in RRMM pose challenges due to patient (pt) and disease heterogeneity. Personalizing the approach to decision-making and Tx choice based on understanding these differences may help improve the overall pt experience and relationships with health care professionals (HCPs). **Methods:** To better understand the unmet need within pt groups, 30-min online surveys were conducted across 7 countries (March-June 2024). Data were analyzed using descriptive statistics and $\chi 2$ tests ($P < 0.01$ for comparisons, unless specified). **Results:** Pts with RRMM (n = 1301) and oncologists (n = 983) participated. Multivariate analysis identified that financial burden, age, and comorbidities are significantly associated with a Tx meeting pt expectations. Pts with high financial burden prioritized slowing down disease (57% v 42%), limiting side effects (AEs; 57% v 34%), and limiting costs (40% v 26%). Their Tx experience was reported to be significantly worse than expected v more financially stable pts. The greatest priorities for pts aged ≥65 y was limiting AEs (53% v 33% for pts <65 y) and slowing disease progression (53% v 40%). They faced worse physical burdens (78% v 69%, P = .024) and their Tx experience was worse than expected for quality of life (QOL; 53% v 20%), AEs (59% v 19%), and mental health (56% v 21%). Emotional/mental burden was not significantly different. Pts with ≥3 comorbidities faced more physical and emotional burdens and experienced worse than expected Tx outcomes than pts with <3 comorbidities (36%-60% v 33%-43%), notably QOL (60% v 38%). Pts with ≥3 comorbidities ranked limiting costs (39%), limiting AEs (53%), and slowing disease worsening (55%) over living longer (30%). Fewer females v males were in remission (27% v 42%). Not being in remission was strongly associated with females feeling greater physical burden (78% v 73%, P = 0.035) and with Tx outcomes being worse than expected for females, including for perceived efficacy (42% v 32%), impact on mental health (52% v 39%) and QOL (50% v 37%), and females facing more financial difficulties (39% v 28%) and comorbidities (76% v 67%). Fewer females were treated by specialists (49% v 59%; weakly associated with remission). Emotional/mental burden was similar (64% v 60%). Pts in 2L Tx considered convenience to be more important than those in ≥3L (35% v 26%). Pts in ≥3L perceived their Tx and care to have a worse impact on mental health than expected (49% v 2L, 36%). Only 13% of pts preferred HCPs to make Tx decisions alone (more so in pts <65 v ≥65 y [21% v 8%] and in 2L v ≥3L [17% v 10%]). However, HCPs reported recommending Tx without discussing pt goals in 22% of cases. Pts wanted more discussion on AEs and safety risks (42%), impact on mental health (42%), and possible impact of AEs on daily life (41%). HCPs reported discussing more topics than pts recalled. **Conclusions:** Pt characteristics are associated with differing burdens, Tx goals, and experiences. Understanding this is vital to tailoring Tx choices to meet pt expectations.

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Differences in Treatment Goals and Expectations Among Patients with Relapsed/Refractory Multiple Myeloma Treated in Academic vs Community Settings

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Introduction: The multiple myeloma treatment landscape is evolving, making treatment decisions challenging. Understanding a patient's goals has become integral to aligning treatments with their expectations. We investigated differences in treatment goals and expectations among patients treated in academic (hospitals associated with a university and stand-alone cancer centers) vs community settings. **Methods:** A prospective study (March–June 2024) used 30-minute online surveys of 1301 patients with relapsed/refractory multiple myeloma across 7 countries. Data were analyzed using descriptive statistics and $\chi 2$ tests. **Results:** Patient demographics were

similar between those treated in academic (n = 776) and community (n = 405) settings. At the time their most recent treatment was decided, patients ranked their top 3 treatment goals. In both settings, the most common top goals were limiting disease progression (academic: 50%; community: 47%) and managing treatment-related side effects (47%; 48%). The third treatment goal varied between settings. A further treatment goal for patients in academic settings was to live longer to reach milestones (41% vs 34%; P = 0.03), whereas those in community settings emphasized being able to perform everyday activities comfortably (40% vs 31%; P < 0.01) and minimizing treatment-related costs (36% vs 29%; P = 0.028). Additionally, convenience, including treatment administration and the timing (including travel, receiving treatment, and follow-up visits), was a top 3 goal for 31% of patients in academic settings and 26% of patients in community settings. All convenience factors were highly important, with avoiding switching healthcare teams more important in community settings than in academic settings (81% vs 74%; P = 0.019). Patients said that when discussing new treatments with their healthcare providers, the information they would find most helpful would be the chances of new treatments improving quality of life (63%), relieving symptoms (57%), and achieving remission (55%), with findings similar across settings. However, patients in community settings also prioritized understanding the science behind a treatment (46% vs 37%; P < 0.01). **Conclusions:** These findings highlight the need for targeted strategies to address distinct patient goals, expectations, and priorities in different settings. Although patients in both settings had similar top treatment goals, other differences existed. Patients in community settings prioritized avoiding switching care teams, maintaining daily activities, and limiting treatment costs. It is thus important that healthcare providers consider treatments that enable continuity of care in the community setting. Addressing these gaps could optimize goal alignment between provider and patient and enhance treatment satisfaction, regardless of the patient's setting. Limitations included that survey questions were closed-ended and that the survey could not account for variability in sites and countries.

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Real-World Healthcare Resource Utilization and Costs Among Triple-Class–Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM) Patients With and Without Extramedullary Disease in the United States

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Introduction: Patients (pts) with RRMM who are TCE (exposed to ≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 monoclonal antibody) have poor outcomes; those who also have extramedullary disease (EMD) have even worse prognoses. Real-world (RW) data in this population is scarce. This retrospective, observational study describes pt characteristics, healthcare resource utilization (HRU), and costs for TCE RRMM pts with and without EMD who started a subsequent line of therapy (LOT). **Methods:** Adult RRMM pts with a subsequent LOT (index LOT) after they were TCE were identified from Komodo's Healthcare Map (a US claims dataset). Pts were followed from the first LOT start date after TCE (index date; between Jan 1, 2020 and Aug 31, 2023) until the earliest of the following: end of insurance enrollment, last claim, death, or end of study period (Aug 31, 2024). Pts with ≥1 mo follow-up were included. EMD pts had an EMD diagnosis (Dx) before or at index. Non-EMD pts had no EMD Dx. Descriptive statistics were used for pt characteristics, HRU, and costs. **Results:** Overall, 278 EMD pts and 4,522 non-EMD pts were included (median follow-up, 10.4 and 12.8 mos, respectively). The median ages were 62 y for EMD pts and 65 y for non-EMD pts. Among EMD pts and non-EMD pts, 43.9% and 45.1% were female, 44.2% and 50.8% were White, 24.5% and 22.8% were Black, and 14.4% and 11.4% were Hispanic/Latino, respectively. The most common insurance types were commercial (47.8% EMD and 35.2% non-EMD) and Medicare (30.2% and 42.0%). Median Quan-Charlson Comorbidity Index values were 3.5 for EMD pts and 2.0 for non-EMD pts. Both cohorts had a median of 3 prior LOTs before index. A higher proportion of EMD pts vs non-EMD pts had ≥1 hospitalization (62.6% vs 58.0%); the mean number of hospitalizations per pt per mo (PPPM) was greater for EMD pts vs non EMD pts (0.22 vs 0.15). Mean length of stay was also longer for EMD pts vs non-EMD pts (2.1 vs 1.5 days PPPM). Mean all-cause costs (2024 USD PPPM) were $40,974 and $33,029 for EMD and non-EMD pts, respectively, driven by inpatient (IP) costs ($12,467 and $7,268), outpatient (OP) costs ($15,531 and $14,172), and pharmacy claims ($12,286 and $11,223). Mean multiple myeloma (MM)-related costs (PPPM) were $39,145 and $31,530 for EMD and non-EMD pts, respectively, driven by MM drug costs ($26,945 and $23,047), IP costs ($6,642 and $4,319), and OP costs ($5,068 and $3,891). Among 110 EMD pts with a subsequent LOT observed, overall mean-all cause costs (PPPM) increased from $43,586 during the index LOT to $54,055 from the start of the subsequent LOT to the end of follow-up; mean MM-related costs (PPPM) increased from $41,541 to $53,327. **Conclusions:** This RW study demonstrates a higher economic burden, with greater HRU and costs, in TCE RRMM pts with EMD compared with those without EMD. Furthermore, costs for pts with EMD are even higher upon disease progression, underscoring the need for more effective treatment options.

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RESCUE-LATAM Study: Real-World Evaluation of Salvage Combinations for Unmet Needs in Expose and Refractory Multiple Myeloma in LATAM Settings

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Introduction: Background: Multiple myeloma (MM) is a chronic, relapsing malignancy requiring multiple lines of therapy. As patients (pts) become exposed and refractory to standard drug classes, options narrow. Salvage combinations remain poorly characterized, especially outside clinical trials. In LATAM, access to novel agents varies across countries, and real-world evidence is scarce. Aims: To describe real-world treatment patterns in triple-class-exposed (TCE) and refractory (TCR) MM pts, assess access to novel therapies in five LATAM countries, and report clinical characteristics, overall response rates (ORR), progression-free survival (PFS), and overall survival (OS). **Methods:** Methods: Retrospective, multicenter, observational study across Argentina, Chile, Uruguay, Mexico, and Peru. Adult TCE/TCR MM pts were included. Variables analyzed: demographics, salvage therapy patterns, ORR, PFS, and OS after anti-CD38 refractoriness (T0). Statistical analyses used SPSS v.27, $p < 0.05$. **Results:** Results: 202 pts were included; median age at T0 was 62 years, 53% male. ISS-3 was present in 33%, and del(17p) in 11%. Median prior lines: 3; 72% had undergone autologous stem cell transplant. All pts were TCE; 27% were penta-refractory. 93.5% received subsequent therapy, but only 8.4% were treated with bispecific antibodies. No consistent standard of care was observed. Salvage regimens included: PI/steroid (6/202), IMiD/alkylator (12/202), PI/alkylator (45/202), PI/IMiD (38/202), IMiD/steroid (5/202), chemotherapy (24/202), and others. With median follow-up of 36.9 months, ORR was 54.5% (≥VGPR in 28%). Median PFS and OS from T0 were 12.1 and 13.3 months, respectively. PFS rate at 18 months was 28.4% (95% CI: 21.1–35.7); OS rate at 18 months was 44.3% (95% CI: 36.5–52.1). Disease progression accounted for 81 of 111 deaths. **Conclusions:** Conclusion: This is the first real-world registry of RRMM in LATAM, focused on TCE pts. It reveals wide heterogeneity in salvage regimens and limited use of novel agents, especially bispecific antibodies. These findings underscore the urgent need to expand access to emerging therapies and develop regionally adapted strategies to improve outcomes.

PA-487

Real-World Evidence of Melflufen Plus Dexamethasone in Heavily Pretreated Relapsed/Refractory Multiple Myeloma Patients: Efficacy and Safety from a Single-Center Experience

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Introduction: Despite recent advances, most patients with relapsed/refractory multiple myeloma (RRMM) develop resistance to standard treatments. Therefore, new therapeutic options are urgently needed, especially for older and frail patients who are ineligible for intensive treatments such as chimeric antigen receptor (CAR) T-cell therapy or bispecific antibodies (BsAbs). Melflufen is a first-in-class lipophilic peptide-drug conjugate with alkylating activity. It showed clinical efficacy, leading to its approval in Europe in combination with dexamethasone for triple-class refractory (TCR) RRMM patients (refractory to ≥1 IMiD, ≥1 PI, and ≥1 anti-CD38 mAb) after ≥3 prior lines and ≥3 years from ASCT, if performed. Real-world data on this combination, especially in more heterogeneous populations than those enrolled in clinical trials, remain limited. **Methods:** We retrospectively analyzed RRMM patients treated with melflufen plus dexamethasone at the "L. and A. Seràgnoli" Institute, Bologna, from Dec 2021 to Dec 2024. Treatment included IV melflufen 40 mg on Day 1 of each 28-day cycle and oral dexamethasone 40 mg (20 mg if ≥75 years) on Days 1, 8, 15, and 22. Responses were assessed per IMWG criteria. **Results:** Fifteen patients (7 female) with median age 71 years (range 59–83) were included. Median prior lines were 4 (range 2–11). All patients were triple-class exposed; 13 (87%) were TCR and 6 (40%) penta-class refractory. Notably, 5 (33%) patients were refractory to prior BCMA-directed therapy and 1 (7%) also to anti-GPRC5D BsAb. Five (33%) patients had undergone ≥1 ASCT. One (7%) had extramedullary disease; 4 (27%) had high-risk cytogenetics (at least one among del17p, t(4;14), t(14;16), or 1q gain/ampl by FISH). Median number of melflufen cycles was 3 (range 1–9). Reasons for discontinuation included progression (n = 9; 60%), adverse events (n = 2; 14%, including 1 fatal case due to septic shock), and planned CAR-T cell therapy (n = 1; 7%). Overall response rate was 47% with

2 patients (14%) achieving a complete response and 5 (33%) partial response (PR). At 8-month median follow-up, mPFS was 4 months (95% CI, 2–NR); median OS was NR. Among responders (≥PR), mPFS was 9 months (95% CI, 8–NR). Most common toxicity was hematologic: grade (G) ≥3 anemia in 6 (40%), thrombocytopenia in 9 (60%), neutropenia in 9 (60%). G ≥ 3 infections (mostly respiratory) occurred in 4 (27%), and G ≥ 3 nausea in 1 (7%). No secondary malignancies were observed. Of 11 patients receiving subsequent therapies, 7 (64%) were treated with new immunotherapies: belantamab mafodotin (n = 2), anti-BCMA BsAbs (n = 4), and CAR-T (n = 1). **Conclusions:** Overall, melflufen plus dexamethasone showed encouraging results and manageable safety profile in heavily pretreated RRMM patients. These data support a role for this combination, even in patients refractory to anti-BCMA therapies, without limiting access to future T-cell redirecting therapies, filling a largely unmet clinical need in this patient setting.

PA-488

Efficacy and Safety of a China-Developed BCMA-Targeted CAR-T Therapy (Eque-cel) in Plasma Cell Leukemia: Real-World Multicenter Experience

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Introduction: Plasma cell leukemia (PCL) is a rare and highly aggressive subtype of multiple myeloma (MM) with a dismal prognosis, presenting significant clinical challenges and an urgent need for innovative therapeutic approaches. Although B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T-cell (CAR-T) therapy has demonstrated marked efficacy in relapsed/refractory MM, most clinical trials have excluded PCL patients, leading to a paucity of clinical data. This study reports the first real-world partial data from multiple centers on a fully human CAR-T therapy (Equecabtagene autoleucel,Eque-cel) in China, aiming to provide new treatment options. **Methods:** This real-world study included a subset of PCL patients who received Eque-cel between June 30, 2023 (product launch) and August 30, 2024. PCL was defined as ≥5% plasma cells in peripheral blood, with patients classified as either primary (pPCL) or secondary PCL (sPCL). Efficacy endpoints included overall response rate (ORR), minimal residual disease (MRD) negativity rate, progression-free survival (PFS), and overall survival (OS). Safety was evaluated by the incidence and severity of cytokine release syndrome (CRS) and other adverse events. PFS and OS were estimated using the Kaplan-Meier method. **Results:** A total of 12 patients with pPCL (42%) or sPCL (58%) were enrolled. The median age was 62 years (range: 55–67), and the median number of prior lines of therapy was 3 (range: 1–6), with 92% being triple-refractory. Immunoglobulin subtypes: 33%IgG (4/12), 42% IgA (5/12). Advanced disease was frequent: 75% (9/12) were DS stage III. 42% (5/12) had received only 1 or 2 prior lines of therapy. High-risk cytogenetic features were observed in 83% (10/12). Three patients had undergone prior transplantation. With a median follow-up of 333 days (range: 281–397), the ORR was 92%, with 92% of patients achieving complete response or better (CR/sCR). 64% experienced their first response within 1 month, with a median duration of response of 282 days (range: 236–339). At the last follow-up, the median PFS and OS had not been reached. Notably, patients with pPCL showed better efficacy compared to sPCL (median PFS: NE vs. 12.3 m). The 12-month PFS was 78.6% overall (pPCL: 80%, sPCL: 75%), and the 12-month OS was 100% for all patients. Regarding safety, most patients experienced grade 1 or 2 CRS (92%), with only one patient developing grade 3 CRS. ICANS occurred in 2 patients, including one grade 3 event. Most patients achieved hematologic recovery within 90 days post-infusion. No deaths occurred during the study period. **Conclusions:** This first real-world data partial on Eque-cel in PCL patients highlights the therapeutic potential of BCMA-targeted CAR-T therapy in plasma cell leukemia. The rapid, sustained, and deep responses, alongside a manageable safety profile, support the clinical feasibility of CAR-T as a treatment option for PCL. However, longer follow-up and studies in larger patient populations are needed to validate these findings.

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Isatuximab Subcutaneous (Isa SC) via On-Body Injector (OBI) or Manual Injection for Relapsed/Refractory Multiple Myeloma (RRMM): Patient Experience from the Phase 2 IZALCO Study

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Introduction: Improved drug delivery methods are needed to reduce patient burden and increase treatment adherence in MM. The OBI is a wearable injector applied by a healthcare professional for delivery of Isa SC. The Phase 2 IZALCO study (NCT05704049) met its primary endpoint, demonstrating efficacy (ORR, 79.7%), safety and similar pharmacokinetic exposure for Isa SC administered via OBI or manual injection in combination with carfilzomib-dexamethasone in RRMM patients. There was a notable low rate of infusion reactions, with no new safety signals except for few low-grade injection site reactions associated with the SC route. On the key secondary endpoint, 74.5% of patients preferred receiving Isa SC by OBI and 17% preferred manual injection ($p = 0.0004$). Here we report a detailed evaluation of patient experience and satisfaction with Isa SC OBI or manual injection in IZALCO. **Methods:** In Part 1 of this multicenter study, 8 of 74 patients received Isa SC by manual injection. In Part 2, patients were randomized to Isa SC OBI or manual injection in cycles (C)1–3 and then crossed over to the other administration method for C4–6. From C7, all patients could choose either treatment modality. Patient expectations were assessed before treatment using the Patient Expectation Questionnaire (PEQ) at baseline and patient experience was assessed during all treatment cycles with the Patient Experience and Satisfaction Questionnaire (PESQ v.2). Quality of life was evaluated with the EORTC-QLQ-C30 questionnaire at C1/day (D)1 or 2, D15 or D16 of subsequent cycles and end of treatment. **Results:** The PEQ was completed by 90.5% (67/74) of patients at baseline and the PESQ by ≥73.8% on treatment (except C12D15, 54.5%). During treatment, the proportion of patients reporting discomfort (OBI: 0–13.3%; manual: 3.4–18.5%), pain (OBI: 0–22.7%; manual: 6.9–20.0%) and side effects from injection method (OBI: 0–12.5%; manual: 3.4–15.4%) was lower than pre-treatment expectations of discomfort (53.7%), pain (56.7%) and side effects (53.7%). Fewer patients treated with OBI vs manual injection reported discomfort, pain and side effects from injection method at most time points. During treatment, most patients were satisfied with either injection method (OBI: 80.6–97.1%; manual: 81.5–95.1%) and would recommend the medication to other patients (OBI: 87.0–100%; manual: 89.6–100%). Global health status on the EORTC-QLQ-C30 was maintained relative to baseline, with no notable difference observed between delivery methods. 89.4% of the C6D15 PESQ respondents opted for Isa OBI at C7 onward. **Conclusions:** In IZALCO, treatment with Isa SC administered via OBI or manual injection alleviated initial patient concerns about discomfort, pain and side effects, and resulted in a high proportion of patients reporting satisfaction. These findings complement the patient preference data reported for Isa OBI vs manual injection and suggest that the OBI is a convenient option for Isa SC administration. **Funding:** Sanofi.

PA-490

Real-World (RW) Treatment (Tx) Patterns and Clinical Outcomes in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) with 2–4 lines of Treatment: Data from the US Flatiron Database

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Introduction: Given the rapidly evolving treatment landscape, RW evidence is critical to better understand disease burden and unmet needs of pts with RRMM and to improve pt care in earlier lines of Tx (LOT). This study assessed RW Tx patterns and clinical outcomes in pts with RRMM who received 2nd line (2L) Tx or progressed to 3rd line (3L) or 4th line (4L) Tx in the US. **Methods:** This study used electronic health records from a longitudinal, nationwide research database (Flatiron Health). Eligible pts were ≥ 18 y, diagnosed with RRMM from Jan 1, 2011 through Dec 31, 2024, and received 2L Tx or progressed from 2L to 3L/4L Tx. Pts who initiated 2L Tx before Jan 1, 2019 were excluded. Index date was the start date of each LOT. Frailty was defined based on a simplified score. Descriptive statistics were used to describe pt characteristics and Tx patterns by LOT. Kaplan–Meier curves were used to describe clinical outcomes from index date including progression-free survival (PFS) and overall survival (OS). **Results:** Overall, 3538 pts who received 2L Tx were included in this analysis; 1514 (42.8%) and 719 (20.3%) went on to receive 3L and 4L Tx, respectively. For pts who received 2L Tx, median age was 71 y (range, 28–85), median follow-up was 20.5 mo (range, 0.1–72.0), 53.3% were male, 19.1% were African American, 74.8% were treated in a community practice setting, and 39.6% were considered frail. Prior to Tx initiation, 70.3% (2L), 83.1% (3L), and 89.2% (4L) of pts had been exposed to lenalidomide (LEN); 78.0% (2L), 84.5% (3L), and 87.1% (4L) to bortezomib (BORT); and 16.4% (2L), 54.2% (3L), and 76.4% (4L) to an anti-CD38 monoclonal antibody (aCD38). Prior to LOT start, 46.5% (2L), 61.8% (3L), and 70.9% (4L) of pts were LEN-refractory; 46.4% (2L), 55.7% (3L), and 59.2% (4L) of pts were BORT-refractory; and 12.8% (2L), 46.2% (3L), and 68.2% (4L) of pts were aCD38-refractory. The most common Tx regimens (± dexamethasone) used in 2L were daratumumab (DARA) + LEN (DRd, 7.2%), DARA + pomalidomide (DPd, 7.2%), and DARA + BORT (DVd, 6.1%); in 3L, DPd (11.0%), DARA (Dd, 6.3%), and DARA +

carfilzomib (CFZ) (DKd, 5.6%); and in 4L, DPd (8.8%), Dd (5.0%), and CFZ (Kd, 4.7%). Only 8, 22, and 27 pts received T-cell engagers and 9, 18, and 24 pts received CAR T cell therapies in 2L, 3L, and 4L, respectively. Overall, median PFS was 12.8 mo (95% CI, 11.9–13.8) for 2L, 8.2 mo (95% CI, 7.3–8.9) for 3L, and 6.9 mo (95% CI, 6.2–7.9) for 4L; median OS was 60.5 mo (95% CI, 55.9–64.5) for 2L, 38.9 mo (95% CI, 33.9–46.1) for 3L, and 29.0 mo (95% CI, 24.3–32.3) for 4L. Pts who were older (≥ 75 y) or frail had numerically shorter 2L and 3L PFS and OS compared with pts who were < 75 y or non-frail. **Conclusions:** There is no clear standard of care for pts with RRMM in RW clinical practice. Despite the availability of numerous Tx options, outcomes remain poor for pts, even in early-line RRMM. This study also highlights higher unmet needs for older and frail pts.

PA-491

Mezigdomide (MEZI) in Novel Combinations Effectively Reactivates Immune System in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Including those after T-Cell–Redirecting Therapies (TCRT)

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Introduction: MEZI, an oral CELMoD™ agent, induces maximal and rapid degradation of Ikaros/Aiolos, causing antitumor and immunostimulatory effects in MM. Exploring the role of MEZI-based regimens in patients (pts) post TCRT, such as chimeric antigen receptor T cells (CAR T) and T-cell engagers (TCE), is crucial given the potential T-cell exhaustion and immune dysregulation after TCRT treatment (Tx). MEZI+dexamethasone (MEZId) combined with novel agents, such as tazemetostat (TAZ), the bromodomain inhibitor (BETi) BMS-986158, and trametinib (TRAM) showed promising efficacy and safety in the phase 1/2 CA057–003 trial in pts with RRMM, including pts post-TCRT. Here, we explore immune composition and changes linked to MEZId-based Tx in pts with RRMM with/without prior TCRT exposure. **Methods:** Pts with RRMM (n = 56) with documented progressive disease during/after last regimen received MEZId-based combinations with TAZ (n = 16), BETi (n = 20), and TRAM (n = 20). The MEZI dose was 0.3–1.0 mg daily for 21/28 days. Last regimen included TCRT (n = 28: BCMA CAR-T, n = 8; GPRC5D CAR-T, n = 6; BCMA TCE, n = 3; GPRC5D TCE, n = 8, BCMA TCE+GPRC5D TCE, n = 2; trispecific T-cell–activating constructs, n = 1), or various non-TCRT regimens (n = 28). Peripheral blood samples were collected from 53 pts at cycle (C)1 day 1 pre-Tx, and at intervals during C1 and C3 on Tx to evaluate immune markers; immune phenotyping was performed by multicolor flow cytometry. **Results:** Prior TCRT Tx did not significantly impact baseline immune status as assessed by relative/absolute numbers of CD4+ T, CD8+ T, B, or NK cells and by levels of Ki67+, CD4+, and CD8+ T cells. TCRT Tx appeared to increase immune subsets relating to persistent activation including activated T helper (CD3+CD4+HLA-DR+), activated central memory T helper (CD3+CD4+CCR7+CD45RA-HLA-DR+), and increased numbers of CD57+ and CD366+ NK and NKT cells. TCRT-exposed pts had lower absolute counts of regulatory T cells (CD3+CD4+CD25+CD127-loFOXP3+) and relative percent of Ki67+ NK cells. Upon Tx with MEZId-based regimens, both TCRT and non-TCRT pts showed increased proliferation and enhanced activation of CD4+ and CD8+ T cells, and NK and NKT cells. Prior TCRT exposure did not affect induction of a shift toward an effector memory phenotype (CCR7-CD45RA-) in CD8+ T cells with subsequent reduction of naive (CCR7+CD45RA-), central memory (CCR7+CD45RA-), and TEMRA (CCR7-CD45RA+) populations in CD4+ and CD8+ T cells upon Tx with MEZId-based regimens. **Conclusions:** MEZId-based novel regimens lead to activation of adaptive and innate immune populations in pts with RRMM regardless of prior TCRT exposure. Dynamics of immune changes with MEZId-based novel regimens agree with MEZId backbone data. Results suggest prior TCRT exposure and addition of novel agents do not affect the ability of MEZI to increase activation and proliferation of NK and T cells, supporting its use in combinations for pts with prior TCRT exposure. This abstract was accepted and previously presented at EHA2025. All rights reserved.

PA-492

Association Between Progression-Free Survival and Overall Survival Outcomes in Patients with Multiple Myeloma Previously Treated with Lenalidomide and an ANTI-CD38 Regimen: A Real-World Perspective

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Introduction: Progression-free survival (PFS) and overall survival (OS) are crucial endpoints in clinical trials for relapsed/refractory multiple myeloma (RRMM). However, due to the extended duration of OS, mature OS data is often unavailable during early trial readouts. In such scenarios, PFS can serve as an early indicator of treatment efficacy. While previous research has investigated the relationship between PFS and OS in the overall RRMM patient population in clinical trials, this relationship has not been examined in patients previously treated with lenalidomide (LEN) and anti-CD38 regimens. This study aims to evaluate the quantitative relationship between PFS and OS in patients with RRMM previously treated with LEN and an anti-CD38 regimen, utilizing real-world electronic heath record (EHR)-data from the United States. **Methods:** This non-interventional, retrospective study used the US-based, EHR-derived deidentified Flatiron Health Research Database. Patients diagnosed with MM on or after January 1, 2011, who were treated with LEN and an anti-CD38 monoclonal antibody, and had a subsequent line of therapy (LOT), were included. The initiation date of this subsequent LOT was considered the index date; the study end date was November 30, 2024. SAS v9.4 was used to assess PFS and OS outcomes post-index. PFS was defined as the time from the index date to the first disease progression, start of a subsequent LOT, or death during the follow-up period, whichever occurred earlier. Kaplan-Meier analyses were used to estimate median PFS and OS. The association between PFS and OS was evaluated using Spearman's rank correlation coefficient, weighted least squares (WLS) regression model, and multivariable Cox proportional hazards regression models. The multivariable model accounted for select baseline characteristics as covariates. A landmark analysis was performed to further explore the relationship between PFS and OS at specific time points. Statistical significance was set at a P value of < 0.05. **Results:** A total of 1,684 patients with RRMM were included in the study. The median age was 69 years (range, 29–85), with 53.8% male. The median PFS was 7.0 months (95% confidence interval [CI], 6.5–7.5 months), and the median OS was 31.5 months (95% CI, 27.9–35.4 months). Spearman's rank correlation coefficient between PFS and OS was 0.62 ($P < 0.0001$). The WLS regression model R^2 value was 0.93 ($P < 0.0001$). Landmark analyses demonstrated a strong association between PFS and OS at 3 months (HR, 2.18; 95% CI, 1.80–2.62), 6 months (HR, 2.22; 95% CI, 1.84–2.67), 9 months (HR, 2.26; 95% CI, 1.84–2.80), and 12 months (HR, 2.22; 95% CI, 1.74–2.87). **Conclusions:** This real-world analysis reveals a robust association between PFS and OS in patients with RRMM who have been previously treated with LEN and an anti-CD38 regimen. In situations where mature OS data are not yet available, these findings suggest that PFS can serve as an early indicator of treatment efficacy to inform policy and decision-making in healthcare.

PA-493

Real-World Use of Melflufen Plus Dexametasone in Relapsed/Refractory Multiple Myeloma: A Retrospective Study from the Valencian Community and the Region of Murcia (Spain)

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Introduction: Melphalan fluflenamide (melflufen) in combination with dexamethasone (Melf-dex) has recently been approved in patients with relapsed/refractory multiple myeloma (RRMM) after ≥3 prior lines of therapy. However, real-world evidence remains limited to small cohorts, and data on patients pre-treated with T-cell engagers (TCEs) or CAR-T cell therapy are lacking. Here, we report data from a larger real-world cohort, including patients exposed to novel immunotherapies- a population not previously studied. **Methods:** Data were retrospectively collected from patients with RRMM who were treated with Melf-dex in the real-world setting from June 2024 to May 2025, at 9 institutions in Valencia and Murcia (Spain). Clinical and biological baseline characteristics, as well as information on treatment efficacy and safety were collected from medical records. Data analysis was performed using Microsoft Excel and R software. The study was approved by the Ethics Committee of the coordinating center. **Results:** A total of 19 patients were included in the cohort. At study entry, the median age was 64 years, with a median of five prior lines of therapy. Seven patients (39%) presented with extramedullary disease, and six (35%) had high-risk cytogenetics, including four with ≥2 high-risk abnormalities. Eighteen patients (95%) were triple-class refractory and 14 (74%) were penta-class refractory. A total of 14 of patients (74%) had previously received

some anti-BCMA and/or anti-GPRC5D therapy, including four cases of dual exposure. An overall response rate of 26% (n = 5) was observed in the total cohort, compared to 23% (n = 3) in the immunotherapy-exposed subgroup. Rates of stable disease were 42% and 38%, respectively. The median progression-free survival was 4.8 months (95% CI: 2.5-not reached), while at a median follow-up of 5.75 months the median overall survival had not been reached. Three patients remain alive and in response after over nine months of Melf-dex initiation. Grade III/IV hematologic toxicities were observed in 89% of patients, most commonly thrombocytopenia (68%), neutropenia (68%) and anemia (47%). Supportive care included G-CSF (n = 15), EPO (n = 14), TPO agonists (n = 6), and platelet and red blood cell transfusions (n = 10 and n = 13, respectively). Infections were reported in 10 patients (53%), including three ≥ grade III cases. One patient permanently discontinued the regimen due to severe thrombocytopenia and bleeding, and another died of sepsis. **Conclusions:** This is the first real-world report on the use of Melf-dex in a cohort of patients previously exposed to anti-BCMA and anti-GPRC5D therapies. Although this population was more heavily pretreated, the efficacy observed was comparable to that reported in clinical trials. These findings suggest that Melf-dex may represent a valuable treatment option in this challenging setting. Longer follow-up and larger cohorts are needed to refine these preliminary results and establish the therapeutic role of this regimen in patients with advanced RRMM.

PA-494

Outcomes in Second-Line Lenalidomide-Refractory Patients in the Phase 3 DREAMM-7 Study of Belantamab Mafodotin, Bortezomib (V), and Dexamethasone (d) vs Daratumumab-Vd in RRMM

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Introduction: Use of lenalidomide (len) in induction regimens and/or maintenance therapy for newly diagnosed multiple myeloma (MM) has increased the number of patients (pts) exposed to or refractory to len at their first relapse, which narrows their treatment options and may lead to suboptimal outcomes. This underscores the need for novel therapeutic combinations to treat MM that is refractory to first-line combinations. The phase 3 DREAMM-7 trial (NCT04246047) compares belantamab mafodotin (belamaf), bortezomib, and dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in pts with relapsed or refractory MM (RRMM) who have received ≥1 prior line of therapy (LOT). DREAMM-7 has previously demonstrated significant and clinically meaningful progression-free survival (PFS) and overall survival (OS) benefits with BVd in comparison to DVd. This post hoc analysis examines outcomes in the subpopulation of len-refractory pts at first relapse. **Methods:** Pts were randomized 1:1 to 8 cycles of BVd (3-week cycles) or DVd (weekly in cycles 1–3 and every 3 weeks in cycles 4–8), followed by belamaf or daratumumab monotherapy, respectively, in cycles 9+. Post hoc analyses of PFS, OS, and duration of response (DOR) were performed in pts who had received 1 prior LOT and were refractory to len. Hazard ratios (HRs) were estimated using the Cox model with Wald CIs. The Kaplan-Meier method was used to compute medians with 95% Brookmeyer-Crowley CIs. **Results:** Approximately half of pts in the intention-to-treat (ITT) population (BVd, 124/243; DVd, 125/251) had only 1 prior LOT, 52% (257/494) had prior len, and 33.6% (166/494) were refractory to len; 21 BVd pts and 27 DVd pts were refractory to len at first relapse. In second-line len-refractory BVd pts, a median PFS of 35.7 mo (95% CI, 17.5 mo-not estimable [NE]) was observed vs 13.5 mo (95% CI, 6.6–26.3 mo) in DVd pts (HR, 0.39; 95% CI, 0.17–0.88). The estimated 24-month PFS was 67% (95% CI, 41%-84%) vs 35% (95% CI, 17%-53%) in the BVd and DVd groups, respectively. At data cutoff (October 7, 2024), 8 (38%) and 12 (44%) pts had died in the BVd and DVd arms, respectively. The median OS was not reached (NR; 95% CI, 35.7 mo-NE) with BVd vs 35.4 mo (95% CI, 24.4 mo-NE) with DVd (HR, 0.64; 95% CI, 0.26–1.59). The 36-month OS rate was 74% with BVd and 50% with DVd. Median DOR was NR (95% CI, 16.2 mo-NE) with BVd vs 13.1 mo (95% CI, 7.0 mo-NE) with DVd. Additional findings will be presented at

the meeting. **Conclusions:** In len-refractory pts at first relapse, BVd showed favorable PFS benefits, early and sustained OS benefits, and durable responses vs DVd. These results support the consideration of BVd as a new potential standard of care for len-refractory pts with RRMM and only 1 prior LOT, addressing a critical unmet need in this population. **Funding:** GSK (207503). Drug-linker technology licensed from Seagen Inc; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

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Outcomes after Second Autologous Hematopoietic Cell Transplant in Patients with Relapsed Multiple Myeloma in Latin America

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Introduction: With the advent of novel therapies, the treatment landscape for multiple myeloma (MM) at relapse has changed substantially and the role of salvage second autologous hematopoietic cell transplant (AHCT2) is debated. However, novel therapies are unavailable in many countries, where AHCT2 is still a choice. We conducted a retrospective analysis of MM patients who underwent AHCT2 after first relapse at two Latin American transplant centers. **Methods:** Retrospective analysis on previously transplanted patients with MM who underwent AHCT2 as consolidation following first relapse between 2013–2024, at two transplant centers from Argentina and Uruguay. The primary objective was to evaluate progression-free survival (PFS2) defined as the time from AHCT2 (infusion date) to the date of relapse, death, or last follow-up. Also, PFS after first transplant (PFS1) was calculated. Overall survival (OS) was estimated after AHCT2. **Results:** Fifty-six patients were included: 70% IgG, 69% kappa light chain, 19% ISS III, 12% R-ISS III and 26% high-risk cytogenetic at diagnosis. The median PFS1 was 51 months. At the time of AHCT2 the median age was 59 years (range 43–73) and the median of prior lines of therapy was 2 (range 2–5). Prior exposure to bortezomib, thalidomide, lenalidomide and daratumumab was 54 (96%), 47 (84%), 32 (57%), and 8 (14%), respectively, while 19%, 19%, 25%, and 5% were refractory to these drugs, respectively. Three patients were triple refractory. All patients received conditioning with melphalan single-drug and cryopreserved grafts in 21 cases (37%). Disease response prior to AHCT2 was: complete response (CR) 8 (14%), very good partial response (VGPR) 14 (25%), partial response (PR) 30 (53%), stable disease (SD) 2 (3%) and progressive disease (PD) 2 (3%). At day +100 post AHCT2 response rates were: CR 18 (32%), VGPR 12 (21%), PR 17 (30%), and no cases of PD (unknown in 9 cases). Maintenance therapy after AHCT2 was administered in 29 (52%) (lenalidomide monotherapy 20/29). With a median follow-up after AHCT2 of 57 months (IQR 30–72), 5-year OS was 54%. PFS2 was 30 months (95%CI:22–41). Lenalidomide refractoriness was significantly associated with shorter PFS2: 15 months (95%CI:11–30) vs 40 months (95%CI:25–69) in non-refractory patients ($p < 0.05$). Median PFS2 in patients who received maintenance after AHCT2 was 30 months vs 15 months in those who did not ($p = 0.3$). The following variables did not significantly impact PFS2: duration of response to the first AHCT, disease status prior to AHCT2, ISS, R-ISS, high-risk cytogenetics and number of prior lines. Thirty patients relapsed after AHCT2 with a 5-year cumulative incidence of relapse of 58%. Twenty-five patients died (14 due to progression, 7 unknown causes, 3 infections and 1 sudden death) with a 3-month cumulative non-relapse mortality of 1.8%. Two patients developed secondary solid tumors after AHCT2. **Conclusions:** In countries with limited access to novel therapies a second AHCT is safe and effective for relapsed MM.

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Time Toxicity Associated with Selinexor-Pomalidomide-Dexamethasone Versus Other Treatments for Relapsed/Refractory Multiple Myeloma

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Introduction: Combination therapies, many of which require injectable administration and extensive time for care coordination, dominate treatment for relapsed/refractory multiple myeloma (RRMM). The 'Time Toxicity' model proposed by Gupta et al. evaluated the trade-off between treatment efficacy and time burden. We applied this framework of 'Time Toxicity' to patients with RRMM treated with selinexor-pomalidomide-dexamethasone (XPd) versus other common treatments. **Methods:** This retrospective, observational cohort study compared patients initiating XPd, elotuzumab-pomalidomide-dexamethasone (EloPd), carfilzomib-pomalidomide-dexamethasone (KPd) or a bispecific antibody (BsAb; teclistamab, talquetamab, elranatamab) treatment for RRMM within the IQVIA Pharmetrics® Plus US insurance claims database between July 2019 and June 2024 (first treatment = "index date"). Patients were required to have ≥1 year of continuous enrollment (CE) prior to and ≥3 months of CE post-index. Time Toxicity was based on health system contact days, calculated as the total number of unique days in contact with the health system divided by the length of the variable post-index period and summarized by care setting (e.g., inpatient, outpatient, etc.). A hierarchy was applied to avoid double counting days for patients with multiple care settings on the same day. Percent of unique health system contact days post-index was used to compare the Time Toxicity associated with the different treatment options. Analysis of variance (ANOVA) test

(mean), non-parametric Kruskal-Wallis Test (median), and chi-square tests (proportions) were used to determine significant differences across cohorts. **Results:** The sample included 62, 155, 356 and 26 patients treated with XPd, EloPd, KPd, and BsAb, respectively. Mean age ranged from 65.4 years for KPd to 69.2 years for EloPD with 52–58% female. Proportion with commercial payers ranged from 28% for EloPD to 45% for KPd while proportion with Medicare Advantage ranged from 42% for KPd to 62% for EloPD. Median baseline all-cause cost for the year prior to starting treatment as an indicator of future utilization was highest for the XPd group ($333,959) followed by BsAb ($289,300), KPd ($281,424) and EloPd ($257,952) ($p = 0.014$). Median follow-up time in days ranged from 149 days for BsAb to 435 days for EloPD. Mean Time Toxicity was significantly different across treatments with the highest percentage of unique health system contact days observed for BsAb (20.6%), followed by KPd (14.6%), EloPd (12.9%) and XPd (12.5%) ($p < 0.001$). The differences were driven by inpatient contact days among patients treated with BsAb (13.6%) whereas all other treatments had rates below 9% ($p < 0.001$). **Conclusions:** Results suggest the all-oral treatment option of XPd could be beneficial when considering Time Toxicity associated with treatments for patients with RRMM. The EMN29 trial (NCT05028348) investigating XPd vs EloPd among patients with RRMM will provide further insight into treatment efficacy.

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Real World Survival Outcomes of Relapsed and Refractory Multiple Myeloma Patients Receiving Second Line Therapy and Beyond in Asia

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Introduction: Multiple myeloma(MM) is the 2nd most common hematological cancer in Asia. Global studies in relapsed/refractory MM(RRMM) lack adequate Asian representation. AMN010, a multi-country, real world retrospective study, aimed to assess treatment patterns and survival of Asian RRMM patients after 1 (2L), 2 (3L) or 3 (4L) prior lines of therapy **Methods:** Patients receiving 2L, 3L or 4L treatment from 25 sites across 6 Asian countries/regions between January 2020 and February 2022 were consented and recruited if they fulfilled IRB approved protocol specific inclusion/exclusion criteria. Primary endpoint was progression-free survival (PFS) analyzed by Kaplan-Meier method; secondary endpoints were overall response rate (ORR), duration of response, time to next treatment or death (TTNTD), prognostic factors and overall survival (OS). Subgroup analyses by age, sex, ECOG, ISS, country and ASCT status were performed. Cox regression was performed to determine prognostic factors and correlation with PFS **Results:** Patients receiving 2L (n = 626), 3L (n = 341) or 4L (n = 156) therapy were analyzed. The most common regimens for 2L, 3L and 4L were carfilzomib/lenalidomide/dexamethasone(KRd); pomalidomide/dexamethasone(Pd); & daratumumab monotherapy, respectively. Overall, median PFS (mPFS) was 16.4 months (mo) (2L), 9.1 mo (3L), 5.3 mo (4L). ORR was 71.6% (2L), 59.2% (3L), 43.6% (4L), with deep responses (sCR/CR) falling from 23.3% (2L) to 5.2% (4L). TTNTD shortened from 26.3 mo (2L) to 15.1 mo (3L). Median OS was not estimable in 2L/3L but was 18.2 mo in 4L. Prior ASCT improved median mPFS (18.7 vs. 14.9 mo) and 24-mo OS (85.9% vs. 75.8%) in 2L. Across lines, longer PFS was observed with ECOG 0, ISS I/II, younger age, and better renal function. IMiD and double class refractory (PI + IMiD) patients in 2L and 3L had mPFS of 5.3–6.6 mo. By the end of the study, 15.5% of 2L, 21.7% of 3L and 51.3% of 4L patients had died.Focusing on the cohort in China, PFS in 2L, 3L, and 4L were 10.7, 10.3, and 5.7 mo respectively. ORR was 58.4% vs 59.4% Vs 34% whereas sCR/CR rates were 21.6%, 18.8% and 1.9% across 2L, 3L and 4L groups. Median OS was not evaluable in all groups. Limitations of the study include retrospective nature, heterogenous population and treatment patterns and selection bias. **Conclusions:** In this largest to date RW study from Asia, survival outcomes of RRMM (notwithstanding the differing treatment patterns) are broadly similar to published earlier western data, with declining ORR/CR/PFS and higher attrition with increasing lines of therapy. Quadruplets and monoclonal antibody-based triplets are used less often in front-line and early relapses, in keeping with the regulatory approvals/reimbursements. Whilst further analysis is being planned, survival outcomes highlight the need for earlier adoption of innovative therapies. We acknowledge and thank patients, research teams, Singapore Clinical Research Institute & International Myeloma Foundation for study support & GSK for funding.

PA-498

Darmma – Real Life Experience of the Use of Daratumumab in Multiple Myeloma in Portugal

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Introduction: Daratumumab (Dara) is an anti-CD38 monoclonal antibody that demonstrated efficacy in the treatment of multiple myeloma (MM) in numerous clinical trials (CT). Real-world data provides an opportunity to study its use in clinical practice and to compare outcomes with those from CT. **Methods:** DarMMa is a national, multicentric, retrospective study to evaluate MM patients (pts) treated with Dara, in monotherapy or combinations, between November 2017 and December 2023. Response was evaluated by the IMWG criteria, high-risk cytogenetics (HRC) defined by the presence of del17p, t(4;14) or t(14;16). Progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and multivariate analysis were performed using Cox regression. **Results:** A total of 343 pts were treated, 58.9% male, with a median age of 67yo (32–89); International Staging System (ISS) was I in 31.6%, II in 33.3% and III in 32.8%, unknown 2.3%. R-ISS available in 292 pts: I in 25.3%, II in 63.0%; III in 11.6% pts. Cytogenetic data were available for 55.5% of pts, 14.7% with HRC. Lytic bone lesions were observed in 66.7% and extramedullary disease (EMD) in 27.6% of pts. Treatment regimens included DRd 58.6%, DKd 10.4%; DVd 10%; DPd 8%; Dara monotherapy 6.3%. The median line of therapy in which daratumumab was administered was 2 (1–7) - 21% of pts had Dara in 1st line, 42% in 2nd line, 19.3% in 3rd line, 11.2% in 4th line, 6.5 in 5th or posterior. With a median follow up of 21 months, the overall response rate (ORR) was 83.6%: sCR 6.3%; CR 16.1%; VGPR 43.1%; PR 18.1%; SD in 7.7%; PD in 8.6%. Autologous hematopoietic stem cell transplantation after Dara was performed in 9.8% pts and only 1.7% were re-treated with Dara. Treatment discontinuation due to toxicity occurred in 9.2% of cases. Cytopenias occurred in 50.4% (33.3% grade ≥ 3, with neutropenia grade ≥ 3 23.3%) and infections in 50.5% pts (17,5% grade ≥ 3). Median PFS was 26 months and median OS was 43 months. Dara in 1st line had superior PFS versus 2nd-3rd line (NR versus 27 months, p = 0.001) and superior OS (median OS 44 vs 33 months, p = 0.001). In multivariate analysis for PFS, treatment with Dara in 1st line (p = 0.002; HR 0.35) and use of DRd (p = 0.001; HR 0.57) were associated with superior PFS, while EMD (p = 0.003; HR 1.64), HRC (p = 0.050; HR 1.48) and ISS 3 (p = 0.015; HR = 1.49) were associated with worse PFS. In multivariate analysis for OS, treatment with Dara in 1st line (p = 0.001; HR 0.39) and use of DRd (p = 0.001; HR 0.45) were associated with superior OS and EMD (p = 0.009; HR 1.48) and ISS 3 (p = 0.077; HR = 1,30) were associated with worse OS. **Conclusions:** The DarMMa study characterizes Dara use in Portugal, showing good ORR, PFS, OS, and tolerability in real-world practice. DRd was the most effective regimen, and 1st line treatment with Dara was associated with better outcomes.

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A Network Meta-Analysis of Belantamab Mafodotin + Bortezomib + Dexamethasone vs Alternative Regimens in 2L+ Relapsed/Refractory Multiple Myeloma: Updated Efficacy Outcomes of DREAMM-7

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Introduction: The Phase 3 DREAMM-7 trial (NCT04246047) recently reported a significant overall survival (OS) benefit with belantamab mafodotin, an antibody drug conjugate targeting B-cell maturation antigen, in combination with bortezomib and dexamethasone (BVd) vs daratumumab plus bortezomib and dexamethasone (DVd) in patients with relapsed/refractory multiple myeloma (RRMM) who had received ³1 prior line of treatment (2L+; 42% reduction in risk of death; hazard ratio [HR] 95% confidence interval [95% CI]: 0.58 [0.43–0.79]; p = 0.00023). Based on the recent efficacy outcomes in the DREAMM-7 trial and emergent results for alternative regimens, it is important to re-evaluate the relative efficacy of BVd compared with other regimens in early RRMM. Here we reported an updated network meta-analysis (NMA) with the DREAMM-7 BVd regimen (median follow-up: 39.4 months). **Methods:** Randomized controlled trials (RCTs) of adults with 2L+ RRMM who progressed on/after most recent therapy were identified

in a systematic literature review (Jan 2008–Jan 2024). RCTs were included if they evaluated PFS, OS, or ORR in a regimen approved/likely to be approved by the US Food and Drug Administration/European Medicines Agency or were of interest for health technology assessment. Trials were linked together by the treatment(s) they shared to form connected networks of evidence for each outcome, and a Bayesian NMA was conducted. **Results:** The connected evidence networks comprised 13 RCTs (including DREAMM-7) for PFS, ORR, and OS. All regimens compared to BVd included a proteasome inhibitor (PI) and were: cyclophosphamide (Cy)+Vd (CyVd), Cy + carfilzomib (K)+d (CyKd), DVd, elotuzumab (E)+Vd (EVd), D+K+d (DKd), isatuximab (Isa)+Kd (IsaKd), panobinostat (Pano)+Vd (PanoVd), pomalidomide (P)+Vd (PVd), selinexor (S)+Vd (SVd), Kd, and Vd. PFS of BVd remained the longest of all therapies included in the fixed-effect NMA, with HRs of 0.15–0.48 and all credible intervals (CrIs) did not cross 1, indicating a high probability that the treatment effect was consistently in favor of BVd. Notable PFS HRs (95% CrI) included 0.43 (0.27–0.68) vs DKd, 0.48 (0.29–0.77) vs IsaKd, and 0.46 (0.35–0.60) vs DVd. OS remained longer for BVd than the other regimens, with HRs of 0.40–0.68, and 95% CrIs that did not cross 1 except for 5 comparisons (BVd vs CyVd, EVd, DKd, IsaKd, and Kd). OS HRs (95% CrI) for noteworthy regimens included 0.68 (0.41–1.11) vs DKd, 0.68 (0.39–1.18) vs IsaKd, and 0.58 (0.43–0.78) vs DVd. Odds ratios for ORR favored BVd over the other regimens (range: 1.14–7.60) with 95% CrIs that crossed 1 for 5 regimens (CyKd, DKd, IsaKd, Kd, and PVd). **Conclusions:** Based on updated analyses, the DREAMM-7 BVd regimen continues to demonstrate superior PFS against all comparators, and additionally superior OS and ORR against most comparator PI-based regimens for 2L+ RRMM in the absence of direct RCTs. **Funding:** GSK (214943).

PA-500

Belantamab Mafodotin in Patients With Relapsed/Refractory Multiple Myeloma and Severe Renal Impairment (Including Dialysis): Results From the Phase I DREAMM-12 Study

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Introduction: Belantamab mafodotin (belamaf) is a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate (ADC) that contains cytotoxic cysteine-monomethyl auristatin-F (cys-mcMMAF). Belamaf has been evaluated in relapsed/refractory multiple myeloma (RRMM) but not in patients (pts) with RRMM and severe renal impairment (RI) or end-stage renal disease (ESRD). The DREAMM-12 study (NCT04398745) assessed belamaf monotherapy in pts with severe RI or ESRD, including pts on dialysis, to provide dose recommendations for these populations. **Methods:** In this phase I study, 4 groups (Grp) of pts with RRMM (≥2 prior lines of therapy [LOTs]) were treated with belamaf (2.5 mg/kg Q3W): Control Grp1, glomerular filtration rate (GFR [mL/min]) ≥60 (normal/mild RI); Grp2, GFR 15 – 29 (severe RI); Grp3, GFR < 15 (ESRD not on dialysis); and Grp4, ESRD on dialysis. Endpoints were pharmacokinetics (PK) by non-compartmental analysis (primary), safety (secondary), and efficacy (exploratory). **Results:** Overall, 36 pts received ≥1 belamaf dose and were eligible for safety analysis. Median (range) age was 72 (48–87) years and median (range) no. of prior LOTs was 4 (2–14). Median (range) no. of treatment cycles was between 2 (for Grp1: [1–23]) and 6 (for Grp3 [2–20] and Grp4 [1–18]). The PK population comprised 29 pts (Grp1, Grp2 and Grp4 n = 8 each; Grp3 n = 5), with Grp1 and Grp2 matched for body weight and albumin. Cycle 1 concentration–time plots and PK parameters were generally similar for ADC and cys-mcMMAF across groups, except for slightly higher average cys-mcMMAF concentrations in Grp3 including higher average maximum concentration and area under the curve. Exposures between groups were largely overlapping and differences were not considered clinically meaningful. A separate population PK analysis confirmed that ADC and cys-mcMMAF exposures were consistent across RI categories irrespective of dialysis status. Urine PK analysis suggested renal elimination was not the primary route of cys-mcMMAF excretion (median fraction excreted 18% in Grp1). Adverse event (AE) incidence and severity were similar across groups (any AE/grade ≥3 AE: Grp1 100%/70%; Grp2 100%/67%; Grp3 100%/100%; Grp4 100%/75%). There were 7 fatal AEs (Grp1 n = 1; Grp2 n = 2; Grp3 n = 1; Grp4 n = 3) with 1 related to belamaf (Grp2). The most common AE classes per pt included eye disorders (Grp1 80%, Grp2 67%, Grp3 60%, Grp4 75%) followed by infections/infestations (50%, 33%, 60%, 75%). Serious AEs were reported in Grp1 in 40%, Grp2 44%, Grp3 60%, and Grp4 50% of pts (infections/infestations were most common [30%, 22%, 40%, 38%]). Investigator-assessed responses (≥partial response) were seen in all groups (overall response rate: Grp1 50%, Grp2 44%, Grp3 60%, Grp4 25%). **Conclusions:** No clinically meaningful PK, safety, or efficacy differences were seen across RI categories, indicating belamaf dose adjustments are not necessary for pts with mild to severe RI or ESRD, including pts on dialysis.

PA-501

Characteristics and Outcomes of Multiple Myeloma Patients with Post-Transplant Relapse: A Latin American Real-World Cohort Study

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Introduction: Therapeutic advances have significantly improved outcomes for patients with multiple myeloma (MM). However, prognosis following relapse remains variable, with early relapse after autologous stem cell transplantation (ASCT) being particularly associated with poor survival outcomes. In Latin America (LATAM), access to novel therapies for relapsed/refractory multiple myeloma (RRMM) remains limited, and real-world data on treatment patterns and outcomes in this setting are scarce. This study aimed to evaluate survival outcomes following first relapse in a large real-world cohort of LATAM MM patients who received a bortezomib-based triplet (BBT) induction regimen followed by ASCT. **Methods:** This was a retrospective, international, multicenter cohort study of patients with newly diagnosed multiple myeloma (NDMM) who received a BBT induction regimen followed by ASCT as frontline therapy between 2010 and 2023. Data were extracted from clinical records using a standardized case report form. Early post-ASCT relapse was defined as disease recurrence within 12 months following ASCT, and high-risk cytogenetics were defined as the presence of del(17)p, t(4;14), or t(14;16). Survival outcomes were analyzed using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. Cox regression analysis was used to evaluate prognostic variables. **Results:** A total of 793 NDMM patients from 10 LATAM countries were included. With a median follow-up of 60 months, post-ASCT relapse occurred in 41% of patients, with a median time to relapse of 25.6 months. Median age was 55 years in the non-relapsed group and 56 years in the relapsed group; 59% and 58% were male, respectively. ISS stage III was reported in 28% of non-relapsed patients and 34% of relapsed patients. Anemia was present in 45% vs. 50%, renal failure in 17% vs. 18%, hypercalcemia in 15% vs. 19%, bone lesions in 76% vs. 77%, and extramedullary disease in 19% vs. 13%, respectively. High-risk cytogenetics were reported in 21% of non-relapsed patients and 27% of relapsed patients. Maintenance therapy was administered in 91% vs. 81%, respectively. Early post-ASCT relapse occurred in 10% of the total cohort (29% of relapsed patients), with a median time to relapse of 6.5 months in this subgroup. The 5-year overall survival (OS) rates for non-relapsed, late-relapsed, and early-relapsed patients were 94%, 78%, and 36%, respectively ($p < 0.0001$). Independent risk factors for early relapse included extramedullary disease at diagnosis ($p = 0.01$), high-risk cytogenetics ($p = 0.006$), and ISS stage ($p = 0.03$). **Conclusions:** This study represents one of the largest real-world cohorts investigating relapse in NDMM patients undergoing ASCT in LATAM. Although early relapse was less frequent than historically reported, it was associated with markedly inferior survival, underscoring its adverse prognostic impact. Our findings highlight the prognostic significance of early relapse in a real-world, resource-constrained setting.

PA-502

Characterization of Infections in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) Treated With Belantamab Mafodotin (Belamaf)–Based Regimens From the DREAMM-7 and DREAMM-8 Trials

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Introduction: B-cell maturation antigen (BCMA) is an established target in patients (pts) with RRMM. Some BCMA-targeting therapies have been associated with increased risk of severe infection. A detailed profile of infections and use of supportive therapies has not been presented for belamaf-based regimens from DREAMM-7 (NCT04246047) and DREAMM-8 (NCT04484623). Here, we characterize the infection profile from DREAMM-7 (data cutoff: October 2, 2023) and DREAMM-8 (January 29, 2024). **Methods:** DREAMM-7 compared belamaf + bortezomib + dexamethasone (BVd) vs daratumumab + bortezomib + dexamethasone (DVd); DREAMM-8 compared belamaf + pomalidomide + dexamethasone (BPd) vs pomalidomide + bortezomib + dexamethasone (PVd). Data were analyzed post hoc to summarize infections and immunoglobulin use. Post hoc exposure-adjusted rates were defined as total number of pts with an event divided by total exposure time in person-years (PYs; per 100 PYs). **Results:** The DREAMM-7 and DREAMM-8 trials were conducted during the COVID-19 pandemic. Median treatment durations were 15.9, 12.9, 16.5, and 8.5 months with BVd, DVd, BPd, and PVd, respectively. Treatment exposure-adjusted any-grade infection rates were similar between BVd (51) and DVd (55), and lower with BPd (59) vs PVd (73); exposure-adjusted grade ≥3 rates were 23 vs 16 per 100 PYs with BVd vs DVd, respectively, and 35 vs 28 per 100 PYs with BPd vs PVd. Grade 5 infection rates were comparable between arms in both trials. The most common infections, by system organ class (occurring in ≥20% of pts in the BVd or BPd arm) were COVID-19, upper respiratory tract infection and pneumonia. Unadjusted incidence of grade ≥3 pneumonia was higher with BVd/BPd vs that with the comparators. Grade ≥3 COVID-19 was more common with BPd vs PVd but similar between the BVd and DVd arms. At data cutoff, infections were resolved/resolving in most pts. Incidence of "CMV reactivation," "pneumonia fungal," "Pneumocystis jirovecii pneumonia," and "polyomavirus-associated nephropathy," was low (≤2% each) with BVd and BPd; none were fatal. Rates of immunoglobulin use were 8%, 4%, 18% and 9% with BVd, DVd, BPd and PVd, respectively. **Conclusions:** Despite the conduct of DREAMM-7 and DREAMM-8 during the COVID-19 pandemic, and low immunoglobulin replacement during treatment, infection fatality rates with belamaf-based regimens were low and similar to those with the comparators; infections were resolved/resolving in most pts. Results suggest that belamaf-based regimens have a manageable infection profile in pts with RRMM. **Funding:** GSK. Drug-linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

PA-503

Trial in Progress: REALiTEC-2, an International Retrospective Study of Clinical Outcomes in Patients with Relapsed Refractory Multiple Myeloma Treated with Teclistamab in the Real World

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Introduction: Teclistamab was the first approved bispecific monoclonal antibody for triple-class exposed relapsed/refractory multiple myeloma (RRMM) patients. This approval followed the promising findings from the pivotal MajesTEC-1 clinical trial, with 63% of patients responding to treatment, 73.2% of those responses being complete response or better (≥CR) and 94.3% very good partial response or better (≥VGPR)1. The first cohort of the REALiTEC study2, primarily comprising heavily pre-treated patients from pre-approval access programs, reported similar outcomes, with an overall response rate (ORR) of 60.3%, of which 86.7% were ≥VGPR. Patients who attained deep responses (≥VGPR) experienced improved duration of response (DOR), progression-free survival (PFS), and overall survival (OS), with a median DOR of 26.1 months and PFS and OS not reached (NR) after a median follow up of 20.7 months. While data from cohorts treated outside of clinical trials provide additional insights and support their findings, there is a need for up-to-date data to better understand the latest results and practices in the real-world setting. **Methods:** REALiTEC-2 is a retrospective, non-interventional, international study to describe the use of teclistamab in RRMM patients in routine clinical practice. Data from patients' medical records will be collected to assess their characteristics and demography, history of prior antimyeloma treatments, treatment patterns, effectiveness (PFS, OS, response rates, DOR, time to response, time to next treatment), safety and subsequent treatments. If feasible, exploratory subgroup analysis will be performed in selected patient populations (renal impairment,

elderly, prior BCMA targeted treatment). To be eligible, patients included in this study will need to have been treated with commercial teclistamab having received the first dose within the period of January 1st, 2023, to 31st of December 2024, inclusive, to ensure sufficient data availability at the time of enrolment. Based on feasibilities and considering the descriptive nature of the study, a sample size of around 400 patients has been established. To reflect the different practices and management strategies between countries, 63 sites from 11 countries in Europe and Israel were approached, and enrolment began in April 2025 and is currently ongoing. **Results:** N/A **Conclusions:** More than 15900 patients have been treated to date with teclistamab in clinical practice worldwide. REALiTEC-2 aims to provide valuable data from patients treated in the real world, complementing REALiTECs first cohort and other ongoing observational studies, to inform about patient populations treated, outcomes and current management of teclistamab in routine clinical practice.

PA-504

Patterns of Use, Outcomes and Tolerance to Daratumumab in Multiple Myeloma: A Single-Centre Retrospective Study

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Introduction: Daratumumab(Dara), a monoclonal antibody targeting CD38, has demonstrated significant efficacy in the treatment of multiple myeloma(MM). However, its high cost restricts its use in many low and middle-income region. This study evaluates the real-world patterns of Dara use, treatment outcomes in MM patients in a resource-constrained setting. **Methods:** A retrospective observational study was conducted at a tertiary care center. The study included all confirmed adult MM patients who received at least one dose of Dara between Jan. 2018 and Dec. 2024 with available data regarding treatment response. Data collected included patient demographics(age, sex), disease characteristics(e.g. newly diagnosed, relapsed/refractory MM), treatment characteristics (regimen,line of therapy,duration,etc), treatment responses (evaluated per IMWG criteria) and reasons for treatment discontinuation. Kaplan-Meier survival analysis was performed to estimate PFS and OS, and Cox regression analysis was employed to identify prognostic factors influencing these outcomes like age,monotherapy vs combination therapy, Dara with IMiD vs. PI and ORR. Statistical significance was set at a p-value < 0.05. **Results:** A total of 98 patients were included in the analysis, with a median age of 61 years(range:26–81 years), of which 68 were male(69.4%) and 30(30.6%) were female. 83(84.7%) patients had relapsed/refractory multiple myeloma(RRMM) and were started on Dara.15(15.3%) patients were NDMM starting Dara as 1st line of therapy (LOT). Of the RRMM patients, Dara was used in 2nd LOT in 33(33.7%) patients and more than equal to 3rd LOT in 50 (51%) patients. The Dara regimens used included Dara with immunomodulators in 52%, proteasome inhibitors in 13.3% and alkylating agents in 4.1%. Quadruplet therapy was used in 26.5% patients, while 4.1% patients received monotherapy. The ORR to Daratumumab-based therapies had 52%. Infusion reactions were noted to be the most common adverse events, reported in 30(30.6%), of which it was Grade 1, 2 and 3 in 17.3%, 8.2%, and 5.1%, respectively. 18(18.4%) patients developed neutropenia, 14(14.3%) patients developed thrombocytopenia and 14 (14.3%) patients developed anemia. Median follow-up duration was 16.95(95% CI: 15.5–18.4)months, median progression-free survival (PFS) was 10.97 (95% CI: 7.8–14.1)months, and median overall survival (OS) was 27.99(95% CI: 16.5–39.4)months, with higher survival rates observed in patients receiving Dara in the earlier LOT. Cox regression showed that patients who received Dara prior to 3rd LOT had significant survival outcomes compared to ones receiving it in 3rd LOT or later. (p value 0.006,hazard ratio 2.9) **Conclusions:** Dara demonstrates meaningful efficacy in RRMM, even in resource-limited setting and optimizing access and early-line use may enhance survival outcomes in real-world practice.

PA-505

Efficacy and Safety of Isatuximab Subcutaneous (SC) Plus Carfilzomib and Dexamethasone (Isa-Kd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Results of the Phase 2 Study IZALCO

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Introduction: Intravenous isatuximab (Isa) can provide benefit to patients (pts) in multiple combinations across the therapeutic spectrum for MM. SC administration would offer a more convenient treatment option for pts and caregivers. Results of a Phase 1b study demonstrated safety and efficacy of Isa SC administration via an on-body delivery system (OBDS; an investigational wearable injector), plus pomalidomide and dexamethasone in RRMM pts. In the Phase 2 IZALCO study (NCT05704049), we evaluated efficacy (primary objective), patient preference, safety, and pharmacokinetics (PK) for Isa SC administered by manual injection or OBDS, in combination with carfilzomib and dexamethasone (Kd), in RRMM pts. **Methods:** Isa SC 1400 mg was given weekly in cycle (C)1 then biweekly. In Part 1 of the study, pts received Isa injected SC manually. In Part 2, pts were randomized to Isa administered SC via OBDS (C1–C3) followed by manual injection (C4–C6), or to manual injection (C1–C3) followed by OBDS administration (C4–C6); from C7, pts could choose either treatment modality. All pts received treatment with carfilzomib (20 mg/m2 on days 1–2 then 56 mg/m2 biweekly) and dexamethasone (20 mg). Primary study endpoint (EP) was overall response rate (ORR); patient preference for Isa SC administration modality was the key secondary EP. **Results:** Overall, 74 RRMM pts were enrolled: 8 in Part 1 and 66 in the randomized cohort (Part 2). At study entry, pts had a median age of 65 (44–85) yrs and a median of 1 prior therapy line (1–5); 56.8%, 32.4% and 10.8% had ISS stage I, II or III, respectively. The ORR rate was 79.7% at a median follow-up of 10.1 months, with very good partial response or better in 62.2% of pts and complete response or better in 21.6%. After treatment with both modalities for Isa SC delivery, 74.5% of pts expressed a preference for the OBDS rather than manual injection (p = 0.0004); 8.5% had no preference. Grade (G) ≥3 treatment-emergent adverse events (TEAEs) occurred in 54.1% of pts (treatment-related ≥G3 TEAEs in 35.1%) and serious TEAEs in 40.5%. Treatment with Isa SC plus Kd was well tolerated. A single infusion reaction event (1 of G1, 1 of G2) occurred in 2 pts (2.7%, both with manual injection at first dose). Six (8.1%) pts had 18 injection site reactions (17 of G1, 1 of G2) in 1297 (1.1%) manual or OBDS injections. Comparable PK exposure was observed between OBDS and manual administration. **Conclusions:** The study met its primary endpoint, demonstrating efficacy, safety, and similar PK exposure of Isa SC administration in combination with Kd, either by manual injection or OBDS. Our study findings are consistent with those reported in the Phase 3 study IKEMA with intravenous Isa. Pts expressed a clear preference for receiving Isa SC by an OBDS. **Funding:** Sanofi. © 2025 American Society of Clinical Oncology (ASCO), Inc. Reused with permission. This abstract was accepted and previously presented at the 2025 ASCO Meeting. All rights reserved.

PA-506

Isatuximab Subcutaneous via an On-Body Injector Plus Pomalidomide-Dexamethasone in Relapsed/Refractory Multiple Myeloma: Subgroup Analysis by Prior Lines of Therapy from the Phase 3 IRAKLIA Trial

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Introduction: The international, non-inferiority, open-label IRAKLIA trial (NCT05405166) of isatuximab (Isa) subcutaneous (SC) vs intravenous (IV) + pomalidomide-dexamethasone (Pd) is the first Phase 3 trial of an innovative on-body injector (OBI) in relapsed/refractory multiple myeloma (RRMM) patients (pts), who have been previously exposed to lenalidomide (LEN) and a proteasome inhibitor; pts with 1 prior line of therapy (LOT) had to be LEN-refractory. Pts with prior anti-CD38 in the last 9 months or intolerance to anti-CD38 were excluded. After 12 months median follow-up, IRAKLIA reported a 71% overall response rate (ORR) for Isa SC OBI vs 71% for Isa IV in RRMM pts (relative risk [95% CI] = 1.008 [0.903–1.126]; lower CI > non-inferiority margin of 0.839). In the Phase 3 ICARIA-MM trial, on which approval for Isa IV + Pd in RRMM was based, ORR and progression-free survival benefit was observed in pts with ≥2 prior LOT. IRAKLIA enrolled pts with ≥1 LOT; this post-hoc subgroup analysis of IRAKLIA evaluates outcomes by 1 or >1 prior LOT after Isa SC OBI vs IV administration

+ Pd. **Methods:** RRMM pts ≥18 years (y) were randomized 1:1 to Isa SC OBI (1400 mg; n = 263) or IV (10 mg/kg; n = 268) weekly in Cycle 1, then every 2 weeks with Pd. ORR was a co-primary endpoint (stratification factors included number of prior LOT [1–2 vs ≥3]). **Results:** Baseline characteristics were balanced across prior LOT subgroups for Isa SC OBI vs IV: median age was 66–67 y for 1 prior LOT and 66 y for >1 LOT. The >1 LOT group had a median of 3 prior LOT. Isa-Pd demonstrated efficacy regardless of the number of LOT; ORRs for Isa SC OBI vs IV were 74% vs 76% (1 prior LOT) and 70% vs 68% (>1 prior LOT) (Table). Among 1 prior LOT pts, 95% (Isa SC OBI) and 90% (Isa IV) were LEN-refractory; among >1 prior LOT pts, 59% (Isa SC OBI) and 52% (Isa IV) of pts were LEN-refractory at last regimen. For pts who were LEN-refractory at last regimen, ORRs for Isa SC OBI vs IV were 72% vs 74% (1 LOT) and 68% vs 62% (>1 LOT); for 1 prior LOT, rates of ≥ very good partial response (≥VGPR) and ≥ complete response (≥CR) for Isa SC OBI vs IV were 42% vs 51% and 15% vs 17%, respectively; for >1 prior LOT, rates were 40% vs 45% (≥VGPR), and 17% vs 20% (≥CR). Among all pts being assessed according to prior LOT, Grade ≥3 treatment-emergent adverse events (TEAE) for Isa SC OBI vs IV were 74% vs 68% (1 LOT) and 85% vs 80% (>1 LOT), with rates of treatment discontinuation due to TEAE of 7% vs 5% (1 LOT) and 9% vs 10% (>1 LOT). **Conclusions:** In IRAKLIA, comparable results were observed between the Isa SC OBI + Pd and Isa IV + Pd arms regardless of the number of prior LOT, demonstrating efficacy of Isa-Pd in the ≥1 prior LOT and LEN-refractory settings. These findings support use of Isa SC administered by the novel OBI plus Pd in RRMM pts regardless of number of prior LOT. **Funding:** Sanofi.

Table

	1 prior LOT		>1 prior LOT	
	Isa SC OBI + Pd	Isa IV + Pd	Isa SC OBI + Pd	Isa IV + Pd
Pts (%)	N = 76	N = 84	N = 187	N = 184
ORR	74	76	70	68
≥CR	16	19	19	21
≥VGPR	43	54	48	42

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Patient Perspectives from the Phase 3 IRAKLIA Study of Isatuximab (Isa) Subcutaneous (SC) via On-Body Injector (OBI) vs Isa Intravenous (IV) in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Noninferiority of Isa OBI vs Isa IV was established for efficacy (overall response rate) and pharmacokinetics (steady state trough level) in RRMM patients (pts) in the global Phase 3 IRAKLIA trial (NCT05405166). Meeting pt expectations and preferences about treatment may reduce their burden and improve adherence. The proportion of pts in IRAKLIA who were satisfied with the injection method at Cycle (C) 5 Day (D) 15 (key secondary endpoint) was higher with Isa OBI than Isa IV (ITT population: 70.0% vs 53.4%). This present analysis details pt satisfaction with the two Isa delivery methods in IRAKLIA. **Methods:** 531 pts aged ≥18 years with ≥1 prior line of therapy were randomized 1:1 to Isa OBI (1400 mg) or Isa IV (10 mg/kg) weekly in C1, then every 2 weeks with pomalidomide-dexamethasone. The patient expectations questionnaire (PEQ) was issued at baseline (BL), the patient experience and satisfaction questionnaire (PESQ) was issued at C1 (D8/15/22), C2 (D1/15), C3+4 (D1), and C5 onwards (D15), and the EORTC Core Quality of Life questionnaire (EORTC-QLQ-C30) was issued at C1D1, C2D1 and C3 onwards (D15). **Results:** Similar proportions of pts in both arms completed the PEQ at BL (≥82%) and PESQ on study (≥72.2%). The proportion of pts in both Isa arms agreeing/strongly agreeing on study that the injection method was uncomfortable, painful, or resulted in side effects was lower than what was expected at BL (Table). Time saving compared with other methods was the most marked difference between Isa OBI and IV pts at BL and on study (Table). A greater proportion of Isa OBI than IV pts were also satisfied with the injection method throughout the study. At each timepoint, a higher proportion of Isa OBI than IV pts agreed/strongly agreed that the medication was worth taking, were satisfied/very satisfied, and would definitely/probably recommend the

Table (abstract PA-507) Descriptive analyses among PEQ/PESQ responders

%	Agree/strongly agree	BL OBI	BL IV	C5D15 OBI	C5D15 IV	On study* OBI	On study* IV
Injection method	Discomfort	35.8	48.6	13.8	16.3	0–13.8	8.3–22.5
	Painful	41.2	39.3	6.9	10.4	0–7.0	6.3–15.2
	Side effects	50.0	51.9	12.2	9.9	0–15.0	4.2–19.0
	Time saving	73.0	40.8	83.1	32.7	74.5–91.7	26.3–52.2
	Satisfied	-	-	96.8	70.8	88.0–100	64.4–78.3
Medication	Side effects	52.2	60.2	13.8	15.8	0–22.3	6.3–29.4
	Worth taking	74.8	73.6	93.1	74.8	76.4–100	66.4–84.9
	Satisfied	-	-	92.1	82.2	78.6–96.8	68.8–87.7
	Recommend	-	-	93.7	81.7	83.7–100	63.6–81.7

*For visits where n≥20.

medication received via that injection method to another patient. The Isa arms did not differ at BL or during treatment in global health status on the EORTC-QLQ-C30. **Conclusions:** During IRAKLIA, pts receiving Isa OBI reported experiencing numerically less discomfort, pain, and side effects, and more time savings, from the injection method than Isa IV. These data suggest Isa OBI pts were more satisfied with and more likely to recommend their therapy than Isa IV pts and support the feasibility of using the OBI for Isa SC administration. **Funding:** Sanofi.

PA-508

Infection Rate Profile of Etentamig Monotherapy in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: Patients (pts) with relapsed/refractory multiple myeloma (RRMM) require novel immunotherapies with improved infection profiles. Etentamig is a differentiated B-cell maturation antigen (BCMA) × CD3 bispecific T-cell engager composed of a high-avidity bivalent BCMA-binding domain, a low-affinity CD3-binding domain to reduce cytokine release syndrome, and a silenced Fc tail for extended half-life to enable convenient dosing. The infection rates of pts treated with etentamig were evaluated in a pooled analysis from 2 ongoing studies: the first-in-human phase 1 study (NCT03933735) and the phase 1b study (NCT05650632). **Methods:** Both multicenter, open-label trials enrolled adults with RRMM with ≥3 prior lines of therapy (LoT), including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. This pooled analysis includes data from pts who received etentamig 60 mg every 4 weeks (Q4W) or 40 mg Q3W. **Results:** Of 146 pts enrolled from 2022–2024, 60% (n = 87) were male; median (range) age, prior LoT, and duration of follow-up was 68 (40–87) years, 4 (3–23), and 13 (1–48) months, respectively. Utilization of intravenous immunoglobulin (Ig) and anti-microbial prophylaxis was per institutional guidelines. In this cohort, 99 (68%) pts experienced all-grade infections, with upper respiratory infection (n = 26 [18%]) and pneumonia (n = 25 [17%]) the most common. Grade 3/4 infections were reported in 32 (22%) pts; pneumonia (n = 18 [12%]) and sepsis (n = 7 [5%]) were the most common. Dose interruptions and discontinuations due to infection were reported in 48 (41%) and 6 (4%) pts, respectively. Within the combined term of serious infections, 35 (24%) pts experienced treatment-emergent adverse events (TEAEs), with pneumonia (n = 17 [12%]) and sepsis (n = 8 [6%]) being the most common; median (range) time to onset of first serious infection was 120 (3–647) days. Median (range) time to onset of first infective pneumonia was 101 (3–272) days. One (0.7%) TEAE of opportunistic infection (cytomegalovirus

reactivation) was reported. Neutropenia (n = 56 [38%]) was the most common Grade 3/4 hematologic TEAE. Overall, hypogammaglobulinemia (≥1 postbaseline IgG level < 400 mg/dL) was reported in 127 (87%) pts. Deaths from infections without intervening post myeloma treatment were reported in 4 (3%) pts with 1 considered related to study drug. **Conclusions:** Etentamig demonstrated a manageable infection profile. Low incidence of Grade 3/4 infections suggests low-affinity CD3 binding may improve the toxicity profile of etentamig. Pts with RRMM should receive appropriate screening, prophylaxis, and be carefully monitored at frequent intervals for effective management of infections.

PA-509

Real-World Use and Effectiveness of Venetoclax in Combination with Carfilzomib Plus Dexamethasone in t(11;14)-positive Relapsed/Refractory Multiple Myeloma: A Single-Center Retrospective Study

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Introduction: The t(11;14) translocation in multiple myeloma (MM) is associated with elevated BCL-2 expression, providing a strong biological rationale for the use of venetoclax, a BCL-2 inhibitor. As BCL-2 is an anti-apoptotic protein, inhibition of BCL-2 by venetoclax leads to the activation of apoptosis and induction of malignant plasma cell death. While clinical trials have shown promising results for venetoclax in this molecular subgroup, real-world data remain limited. **Methods:** We retrospectively analyzed the outcomes of four patients with relapsed/refractory multiple myeloma (RRMM) harboring t(11;14), treated at our institution with a combination of venetoclax, carfilzomib, and dexamethasone (VenKd). All patients were triple-refractory to proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies, with a median of three prior lines of therapy (range: 2–5). Three out of four patients (75%) had previously undergone autologous stem cell transplantation (ASCT), and 75% had additional high-risk cytogenetic features. Data on treatment duration, response, and progression-free survival (PFS) were collected. **Results:** The median age was 69 years (range: 58–78), and all patients had ECOG performance status 0–1. Three patients (75%) achieved a stringent complete response (sCR), while one (25%) attained a very good partial response (VGPR). Notably, all responses were achieved within the first three cycles of treatment. At a median follow-up of 15.5 months (range: 5–23), all patients remained progression-free. The regimen was well tolerated, with no grade ≥3 adverse events or unexpected toxicities. No early discontinuations occurred. **Conclusions:** In this small but clinically significant real-world cohort, the VenKd regimen demonstrated notable efficacy and an excellent safety profile in t(11;14)-positive RRMM, including patients with high-risk cytogenetics. Importantly, all patients were heavily pretreated and triple-class refractory, and all responses occurred within the first three treatment cycles. These results are particularly impressive given that, in the relapsed/refractory (RR) setting, multiple myeloma tends to become increasingly aggressive, with progressively shorter remission durations following each subsequent line of therapy. This underscores the rapid and deep activity of the VenKd regimen in a difficult-to-treat population. These findings support further prospective evaluation of venetoclax-based combinations in genetically defined subgroups of MM.

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Delayed or Salvage Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma

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Introduction: There are limited data on the outcomes of multiple myeloma (MM) patients who receive delayed/salvage autologous transplant (autoHCT) in the era of modern anti-myeloma agents. **Methods:** Single-center retrospective chart review of consecutive adult MM patients that received delayed (≥1 year from diagnosis) or salvage (≥1 year from 1st transplant) autoHCT between 2006–2023. **Results:** 650 patients were included: 335 (52%) received delayed autoHCT and 315 (48%), salvage autoHCT. Median age at autoHCT was 61 years, 23% of patients were Black, and 24% of patients had high-risk cytogenetic abnormalities (HRCA). 56% of patients received post-transplant maintenance, mostly lenalidomide (len) alone (44%). Within the salvage autoHCT cohort, 84% had achieved ≥VGPR at best response after 1st autoHCT, and the median time from 1st to 2nd transplant was 4.6 years. Median time to both neutrophil engraftment (ANC >500) and to platelet engraftment (Plt >20 K) was 11 days. Prior to autoHCT, 26% of patients achieved ≥VGPR, which increased to 62% and 70% at day 100 and at best post-transplant response evaluation, respectively. After a median follow up of 37 months, the median PFS and OS for the entire cohort were 17 (95% CI 16–19) months and 47 (95% CI 41–52) months, respectively. There was no significant difference in either PFS (hazard

ratio (HR) 0.91, p = 0.26) or OS (HR 0.89, p = 0.23) between patients who got delayed or salvage transplant. In multivariable analysis (MVA) for PFS, R-ISS (stage III HR 2.55, p < 0.001), HRCA (HR 1.47, p = 0.002), >3 prior lines of treatment (HR 1.38, p = 0.002), being len-refractory (HR 1.34, p = 0.005), carfilzomib-refractory (HR 1.73, p = 0.004) and not being exposed to an anti CD38 drug (HR 1.62, p = 0.012) were associated with worse PFS. In MVA for OS, R-ISS (stage III HR 2.60, p < 0.001), >3 prior treatment lines (HR 1.47, p < 0.001) and being carfilzomib-refractory (HR 1.57, p = 0.017) were associated with inferior survival. In contrast, achieving ≥CR at best post-transplant response (PFS: HR 0.53, OS: HR 0.37; p < 0.001 for both) and use of post-autoHCT maintenance (PFS: HR 0.80, p = 0.021; OS: HR 0.54, p < 0.001) were associated with better survival outcomes. Within the salvage autoHCT cohort, those transplanted >2 years after the first autoHCT had better PFS (HR 0.51, p = 0.002) and OS (HR 0.53, p = 0.004) in MVA. 56 patients developed a second primary malignancy (SPM), 21 (6%) in the delayed group and 35 (11%) in the salvage group. Leading cause of death was MM progression (87%), followed by infection (4%). Rate of non-relapse mortality (NRM) was 3% at day100 and 4% at 1-year post autoHCT. **Conclusions:** This is the largest study to date to evaluate outcomes of delayed/salvage autoHCT for MM, showing a median PFS of 17 months and OS of almost 4 years. NRM rates were higher than observed in the upfront setting, although SPM rates were similar. These results can serve as a benchmark for novel treatment modalities for patients with relapsed/refractory MM.

PA-511

Exploration of Efficacy for Frailty-Adjusted Dose-Reduced Pcd Regimen in Relapsed/Refractory Multiple Myeloma

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Introduction: According to International Myeloma Working Group (IMWG) criteria, the efficacy and safety of reduced-dose Pcd is evaluated for the frail patients with relapsed/refractory multiple myeloma (RRMM) in re-induction therapy. **Methods:** This multi-center study enrolled 21 patients with IMWG-defined frail/unfit RRMM across four centers in Shanxi, China, from July 2022 to May 2025. Patients received reduced-dose PCd therapy, consisting of pomalidomide (2 mg/day on days 1–21), cyclophosphamide (50 mg orally every other day), and dexamethasone (10 mg/week during weeks 1–4, and 5 mg/week during weeks 5–8). Efficacy, quality of life, and adverse events (AEs) were systematically assessed. **Results:** The median age was 73 years (range, 42–88); 57.1% (12/21) were male. All patients had an ECOG performance status of ≥2 (95.2% had ≥3). At baseline, 90.5% (19/21) exhibited cytopenia (excluding anemia), 90.4% (19/21) had ISS stage III disease, 63.1% (12/19) were R-ISS stage III, 66.7% (12/18) harbored high-risk cytogenetic abnormalities, and 14.3% (3/21) presented with extramedullary soft-tissue involvement.After a median follow-up of 10.0 months (range, 0.5–24.4), the overall response rate (ORR) was 71.4%, including a 28.6% complete response (CR) rate. The median progression-free survival (PFS) was 4.0 months (95% CI, 2.3–5.7), and the median overall survival (OS) was 13.6 months (95% CI, 9.8–17.4). The most common AEs were hematologic suppression, rash, and gastrointestinal reactions; no thromboembolism, peripheral neuropathy, or severe infections occurred. Dose adjustments due to hematologic toxicity were required in 28.6% of patients. Notably, frail patients did not experience higher rates of grade ≥3 treatment-emergent AEs (TEAEs). **Conclusions:** The all-oral attenuated Pcd regimen demonstrates promising efficacy and tolerability in frail RRMM patients, showing non-inferior efficacy compared to standard regimens while providing a therapeutic platform for treatment-failed patients to improve their clinical status

PA-512

Real-World Analysis of Teclistamab Treatment for Relapsed Refractory Multiple Myeloma in Three Belgian Academic Hospitals

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Introduction: T-cell redirection therapies, including bispecific antibodies and CAR-T cells, are transforming the treatment landscape of relapsed/refractory multiple myeloma (RRMM), offering remarkable and durable responses. Teclistamab (Tec) is the first BCMA × CD3 bispecific antibody approved in this setting, based on the MajesTEC-1 phase 1/2 trial. Recently introduced in Belgium, we report on our real-world experience. **Methods:** We conducted a retrospective analysis to assess the efficacy and tolerability of Tec in 36 patients treated at three Belgian academic centers, comparing real-world outcomes with those from clinical trials. Tec was administered weekly at 1.5 mg/kg after two step-up doses (0.06 and 0.3 mg/kg), following standard guidelines. High-risk (HR) cytogenetics were defined by t(4;14), t(14;16), and/or del(17p). Responses were evaluated according to IMWG 2016 criteria, with survival analyses performed using the Kaplan-Meier method. Adverse events (AEs) were graded per CTCAE v5.0, and CRS/ICANS were graded per ASTCT criteria. **Results:** From December 2022 to January 2025, 53 patients received at least one dose of Tec. The median age was 68.5 years (range, 52–83), with 45% female patients. HR cytogenetics were observed in one-third, ISS stage III in 28%, circulating plasma cells in 8%, and extramedullary disease (EMD) in 28%. ECOG was 3–4 in 21% of patients. Patients had received a median of 4 prior lines

of therapy (LOT) (range, 2–11); 55% had undergone at least one autologous stem cell transplantation. All were triple-class exposed; 50% were penta-exposed, and 34% were penta-refractory. All patients were refractory to their last LOT, with no prior exposure to BCMA-directed therapies. At a median follow-up of 10 months (range: 0.25–29.5), the ORR was 85%, with 79% achieving at least a VGPR. The median time to first and best response was 35 (range, 6–126) and 97 days (range, 12–363), respectively. Median progression-free survival (PFS) was over v2 years, but less than 6 months for patients with EMD. At the time of analysis, 15 patients (28%) had died, predominantly due to progressive disease. Median overall survival (OS) was not reached. All patients experienced at least one AE, with grade ≥3 events in 77%. CRS occurred in 50% of them with only one grade ≥3, all during step-up dosing. ICANS was observed in 7 patients (15%) with grade 3 in 1 case. Cytopenias were common: anemia (89%/39% grade ≥3), neutropenia (68%/43%), thrombocytopenia (60%/26%), and lymphopenia (87%/70%). Infectious episodes occurred in 32 patients (60%), with grade ≥3 infections in 37%. Immunoglobulin substitution was administered to 89% of patients. **Conclusions:** Our real-world data demonstrate that teclistamab achieves comparable efficacy and safety outcomes to those reported in pivotal trials and other real-world studies. The toxicity profile was consistent with previous reports. These findings also underscore the urgent need for novel strategies to improve outcomes in patients with EMD.

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Clinical Features and Management of GPRC5D related AE in Chinese Relapsed/Refractory Multiple Myeloma Patients Treated with Talquetamab: MonumenTAL-1 China Cohort Experience

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Introduction: Talquetamab (tal) is the first and only approved BsAb targeting novel antigen, GPRC5D. Tal has shown overall response rates of >70% in patients(pts) with relapsed/refractory multiple myeloma (RRMM) in the MonumenTAL-1 study. Efficacy and most safety data of China cohort had shown consistency with global cohort, but taste-related events were lower (25.0–41.1%) compared with global cohorts (71.0–72.0%). Here we report the clinical management of GPRC5D related AEs of MonumenTAL-1 China cohort. **Methods:** MonumenTAL-1 is a phase 1/2, open-label, multicenter study of tal monotherapy in RRMM pts. Phase 1 identified 2 RP2Ds, 0.4 mg/kg QW and 0.8 mg/kg Q2W, which were further assessed in phase 2. Chinese pts were enrolled in phase 2. CRS and ICANS were graded by ASTCT criteria; all other AEs were graded by CTCAE v4.03. Response was assessed per IMWG 2016 criteria. **Results:** 29 pts were enrolled in 0.4 mg/kg QW cohort and 12 pts were enrolled in 0.8 mg/kg Q2W cohort. Updated median follow-up time was 16.3 mo and 13.9 mo respectively ORR was 69% and 67%, > = VGPR rate was 59% and 58%, > = CR rate was 38% and 58%. Median DOR was 15.7 mo and not reached. Median PFS was 8.3 and 10.7 mo, 12-month OS rate was 82.2% and 81.8% respectively.GPRC5D "on-target, off-tumor" AE, included oral, skin and nail toxicities. The incidence of dysgeusia was 41% (12/29) in QW cohort and 25% (3/12) in Q2W cohort, median onset time was 15–17 days, median duration was 160–231 days, only 2 pts reported concurrent decreased appetite, and 4 pts reported concurrent > = 10% weight decrease. 50%-58% dysgeusia was totally resolved at data-cut date Con-medication for dysgeusia including dexamethasone acetate, prednisone, olanzapine, riboflavin and Chinese herbal. Only 1 pts in Q2W cohort reported dry mouth. No pts had dose modification due to dysgeusia and dry mouth.Skin AEs included rash and non-rash AEs. The incidence of rash was 38% and 25% respectively, with median onset time of 9–25 days and median duration of 17–23 days. Only 1 pts experienced grade 3 rash. Incidence of non-rash skin AEs were 52% and 42%, which included skin exfoliation, dry skin, and pruritus. Only 1 pts reported grade 3 event. Median onset time was 19–62 days, with a median duration of 28–40 days. Supportive care included topical moisturizers, topical corticosteroids, oral corticosteroids, oral anti-allergic medication and Chinese herbals. 79–100% rash were resolved, and 68–100% non-rash skin AEs were resolved. No event led to dose modification.The incidence of nail disorders was 14% and 33% respectively, all grade 1/2, none lead to dose modification. Median onset time was 39–45 days, median duration of 223–301 days. Only 2 pts took topical paraffin and Vitamin E. **Conclusions:** Tal demonstrates deep responses in heavily pre-treated Chinese RRMM patients, with a clinically manageable safety profile. Clinical features of GPRC5D related AEs were similar to global cohort. No dose modifications were required to manage these GPRC5D related AEs in China cohort.

PA-514

Real-World Treatment Patterns, Effectiveness, and Safety of Daratumumab-based Regimens in Chinese Patients with Multiple Myeloma: Final Analysis of the MMY4032 Study

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Introduction: Daratumumab, a monoclonal antibody targeting CD38, has demonstrated efficacy in several multiple myeloma (MM) clinical trials. However, real-world data of daratumumab in a Chinese population which would reflect routine clinical practice is still needed. Daratumumab appeared effective and tolerable in Chinese MM patients in the first interim analysis of the real-world MMY4032 study (ChiCTR2200055491). Here we present the final analysis of MMY4032. **Methods:** This is an observational study across 13 sites enrolled Chinese patients with MM who started daratumumab after August 1, 2019, and were to continue daratumumab at the time of study initiation (November 3, 2021) or started daratumumab after study initiation, and who had received ≤3 prior lines of therapy (LOT), until up to 2 years, lost to follow-up or death for the last patient. Data were collected retrospectively using medical charts for patients who initiated daratumumab after August 1, 2019, but prior to study initiation, and were collected prospectively thereafter. **Results:** Overall, 212 patients were enrolled in the study, with a median follow-up of 23.7 months and median duration of treatment (DOT) was 11.7 months. Of these 212 patients, 35.4% completed the study including 11.3% still under ongiong daratumumab treatment and the reasons for discontinuation were withdrawal by patient (29.2%), death (20.3%), lost to follow-up (7.1%) and other (8.0%). Of the 185 patients evaluable for response, the overall response rate (ORR) was 76.8%, with 57.2%≥very good partial response (VGPR) and 39.4%≥complete response (CR). Of 212 patients, the median progression-free survival (PFS) was 34.1 months, while the median overall survival (OS) and time to next treatment (TTNT) were not reached, with 36-month OS of 72.8% and 24-month TTNT rates of 72.3%. Notably, higher response rates were observed with earlier daratumumab LOT (Table 1). The 36-month PFS/OS and 24-month TTNT rates were higher with earlier daratumumab LOT (Table 2). These findings highlight the enhanced effectiveness of daratumumab-based regimens when used in earlier treatment settings.

Table 1 Response Rate in each LOT

	ORR	≥CR	≥VGPR
1L(n = 28),%	89.3	46.4	75
2L(n = 107),%	83.2	46.7	67.3
3L(n = 26),%	57.7	19.2	23.1
>3L(n = 24),%	54.2	20.8	29.2

Table 2 PFS, TTNT and OS in each LOT

	36-month PFS	24-month TTNT	36-month OS
1L(n = 35),%	53.7	72.9	76.6
2L(n = 115),%	57.8	78.5	81.2
3L(n = 33),%	25.6	61.8	58.2
>3L(n = 29),%	18.1	58.5	45.9

Adverse drug reactions (ADRs) and serious adverse events (SAEs) were reported in 22.2% and 16.5% of patients, respectively. Importantly, no new safety concerns were identified with daratumumab-based regimens. **Conclusions:** In the final analysis with a longer follow-up, daratumumab-based regimens continue to demonstrate robust real-world effectiveness and manageable safety profiles in Chinese MM patients, particularly in earlier LOTs. These findings support the clinical utility of daratumumab and highlight its role in improving long-term outcomes in MM.

PA-515

Real-World Characteristics and Outcomes of Patients with Relapsed or Refractory Multiple Myeloma Treated with Talquetamab: Early Results from eMMpower Consortium

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Introduction: Talquetamab (TAL) is a novel treatment for relapsed or refractory multiple myeloma (RRMM) (US approval: 9 Aug 2023). The efficacy and safety of TAL were demonstrated in clinical trials (e.g., MonumenTAL-1). Existing real-world (RW) studies tend to include a single center or a small sample size. To address this evidence gap, this study described RW patient profiles, patterns of care, and clinical outcomes of patients treated with TAL using a large, multi-center consortium in the US. **Methods:** This

study used data from eMMpower, a large, ongoing, longitudinal, multi-center chart review consortium for MM (data cutoff date: 31 March 2025). Adults with confirmed MM receiving TAL monotherapy on or after the US approval date were included. Patients receiving TAL as bridging therapy for CAR-T, in a clinical trial, in an expanded access program, or as a combination regimen were excluded. **Results:** A total of 85 patients were included, 76.5% and 23.5% from academic and community centers, respectively. The mean (median) age at treatment initiation was 65.6 (65.9) years; 37.6% were female and 82.4% were White. There were 29.4% with ECOG score ≥2, 14.1%, 27.1%, 36.5% and 22.4% with R-ISS stages I, II, III and unknown, respectively, and 44.7% with a Simplified Frailty Score indicating frailty. Additionally, 67.1% had high-risk cytogenetics and at treatment initiation, 45.9% had bone marrow monoclonal plasma cells ≥60%. Patients received a median of 6 (IQR: 5.0, 7.0) prior lines of therapy. A total of 67 patients (78.8%) received a treatment dose after step-up dosing, 80.6% having 0.8 mg/kg biweekly (Q2W). Over a median follow-up time of 4.1 months, the ORR was 75.6% (≥CR rate: 19.2%; VGPR rate: 29.5%; PR rate: 26.9%) with a median duration of response of 7.5 months. The median PFS was 7.9 (95% CI: 5.3, 10.1) months, while the median OS was not reached. A total of 49 patients (57.6%) experienced cytokine release syndrome (CRS, 43.5% grade 1, 11.8% grade 2, 2.4% grade 3). 43 patients (50.6%) experienced weight loss, of which 19 (44.2%) had weight stabilization after a mean (median) of 77.7 (32.0) days, and 8 (18.6%) had resolution after a mean (median) of 95.0 (34.0) days. Among 62 patients (72.9%) with dysgeusia, 45.2% had improvement after a mean (median) of 105.0 (78.5) days while on treatment. Common dysgeusia management strategies included saline mouthwash (43.5%), biotene mouthwash/spray (30.6%), dexamethasone mouthwash (17.7%), and zinc (11.3%). **Conclusions:** In this real-world study of heavily pretreated and high-risk patients with RRMM using TAL as monotherapy, the real-world effectiveness is consistent with the pivotal trial findings. Most CRS events were mild, and the majority of patients reporting dysgeusia experienced improvement. Various supportive treatments were used in dysgeusia management. Overall, TAL was an effective treatment option even in these heavily pretreated and high-risk patients with RRMM and common AEs were manageable.

NURSING SYMPOSIUM ORAL PRESENTATIONS

NSO-01

Supporting the Shift: Inpatient Review of BCMA CAR-T Therapy in Multiple Myeloma Reveals Early Safety and Feasibility for a Nurse Lead Outpatient Model of Care

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Introduction: BCMA-directed CAR-T therapy has significantly improved outcomes for patients with multiple myeloma (MM). Due to the potential for immune-mediated toxicities, the CAR-T infusion is traditionally administered in the inpatient setting. However, products utilising a 4–1BB co-stimulatory domain are often associated with a more delayed onset of toxicity, suggesting early post-infusion monitoring may be safely managed outside of hospital. This abstract presents a retrospective analysis of inpatient CAR-T recipients and proposes a model for outpatient care led by Advanced Practice Nurses (APNs). **Methods:** A retrospective review of clinical outcomes of 37 MM patients who received BCMA-targeted CAR-T therapy as inpatients was conducted. Two patients were classified as high risk and were admitted at the commencement of lymphodepleting chemotherapy (LDC); these patients were excluded from the outpatient feasibility analysis. All remaining patients (n = 35) were monitored closely for cytopenias and immune-related adverse events following LDC and CAR-T infusion. The focus of this analysis was to evaluate the incidence and timing of early complications (Day 0 to Day +4 post-infusion), with the aim of informing a future outpatient delivery model. **Results:** The median time to onset of cytokine release syndrome (CRS) was Day +7 (range: Day +5 to +13), and the median onset of immune effector cell-associated neurotoxicity syndrome (ICANS) was also Day +7. No patients experienced severe immune-related toxicities or cytopenias that would have necessitated an emergency department presentation or unplanned escalation of care within the first five days post-infusion. BCMA CAR-T was associated with a delayed immune activation profile, with the majority of CRS and ICANS cases occurring on or after Day +5 compared to Lymphoma groups utilising a CD28 costimulatory domain. Cytopenias varied and were managed effectively with supportive care therapies. **Conclusions:** This inpatient analysis demonstrates that early complications following BCMA-directed CAR-T cell therapy are infrequent and clinically manageable, with most immune-mediated toxicities emerging after Day +5. These findings support a proposed hybrid model of care in which patients are managed in the outpatient setting from the commencement of LDC through to Day +4. During this period, patients should undergo daily ambulatory assessments including blood tests, ICE scoring, and neurological evaluations, coordinated and overseen by an APN with specialised expertise in early toxicity detection and supportive care management. Patients would then transition to inpatient admission on Day +4 for high-risk monitoring during the peak period of CAR-T expansion. This model is dependent on the patient having a 24/7 caregiver, access to a dedicated haematology on-call service, and being located in close proximity to the treating centre. It prioritises patient safety while promoting healthcare sustainability and a more patient-centred approach to CAR-T delivery.

NSO-02

Improving Capacity in the Malignant Hematology Day Unit by Increasing Subcutaneous Immunoglobulin Replacement Treatment in the Community

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Introduction: Intravenous immunoglobulin (IVIG) is a therapy used to treat patients with secondary immunodeficiency. A subcutaneous home-based immunoglobulin treatment (SCIG) has proven to be as effective as the hospital-based intravenous form. There is an opportunity to increase SCIG referrals across the Malignant Hematology Program, particularly for patients diagnosed with secondary immunodeficiency whereby the majority of patients have multiple myeloma. The aim was to establish a new best practice standard for treating eligible patients with secondary immunodeficiency using SCIG instead of IVIG. The transition of eligible patients aims to alleviate patient burden, reduce in-clinic infusion times, and optimize nursing resources. **Methods:** As part of the initial needs assessment, clinical groups were consulted to provide feedback on their use of IVIG and SCIG. Interventions were implemented using a multi-phase approach that was carried out over three Plan-Do-Study-Act (PDSA) cycles. Family of measures were analyzed for both the outcome measures and the process measures. For the data analysis, aggregate monthly SCIG referral numbers were provided by the SCIG community programs on a quarterly basis. Once the electronic referrals to both community partners were built, a data report in the institution's health informatics system was developed to automatically track SCIG electronic referrals made in real time. **Results:** Results of IVIG use was split into two groups: new patients receiving IVIG and ongoing patients. The average number of first time IVIG treatments decreased, while the number of patients with at least 1 previous month of IVIG treatment increased. In analyzing chair time in MHDU, patients receiving both short and long IVIG treatment increased. SCIG referrals accounted for nursing hours saved and significant annual cost savings. **Conclusions:** SCIG referral increased in response to rising IVIG demand, driven by novel therapies (e.g., Chimeric antigen receptor (CAR) T-cell therapy, bispecific T-cell engagers). While the intervention improved SCIG uptake, it did not reduce monthly IVIG utilization. The number of IVIG patients increased largely because early PDSA cycles targeted new referrals rather than existing IVIG users. Barriers to SCIG adoption—such as needle phobia, lack of social support, and self-administration challenges—persisted. These require targeted strategies for patient education and support. The ongoing expansion of novel therapies alongside evolving eligibility criteria for multiple myeloma patients increases IVIG demand and offsets gains in reducing overall utilization. This has implications for outpatient resource strain and can delay or limit access to other treatments. Patient burden remains high with monthly clinic visits impacting quality of life. Transitioning appropriate multiple myeloma patients to SCIG can alleviate this, but broader implementation requires addressing logistical and patient-centered barriers to inform a more sustainable model of supportive care.

NSO-03

Reframing Myeloma Supportive Care: Nurse-led Leadership to Improve Patient Outcomes

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Introduction: Our specialist haematology nursing team developed a collaborative supportive care program in 2016. The philosophy of the program is early engagement of patients in health promotion, autonomy for their health care needs and focused and systematic assessment of physical and psychosocial complications. We describe three examples of our multiple myeloma (MM) nurse practitioner (NP) supportive care program for individuals with a diagnosis of a plasma cell dyscrasia. These include two supportive care clinics (SCC), a monoclonal gammopathy of undetermined significance (MGUS) and post autologous stem cell transplantation (ASCT) and the MM therapy at home program. This groundbreaking program commenced in 2020 enabling eligible individuals with a diagnosis of MM who live within 30 km from our centre to receive bortezomib or daratumumab at home. **Methods:** Individuals with MGUS are seen in the plasma cell disorder SCC at 6 or 12 month time points. Individuals are seen in the post-ASCT SCC from discharge until 3 months. Demographic, disease and supportive care needs of individuals are collected at each clinic attendance. Details on hospital readmissions in the first 12 months post ASCT was also collected as well as number of MM treatments delivered in the cancer at home program since its commencement in 2020. **Results:** Between June 2016 and May 2025 there were 634 MGUS patient encounters in the MGUS SCC, patients were predominantly male (64.35%) with a median age of 65.5 years. Disease understanding was the most common unmet need in this cohort (75%). Between March 2023 and May 2025, 79 MM patients were seen in the post ASCT SCC. Patients were predominantly male (64.56%). More than 20% were from regional centres. There were 20 (25.32%) readmissions in the first 12 months post-ASCT due to varying infection complications and 6 (7.59%) non-infectious readmissions. The most common symptom post-ASCT was fatigue 61 (77.22%) patients followed by gastrointestinal disturbance 42 (53.16%) patients. From 2020 a total of 661 MM cancer at home treatments were delivered. **Conclusions:** These examples of our supportive care program in the plasma cell dyscrasia disease group demonstrate the power of collaborative nurse led programs. In the MGUS group an education gap has led to the development of a consumer endorsed education resource. Following MM ASCT the work to identify all readmissions and their causes will support the development of a re-admission prevention protocol. The leadership of the MM NP to identify opportunities for care at home

has led to a reduction in ambulatory treatment booking requirements as well as reducing patient travel burden.

NSO-04

Patient Perspectives of Receiving Out-patient Step-up Dosing with Bispecific Antibodies (BsAb) for Relapsed Multiple Myeloma (MM)

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Introduction: Delivering bispecific antibodies (BsAb) in out-patients (OP) vs an inpatient setting is often preferred by multiple myeloma (MM) patients and improves inpatient bed capacity. However, these therapies require close monitoring for side effects particularly cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) which many patients may not be familiar with. This may pose potential barriers to OP dosing and we therefore sought to evaluate the experience of MM patients who received OP step-up dosing to identify how best to support patients. **Methods:** Patients were treated in ambulatory care (AC) and stayed in designated accommodation located 170 metres from the treating centre with a caregiver. All patients were educated regarding toxicities including CRS and ICANS. Patients were prospectively interviewed later in treatment using semi-structured interviews. Interview transcripts were analysed using the Framework Method, a systematic and flexible approach for analysing qualitative data. **Results:** Six patients (age range 51 to 74; two males) received step-up dosing in AC. This was a heavily pre-treated cohort (median prior lines: 5, range: 4–11). Four patients felt they had been given adequate information and education by clinicians and pharmacists about logistics of treatment in AC, toxicities and when to seek medical attention. All patients preferred receiving BsAb in AC due to increased freedom and privacy compared to being an inpatient. Two expressed feeling anxious and more alone in AC, but all patients felt they were adequately supported by nursing teams whilst being treated in AC. Four of the six patients required transfer to hospital due to G1 CRS (fever) within 2 days of treatment (range:2 hours-3 days) and 2 further developed G2 CRS requiring tocilizumab and dexamethasone. No patients developed ICANS or G3 CRS. All patients interviewed were anxious about toxicity, particularly CRS but most (n = 4) felt their side effects were mild/moderate. Four patients were admitted via Emergency Department (ED) with long waits, causing anxiety and frustration. Median inpatient stay was 10 days (range:5–13) and all patients completed step-up dosing as an inpatient thereafter. Notably, 3 caregivers voiced pressure from the responsibility of caring for and undertaking monitoring for their relative whilst in AC compared to inpatient care. Overall, all patients interviewed felt that delivery of BsAb in AC was well managed and 3 would be happy to have treatment again in AC, whilst the others were happy to receive treatment in either setting. **Conclusions:** Patient feedback from this study suggests that step-up dosing of BsAb in AC is acceptable and provides advantages eg. greater freedom and privacy. Further work is needed to improve patient experience by streamlining admission pathways, particularly via ED and improving support and education to caregivers.

NSO-05

Patient Perceptions of Frailty and its Assessment in those Living with Myeloma

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Introduction: Multiple myeloma is an incurable cancer of the blood, predominantly affecting older adults. With an ageing population comes an increase in patients with multi-comorbidities, polypharmacy and other issues associated with ageing. Frailty is defined as a state of increased vulnerability to stressors due to a clinical decline in physiological reserves. It is recognised that the assessment of frailty is complex, existing frailty definition tools present challenges of subjectivity and a need for protracted clinical time. It is accepted that frailty needs to be defined in a personalised way. Existing literature lacks the perception of patients living with myeloma with regards to frailty. This study seeks to fill this gap. **Methods:** This was a single centre pilot study undertaken at a UK haematology centre. 9 patients and a carer were recruited into a patient focus group by open invitation. The aim of the group was to explore perceptions of frailty, frailty assessment tools (IMGW and G8) and consider the use of medical technology in frailty assessment. Data was obtained via semi-structured group discussions, questionnaires and conducting the G8 screening tool and IMWG frailty assessments on participants. Data was analysed via thematic analysis. **Results:** Responses around perceptions of frailty were categorised into 4 themes – physical restrictions, psychological wellbeing, social impact and treatment related issues. Physical restrictions had the most responses. Perceptions of frailty were explored at the meeting outset. No patients considered themselves frail pre diagnosis. 44.4% considered themselves as frail now. At the end of the session, after more detailed exploration of frailty, 100% thought they would be considered frail based on the IMWG and G8 screening tools. Objectively, the IMWG classified 6 (66.7%) as intermediate fitness and 2 (22.2%) as frail. The G8 screening tool identified 8 (88.89%) as requiring full geriatric evaluation. Participant perceptions of the tools were entirely negative, largely owing to what participants felt was their 'impersonal' nature. Participants gave feedback on the positive and negative aspects of

wearable monitoring devices, with 88.89% willing to wear a device. **Conclusions:** Frailty is a relevant topic in myeloma, yet patient perspectives have not been explored. This study highlighted a clear and marked disparity between patient perceptions of frailty and how this links to existing frailty assessments. Mentioning the terminology 'frailty' provoked exclusively negative impressions and thought may be given to re-framing this area of medicine to improve concordance between patients and their care team. It is clear from the results we need to define frailty in a more personalised and accurate way, giving consideration to how medical technology can potentially play a role in increasing the accuracy of data. This was a small pilot study which will be expanded upon and explored further with larger patient groups.

NSO-06

Identifying Gaps and Opportunities in Multiple Myeloma Care: Results from the "Opinions in MM Approaches and Challenges" Interactive Workshop Series

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Introduction: The increasing complexity of treatment options for multiple myeloma (MM), including the integration of novel agents such as bispecific antibodies (BsAbs) and chimeric antigen receptor (CAR) T-cell therapies, has created variability in clinical practice, particularly between academic and community settings. The Interactive Workshop Series aimed to assess real-world practice patterns, barriers to advanced therapies, and referral behaviors through a series of moderated, interactive workshops. **Methods:** Four workshops were conducted between October and November 2024 in the suburban New York City area, which included Brooklyn, Queens, Harlem, and Newark, NJ. A total of 38 oncology providers (24 medical oncologists, 11 nurse practitioners, 3 physician assistants) participated. Structured polling and moderated discussions captured data on MM management, treatment selection, access to novel therapies, and clinical trial participation. Data were analyzed descriptively, and key themes were identified through qualitative feedback. **Results:** Participants expressed high comfort with daratumumab-based triplet and quadruplet regimens in newly diagnosed MM (NDMM), though concerns about frailty influenced therapy selection. Treatment sequencing in relapsed/refractory MM (RRMM) remained a major challenge, with variability in access to CAR T-cell therapies and BsAbs—88% of university-based versus 16% of community-based participants reported direct access to CAR T, and 94% of university-based versus 37% of community-based participants reported direct access to BsAbs. Referral rates were low (<25% of patients), largely due to patient-related barriers (transportation, social support, cost). Despite a strong willingness to enroll patients in clinical trials, community centers faced staffing limitations, trial access restrictions, and logistical burdens. Coordination between academic and community centers was often suboptimal, with inconsistent handoff practices post-referral. **Conclusions:** The analyzed data highlights the persistent disparities in MM care delivery between practice settings. Strategies are needed to enhance access to advanced therapies, improve academic-community collaboration, and reduce patient and system-level barriers to clinical trial enrollment and referral, thereby optimizing outcomes.

NURSING SYMPOSIUM POSTER PRESENTATIONS

NSP-01

The use of a BCMA-directed Bispecific Antibody to Treat Relapsed Myeloma in a Liver Transplant Patient Receiving Continuous T-cell Immunosuppression and Concurrent Hemodialysis

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Introduction: Bispecific T-cell Engagers bind to CD3 receptors on T cells and an antigen on the surface of tumor cells. This interaction activates T cells, stimulating an immune attack leading to destruction of malignant cells. Properly functioning T cells play a crucial role in this pathway and inhibition of T cell activity would be expected to blunt the response of these agents. There is no published data concerning the use of these agents in patients having had a solid organ transplant who are receiving immunosuppression and little data regarding their use in patients requiring hemodialysis. **Methods:** Case Study **Results:** We present the case of a 75-year-old male status post deceased donor liver transplant Jan 1998. He subsequently developed ESRD secondary to sirolimus and cyclosporin toxicity necessitating renal transplantation (deceased donor) in Sept 2002. Upon routine monitoring, in Mar 2004 he was noted to have an IgA lambda monoclonal protein present on UPEP-IFE. Oncology workup noted this to be a low risk MGUS and he was monitored every 6 months. In Mar 2010 he developed worsening renal function with renal biopsy noting focal segmental glomerulosclerosis and no evidence of rejection or light chain deposition. Following 12 years of monitoring, in July 2016 he experienced rapid progression of MGUS to myeloma noted by an elevation of serum lambda light chains to 7793 mg/L with an involved-uninvolved ratio of 371. Bone marrow biopsy (BMBx) noted 20% lambda-restricted plasma cells with normal FISH. He began treatment with lenalidomide-bortezomib-dexamethasone (dex) followed by bortezomib maintenance. Over the next 8 years, he experienced two relapses which were treated with daratumumab-dex and carfilzomib-daratumumab-dex. During this time frame he also developed new onset A-fib and CHF resulting in acute kidney injury and the requirement for hemodialysis 3 times weekly. At his 3rd relapse in Jan 2024, PET scan was unremarkable but BMBx noted 10–15% lambda-restricted plasma cells now with multiple (9) new cytogenetic abnormalities including amp 1q (9%).

He initiated teclistamab Mar 2024, continuing full dose T-cell immunosuppression with sirolimus and cyclosporin. His dialysis sessions occurred on the day prior to receiving teclistamab, then 2 days and 4 days following. He achieved a rapid normalization of serum lambda light chains within 3 weeks of starting therapy. Following 5 months of weekly therapy, BMBx July 2024 noted an MRD negative CR (normal FISH) and teclistamab was converted to every other week (cycle 7). Following 14 months of therapy, BMBx May 2025 noted a continued MRD negative CR (normal FISH) and teclistamab was converted to monthly dosing. **Conclusions:** This case supports the efficacy and safety of teclistamab in a patient receiving T-cell immunosuppression following solid organ transplant, even when complicated by the necessity for concurrent dialysis.

NSP-02

Expanding Access to Bispecific Antibodies for Multiple Myeloma: A Multidisciplinary Model to Bridge Academic and Community Care

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Introduction: T-cell redirecting BsAbs for MM offer high efficacy but carry early toxicity risks,typically necessitating initial inpatient administration and specialized monitoring during the ramp-up phase. This has limited treatment availability to larger cancer centers and created disparities in access for patients in rural or community settings.To address this gap, our multidisciplinary team launched a structured education and referral program aimed at safely expanding BsAb access beyond academic centers. **Methods:** This initiative included the development of comprehensive educational resources covering mechanisms of action,eligibility, toxicity management, efficacy, and drug sequencing.Training for community based oncology teams was delivered via inperson sessions and virtual telementoring, led by a physician,APP,pharmacist, and nurse navigator.Standardized outpatient workflows were also created, incorporating a wearable monitoring device,home-based care services, and escalation protocols for managing CRS and neurotoxicity. Electronic, real-time surveys were employed to assess knowledge and comfortability with BsABs before and after each educational session. **Results:** Fifty interdisciplinary clinicians participated in pre- and post-training surveys assessing knowledge and confidence related to BsAb therapy.While not all participants answered every question, the data showed consistent improvements across all measured domains. Comfort with managing BsAb-associated toxicities increased from less than half of respondents(47%,14/30)pretraining to nearly all respondents(95%,35/37)posttraining, the most substantial gain. Knowledge of infection monitoring improved from 46% to 90% while the ability to identify neurotoxicity symptoms rose from 66% to 88%.Recognition of appropriate medications for CRS symptoms increased from 67% (33/49) to 92% (45/49)while knowledge of eligibility criteria for prior therapies improved from 32% to 64%. Additionally,Confidence in recognizing fever as the most common CRS symptom increased from 59% to 96%.1/3of respondents felt side effect management,inpatient bed constraints,and staffing limitations were barriers to initiating ramp-up, hough 100% of centers hoped to initiate treatment when possible. All respondents reported satisfaction with the training and indicated they would recommend it to colleagues. **Conclusions:** Despite educational improvements, barriers remain primarily staffing limitations and ongoing needs for team-wide education.Formal care pathways were established to support transitioning patients back to local providers following initial dosing,ensuring continuity and safety across care settings.This model of collaborative education,referral,and shared management has demonstrated early success in increasing provider readiness and creating safer,more equitable access to BsAb therapies for MM. Ongoing expansion and refinement aim to further close the access gap and ensure community teams are equipped to deliver high-quality care with appropriate academic support.

NSP-03

Establishing Barriers and Enablers to Nurse-Enabled, Subcutaneous Therapy Self-administration Programs for Myeloma Patients - Description of an Implementation Science Study Design

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Introduction: Multiple myeloma (MM) carries the highest symptom burden of all blood cancers, with patients often requiring multiple lines of treatment over many years. Subcutaneous (SC) injections are a common delivery method for both current and emerging therapies. Experience from our nurse-enabled, subcutaneous therapy self-administration program (NESTSP)—which allows patients or carers to administer SC treatments at home—has resulted in reduced hospital visits, lower time and cost burden of treatment, improved quality of life (QoL), and increased healthcare capacity. Despite these benefits, implementing this model in other healthcare settings has proven challenging, largely due to the complexity and variability of healthcare environments. Implementation Science (IS) has emerged as an evidence-based approach to study and understand how best to support, embed, and sustain evidence-based innovations in different contexts. Here we describe an IS-informed approach to explore barriers and enablers to implementing NESTSPs, guided by the Consolidated Framework for Implementation Research (CFIR) and the CFIR–Expert Recommendations for Implementing Change (ERIC) matching tool. Applying the CFIR and CFIR–ERIC matching tool provides an evidence-informed approach to

understanding how discrete and intersecting factors influence program implementation and sustainability. Data generated will inform the development of a national Implementation Roadmap for NESTSPs. **Methods:** A qualitative descriptive study was undertaken. Participants included key stakeholders from across the country, including patients, carers, health professionals, industry representatives, and policy makers with experience of implementation, facilitation, and participation in NESTSPs. Purposive sampling was used to ensure recruitment included participants with and without experience of successful implementation of a NESTSP. Data were collected via virtual focus groups or semi-structured interviews, and analysis was guided by the Framework Method to explore barriers and enablers according to the domains and constructs of the CFIR. The CFIR–ERIC matching tool was used to develop strategies to target barriers and enhance enablers. These strategies will be reviewed and refined in a future study with two regional cancer centres to inform the development of a national Implementation Roadmap. **Results:** n/a **Conclusions:** To our knowledge, this study is the first to identify and compare barriers and enablers to implementing NESTSPs for patients with MM. The implications of this work extend beyond MM due to the increasing use of SC therapies for myeloma, other cancers and chronic diseases. Approaches that enable patients to safely self-administer effective treatments could positively impact patient QoL and optimise healthcare utilisation.

NSP-04

Enhancing Patient Education and Support in Multiple Myeloma: A Toolkit-Based Nursing Intervention

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Introduction: The complexity of novel therapies for multiple myeloma (MM) has resulted in continuous treatment regimens with distinct side effects, requiring patient-centered education tailored to specific drug classes. Standardized education that aligns with patients' individual needs and learning styles can improve understanding, adherence, satisfaction, safety, and outcomes. Nurses in MM clinics are uniquely positioned to deliver structured education for both newly diagnosed (NDMM) and relapsed/refractory (RRMM) patients, ensuring they are prepared for treatment initiation and ongoing management. **Methods:** Nurses at our center provided structured education to patients with NDMM or RRMM initiating a new regimen. NDMM education included disease overview, lab and test monitoring, treatment goals, and support resources. RRMM education covered treatment plan, mechanism of action, side effects, when to seek help, and a treatment calendar. Education sessions allowed for questions and emphasized follow-up plans and care team contact. Patients completed pre-surveys to assess distress and post-surveys for distress and education satisfaction. Nurses also completed surveys assessing satisfaction with the standardized education process. **Results:** Utilizing monitoring designed for this pilot, 66 total patient visits were identified as eligible for survey distribution. Ten patients completed the pre- and post-survey, reporting high satisfaction with education. The highest-rated item was respect from the care team (mean = 5.0); the lowest, though still favorable, was feeling listened to (mean = 4.8). Overall, responses indicate patients felt the education was clear, respectful, and supportive. Education was most often provided by Advanced Practice Providers (63.6%), nurses (54.5%), and pharmacists (45.5%). Distress scores showed no significant change pre- to post-intervention ($p = 0.87$). Most patients preferred visual (100%) and reading/writing (81.8%) learning styles. Nurse feedback showed stable satisfaction over time. **Conclusions:** Small sample size and low variability reflect real-world challenges in nursing settings, including time constraints and competing clinical duties. Most participating nurses were new to their roles (within a year of hire), possibly affecting confidence in delivering education and navigating research procedures, while also prioritizing clinical responsibilities over study participation. Despite this, the program was well received. Future improvements may include using telehealth instead of phone calls to allow patients to view visual materials in real time, better supporting the predominantly visual learning preferences identified, and increasing patient engagement.

NSP-05

Bispecific Antibody Therapy in Haematology: A National Cancer Nurse Education Needs Assessment in the United Kingdom

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Introduction: Bispecific antibodies (BsAbs) were funded in the UK for patients with relapsed/refractory multiple myeloma in late 2024, offering a promising new treatment option. However, regional inequities in access were anticipated due to variable levels of experience and infrastructure. Patient feedback highlighted the importance of knowledgeable nurses in their understanding and experience of treatment. As a result, education was prioritised within a national quality improvement initiative. To inform this, we developed a survey to assess cancer nurses' confidence in managing BsAb therapy and to explore their preferred learning methods. **Methods:** We developed a 27-question survey (25 multiple-choice, 2 open-ended) using the platform Qualtrics. To accommodate clinical pressures, all questions were optional. The survey was distributed through professional networks, social media, and snowball sampling. Data were analysed using R Studio (v4.4.2). **Results:** 149 nurses responded from across the UK. Respondents represented a range of hospital types (specialist 56% (n = 83), regional 42% (n = 62)) and roles (nurse specialists 33% (n = 49), ward/daycare nurses 31% (n = 46), research nurses 11% (n = 17), nurse practitioners 7% (n = 11), other 17%

(n = 25)). Overall, confidence in managing BsAbs was low. Only 17% (n = 25) felt very confident identifying BsAb-related toxicities, while 44% (n = 65) were somewhat confident and 18% (n = 24) not confident. Confidence in managing toxicities was even lower, with just 11% (n = 17) very confident, 41% (n = 61) somewhat confident, and 26% (n = 39) not confident. Confidence levels did not differ significantly between nurses in specialist and regional hospitals for identifying ($\chi^2 = 0.65$, $p = 0.72$) and managing toxicities ($\chi^2 = 2.31$, $p = 0.32$). Confidence in counselling patients about supportive medications was also limited: 23% (n = 34) were not confident, 27% (n = 55) somewhat confident, and 19% (n = 28) confident. Similarly when discussing potential side effects, 20% (n = 30) felt very confident, 39% (n = 58) somewhat confident and 20% (n = 29) not confident. No significant differences were observed between hospital types for counselling on expected toxicities ($\chi^2 = 1.33$, $p = 0.51$) or supportive medicines ($\chi^2 = 0.02$, $p = 0.99$). Nurse specialists reported the highest confidence across all domains, while other roles showed notably lower levels. In-person training was the preferred educational format, with 74.3% (n = 110) rating it as very helpful, though respondents reported challenges attending due to time and funding constraints. Case-based eLearning and short videos were the next favoured formats, with 61.5% (n = 91) and 54.1% (n = 80) respectively rating them as very helpful, indicating they may offer acceptable more accessible alternatives. **Conclusions:** This national survey highlights low confidence among cancer nurses in managing and educating patients on BsAbs. As these therapies are now standard of care, tailored nurse training is essential to ensure patient safety and enhance patient experience.

NSP-06

Supportive Care Needs and Interventions Among Hospitalised Patients with Myeloma Bone Disease: A Single-Centre Experience

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Introduction: Myeloma bone disease (MBD) is among the most prevalent and debilitating complications of multiple myeloma (MM), affecting approximately 80% of patients. Characterised by osteolytic lesions, MBD leads to skeletal-related events such as pathological fractures, spinal cord compression and severe bone pain. These complications contribute significantly to morbidity, hospitalisation, functional decline, productivity, quality of life, and increased mortality following major events. Consequently, MBD increases health care costs and strain, underscoring the need for effective multidisciplinary care strategies in the management of MBD. **Methods:** To address these challenges, our institute, established the Myeloma Supportive and Integrated Care (MySTIC) team – a multidisciplinary group led by a Haematology Advanced Practice Nurse (APN) in partnership with haematologists, palliative care specialists, radiation oncologists, interventional radiologists, orthopaedic surgeons and allied health professionals. The MySTIC model emphasises a patient-centred approach aimed at early diagnosis and timely intervention. This includes expediting imaging, early interventions when necessary, and coordinated rehabilitation. The APN plays a pivotal role in MBD management and multidisciplinary meetings across bone intervention, palliative care and cancer rehabilitation. Here, we conducted a retrospective analysis of 30 MM patients reviewed by MySTIC between January 2024 to December 2024. Data on patient demographics, interventions and patient reported outcomes were collected. **Results:** Of the 30 MM patients, 21 were newly diagnosed and 9 had relapsed disease. The median age at presentation was 72.2 years (range: 51–86), and 66.7% were female. Before diagnosis/ relapse, 90% had an Eastern Cooperative Oncology Group (ECOG) performance status 0–1. On admission, declined to $^{3}2$ in 92% of the patients. Spine involvement was present in 60% of the patients. Pain was a predominant symptom: 80% reported moderate to severe pain. Vitamin D deficiency (25(OH)D < 30 ng/mL) was present in 50% of the patients. Interventions included analgesia, bone augmentation or osteosynthesis (53%), and radiotherapy (7%). The average hospital stay was 30.4 days (range: 0–112). Key patient-reported concerns included pain, loss of mobility, emotional distress, and difficulties related to financial burden and transportation. **Conclusions:** MBD remains a major contributor to morbidity, hospitalization, and symptom burden in patients with MM. Optimal outcomes depend on early integration of bone-targeted therapies, surgical consultation, correction of vitamin D deficiency, and access to psychosocial support. These goals are optimally achieved through coordinated, multidisciplinary care. Future care models should incorporate structured supportive pathways to address the complex and multifaceted needs of patients with myeloma-related skeletal complications.

NSP-07

Energy and Macronutrient Deficits in Multiple Myeloma: The Hidden Burden Across the Disease Spectrum

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Introduction: Malnutrition is a frequent but often under-recognized complication in patients with multiple myeloma (MM), affecting outcomes. In resource-limited settings, with limited dietary access, these challenges are often exacerbated. Nutritional needs vary across the disease trajectory—from newly diagnosed patients on induction therapy to post-transplant individuals and those with relapsed/refractory MM (RRMM). This study aimed to compare

nutritional status, energy intake, and macronutrient distribution across these groups. **Methods:** This cross-sectional observational study was conducted over one month at a tertiary care teaching hospital in North India, a representative setting. All patients diagnosed with MM (IMWG criteria) and treated were included. Nutritional status was assessed with the Mini Nutritional Assessment (MNA). Dietary intake was assessed using a 3-day recall and analyzed for energy and macronutrients. Patients were grouped into newly diagnosed on induction therapy, post-transplant on maintenance, and RRMM. Statistical analysis included Chi-square and ANOVA tests. **Results:** Seventy-five patients were evaluated (median age 61 years, male-to-female ratio 8:7): 42 on induction, 20 post-transplant, and 13 RRMM. Malnutrition was most prevalent in RRMM (50%), while 71.4% of newly diagnosed patients were at risk. Post-transplant patients had the most favorable nutritional profile, with 45.7% well-nourished (Chi-square = 21.04, $p = 0.0003$). Mean daily energy intake was highest in transplant patients (1250 kcal), followed by MM (986 kcal) and RRMM (780 kcal) (ANOVA $F = 128.8$, $p < 0.000001$). Macronutrient intake varied significantly (Protein: $p < 0.00001$; Carbohydrates: $p = 0.00012$; Fat: $p < 0.00001$). Compared to the estimated TEE of 1574 kcal and protein requirement of 78 g/day, RRMM patients had the greatest deficits —50.4% in energy and 82.4% in protein. MM patients had 37.4% and 62.2% deficits, respectively, while transplant patients had 20.6% and 43.8% deficits. Carbohydrates contributed 82% of energy in RRMM, 70% in MM, and 65% in transplant—above the ideal (~60%). Fat intake was below the 22% threshold across all groups (RRMM: 11%, MM: 18%, transplant: 21%). These patterns highlight a carbohydrate-heavy, protein- and fat-deficient intake, notably in RRMM. **Conclusions:** In this resource-limited setting, nutritional deficiencies are common across all MM stages, with RRMM patients showing the most severe imbalances. Even post-transplant patients had notable deficits. The dominance of high-carbohydrate, low-protein, low-fat diets reflects disease and systemic challenges. Targeted nutritional support is essential in routine myeloma care.

NSP-08

A Randomized Controlled Trial of Bone-Targeted Exercise for People with Multiple Myeloma: The MyeEx-Impact Study

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Introduction: Level 1 evidence supports the safety and feasibility of exercise for people with multiple myeloma (MM). Our recent work identified individualized targeted exercise can reduce bone pain; however, research is yet to explore the potential effect of exercise on bone health. Preclinical models using osteogenic exercise have demonstrated mechanical load-induced changes delay osteolytic activity and rescue bone loss. Therefore, the MyeEx-Impact multi-site randomized controlled trial aims to examine whether bone-targeted exercise can improve bone health in people with MM. **Methods:** People with MM (n = 78) residing in Queensland and New South Wales in Australia are invited to participate in this study. Following baseline testing, participants are randomized to exercise (EX) or control (CON). The EX group performs two supervised and one unsupervised sessions of individualized bone-targeted exercise each week over 9 months. The CON group receives usual care and a copy of the Myeloma Australia physical activity recommendations. Primary outcomes (bone density and microarchitecture measured via dual-energy x-ray absorptiometry and peripheral quantitative computed tomography) and secondary outcomes (bone pain, quality of life, fatigue, physical function, psychological constructs, gut microbiome, disease response, biomarkers of bone health, immune function, and disease progression) are assessed at baseline, 3-, and 9-months. Adverse events, and adherence to the exercise program are monitored. **Results:** The MyeEx-Impact trial is on track to reach its a priori recruitment target. Participants have had high adherence to the resistance and impact loading exercises. Seven low-grade (Grade 1 and 2) adverse events have been reported; none of which have impacted subsequent exercise or study participation. **Conclusions:** The findings of this study will identify whether bone-targeted exercise is safe, feasible, and can improve bone health in people with MM. Furthermore, this study will provide evidence of the effects of bone-targeted exercise on common MM- and treatment-related side-effects, as well as the potential mechanisms underpinning these effects. Collectively, this novel study will identify the potential role of exercise as an adjuvant therapy for the management of bone health for people with MM.

NSP-09

Characterising Critical Disease Burdens: Integration of Primary Care Data and Real-Time Patient Monitoring to Transform Multiple Myeloma Care in the UK

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Introduction: With improving survival rates in Multiple Myeloma (MM), patients face complex treatment regimens and symptom burdens. Real-world data remains fragmented, and while

primary care (PC) records offer insight into treatment exposure and care trajectories, they lack resolution on daily symptoms and quality of life (QoL). This work combined PC data with that from 'MyMM', a patient-designed tool capturing real-time patient-reported outcomes (PROs) and wearable metrics, to better understand MM burden and unmet needs. **Methods:** Retrospective analysis was performed for 275 UK patients with MM-linked CTV3 codes in PC records, linked across events, medications, and demographics. Prospective data (n = 36) from MyMM's PRO interface (e.g., EQ-5D-5L and symptoms extracted from 'My POS') alongside wearable (n = 19) metrics through an FDA-approved device were collected (Jan-May 2025). Variation by sex, age, and treatment line was analysed for all metrics using a linear mixed model. **Results:** The PC cohort (51% female; mean age 77 (53–99)) had a mean of 11 years since first recorded diagnosis; 186 were deceased at censure (53%; 79 (53–99)). Patients had a mean of 20 unique repeat PC-issued medications (excluding hospital prescriptions, most commonly Lansoprazole (44%), Paracetamol (43%), and Amlodipine (41%)) and 31 CTV3 codes (essential hypertension (27%), deep venous thrombosis (17%), lower back pain (16%), and type II diabetes (15%)) over their PC history, with 16 clinical PC contacts annually post-diagnosis. Females had higher prescribing (21.5 vs. 18.4) and comorbidity burden (35.5 vs. 25.5) than males. Patients aged 80+ had fewer contacts but greater comorbidity (34.5) and prescribing (22.5). Annual events and repeat prescriptions increased stepwise with rising code counts and assumed complexity. App data (58% female; age 58 (36–78)) over a median 70 (7–126) days captured 38,827 datapoints: 4,561 activity, 4,207 sleep, and 30,023 PRO. 23 patients reported first (1L), 4 second (2L), 3 third-line or above (3L+), and 4 off treatment. Weakness demonstrated the highest severity score (1 = least-5 = most) at 3.8, followed by drowsiness (2.7), poor mobility (2.6), tingling (2.5), and difficulty remembering (2.0). EQ-5D-5L averaged 0.706 and VAS 66.0. Borderline significant sex-based differences were seen in EQ-5D-5L (female: 0.703 vs. male: 0.575, $p = 0.051$), with significant differences in nightly SpO2 (96% vs. 98%, $p = 0.002$). Tingling severity increased with age (+0.085/year, $p = 0.031$). 3L+ patients showed higher 'shortness of breath' than off treatment (4.9 vs. 0.5, $p = 0.050$), and 1L recorded higher nightly SpO2 than 3L+ (98% vs. 96%, $p = 0.046$). **Conclusions:** This work demonstrates the feasibility of integrating longitudinal PC data with real-time app-based symptom and biometric monitoring to deepen MM burden characterisation. Differences by patient subgroup were evident across both datasets, with findings supporting the value of combined clinical and digital data to enhance stratified, personalised care in MM.

NSP-10

Evaluating a Hybrid Approach to Oncology Pharmacy: A Comparison of Service Delivery Models for Immunomodulatory Drug Management

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Introduction: The value of clinical pharmacists in the management of patients receiving oral anticancer medications has been increasingly recognized in recent years. Pharmacists are uniquely equipped to provide comprehensive care to patients prescribed these agents, which often have specific monitoring requirements and require frequent assessment for adverse effects. Immunomodulatory (IMiD) drugs such as lenalidomide and pomalidomide are anticancer agents that can be used in the treatment of multiple myeloma (MM) and are subject to strict dispensing regulations. Historically, patients in one regional health authority were required to travel to one of five designated cancer care centres to meet with their oncology team, after which they received their medication from a specialty pharmacy. This model presented significant challenges, including fragmented communication between the dispensing pharmacy and the oncology team, often placing the burden on patients to coordinate care. Additionally, the need for travel imposed additional financial and logistical strain, particularly for those living in rural or underserved areas. To address these gaps and promote equitable, patient-centred care, a novel hybrid care model was introduced within the health authority. In March 2024, a three-year-pilot program was launched, establishing a dedicated IMiD pharmacist to support all patients on IMiD therapy. The pharmacist provides comprehensive patient education, proactive monitoring, prescribes supportive care medications, and communicates with both the dispensing pharmacy and cancer care team to provide comprehensive, efficient care and improve patient's access to specialized cancer care through virtual or in-person appointments. The objective of this study is to evaluate the impact of the hybrid pharmacist monitoring program on patient outcomes, specifically examining the tolerability of IMiD therapy before and after implementation. Findings from this evaluation will inform future decisions by health authorities regarding the continuation or expansion of the hybrid pharmacy service and support the development of additional pharmacist-led clinical care models. **Methods:** A matched cohort study design will be utilized to compare patient outcomes of a historical cohort of patients within the health authority before the service was introduced to a cohort of patients who received care from the IMiD pharmacist beginning in late March 2024. Included patients will have a diagnosis of MM and treatment with lenalidomide or pomalidomide. The historical cohort will be constructed using pairwise matches to facilitate equal baselines. Outcomes measured will include total days of treatment, dose reductions, dose delays, discontinuations, Emergency Department visits/hospital admissions, and incidence and severity of toxicities. **Results:** Results to be determined, with data collection to occur in Summer 2025. **Conclusions:** Conclusion to be determined following data collection in Summer 2025.

NSP-11

Clonal Hematopoiesis in Multiple Myeloma: Current Implications and Future Directions

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Introduction: Clonal Hematopoiesis of Indeterminate potential (CHIP) is an emerging area of interest in multiple myeloma (MM) due to potential association with poorer outcomes, early relapse and increased risk of treatment related myeloid neoplasm (TMN). As MM treatments improve and survival increases, CHIP will be identified more frequently due to better testing. CHIP is defined by age-dependent accumulation of somatic leukemia-associated driver mutations in hematopoietic stem cells in individuals with normal blood counts and no underlying myeloid neoplasm. This review summarizes recent literature on the topic to define areas of consensus, uncertainty and future directions for prospective studies to assess CHIP in MM. **Methods:** PubMed was searched using terms clonal hematopoiesis, indeterminate potential and multiple myeloma. Inclusion criteria: publication 2020 or later, specific focus on CHIP in MM and addressing auto stem cell transplant (ASCT) and/or maintenance excluding immunotherapy. Of 96 identified articles, 18 met criteria for full review. **Results:** Three retrospective cohort studies of CHIP in MM were identified. In one study, 629 patients receiving ASCT, CHIP was detected in 21.6%. Of patients receiving first-line immunomodulatory drugs (IMIDs), 3.3% developed TMN. IMID maintenance improved progression free survival (PFS) and overall survival (OS) regardless of CHIP. OS was lower in CHIP positive patients not receiving IMID maintenance due to disease progression. In another cohort of 101 patients 23% had CHIP at diagnosis. ASCT and IMID maintenance were given to 43% of CHIP positive and 38% of CHIP negative patients and no difference in PFS, OS, or TMN were observed. In the CoMMpass study, (986 ASCT eligible and ineligible patients) CHIP was present in 10% at diagnosis and increased to 25% over 3 years. No significant association was found with advanced R-ISS, high-risk cytogenetics or inferior PFS/OS regardless of ASCT. IMID maintenance provided benefit independent of CHIP status. CHIP was associated with increased risk of cardiovascular disease (CVD) and infections. In smaller studies suggested possible impact of CHIP on CAR-T response, earlier progression, cardiovascular events (CVD, HF, stroke), venous thromboembolism (VTE), stem cell mobilization and platelet engraftment. **Conclusions:** As MM patient survival improves understanding the clinical implications of CHIP is increasingly important. While CHIP may contribute to adverse outcomes, these risks may be mitigated by the use of IMID maintenance and ASCT may not worsen CHIP associated TMN. Additionally, CHIP may influence treatment response, count recovery, CVD, stroke and VTE. Prospective research is needed to define clinically relevant variant allele frequency thresholds, assess the impact of specific CHIP mutations (alone and in combination) and clarify their role in secondary malignancy and TMN risk. Improved understanding of CHIP in MM may lead to risk adapted strategies to reduce harm and optimize outcomes.

NSP-12

Quality Improvement Intervention, the Addition of Lifestyle Medicine Group Sessions in Multiple Myeloma Population

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Introduction: Multidisciplinary lifestyle medicine education for patients with multiple myeloma is limited despite lifestyle evidence-based recommendations for cancer patients (NCCN,ASCO/ACS, IMF). Lifestyle interventions, including tailored physical activity, sleep/stress reduction, nutrition interventions, may be valuable information and changes for MM patients to assist in managing their health. The goal to lessen side effects and perhaps improve their physical functioning, decrease fatigue and psychological distress, improve their quality of life and long-term health outcomes. **Methods:** A QI pilot study employing lifestyle medicine education specific to multiple myeloma was facilitated by two ACLM-certified providers and a program coordinator at Massachusetts General Hosptial. For the pilot study, a total of seven participants were recruited by MM providers through clinical referrals to take part in virtual visits once a week over the course of 6 weeks (6 total sessions). The visits were structured with a brief introduction of the topic, follow up about previous week, provider-led medical education, group interaction and peer support, and closing review of goals to incorporate into daily living. Session topics included: physical activity, healthy eating, sleep, social connections, stress and anxiety, and time-outs, energy and purpose. **Results:** Participant surveys were reviewed at the conclusion of the program. All participants marked either "agree" or strongly agree" to the statements "this group motivated me to take better care of myself" and "this group is a valuable addition to my care at MGH." Self- reported healthy behavior changes made following the visit included: more intentional eating, making more time for social interaction, adding 30 minutes of daily exercise, exploring meditation and taking time to reflect on the day. All participants noted gratitude for having a space to connect with others with a diagnosis of multiple myeloma. **Conclusions:** This pilot study developed as a QI project, demonstrated that the lifestyle medicine group virtual visits are a valuable addition to care of patients with multiple myeloma. All patients reported benefitting from the program in terms of: better eating habits, quality of life, improved physical activity and social connection. Future research needs to further evaluate the effectiveness of multi-disciplinary lifestyle medicine group programs for the multiple myeloma population.

NSP-13

Strategies for a Successful Transition to Short infusion Isatuximab for Patients with Multiple Myeloma

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Introduction: Transitioning to a shorter infusion schedule represents an opportunity to enhance patient care by reducing patient time at the hospital. Strategies to safely reduce chair time can positively impact appointment wait times. Changes to existing protocols require involvement of the multidisciplinary team (MDT). Informing key stakeholders ahead of time can help facilitate a smooth and efficient transition. This study aims to describe the logistical considerations used for an efficient transition to short infusion IV isatuximab and evaluate the incidence of infusion related reactions (IRR) with the short infusion rate. **Methods:** The MDT of hematology pharmacist, hematologist, and nurse educator met in Spring 2024 to plan the logistics to transition to short infusion IV isatuximab. Sept 3, 2025 was chosen as the go-live date. During summer months hematology pharmacists cut over orders for existing patients. The MDT used various strategies (patient clinic visits, support group meetings, chart messages) to notify patients of the upcoming change. The pharmacists updated orders for existing patients and notified the physician to review and sign. Pharmacists updated the master treatment plans templates in the computer system and infusion rates in the IV pump library. The nurse educator reviewed changes in premedications and infusion rates. They assessed updated chair times for pressure points and workflow. The pharmacy technician assessed workflow changes of shorter chair times. All stakeholders were encouraged to provide feedback. A retrospective descriptive cohort study was completed. Patients with multiple myeloma receiving an isatuximab containing regimens (IsaCarfDex, IsaPomDex) in the ambulatory chemotherapy unit from Sept 3, 2024 to Jan 31, 2025 were included in data collection and analysis. Outcomes to measure included: the number patients receiving a short infusion of IV isatuximab, the number of infusion related reactions (IRR) that occurred while receiving the short infusion rate, the number of patients receiving the short infusion rate at time of study closure. **Results:** Twenty-seven patients received short infusion IV isatuximab during the study period. No patient experienced an infusion-related reaction while receiving the short infusion rate during the study period. At time of study closure, 22 patients were actively receiving isatuximab as a short infusion. **Conclusions:** Transition to short infusion isatuximab represents an improvement in efficiencies in healthcare resources. By addressing logistical factors including patient selection, cutover of existing plan modifications, go-live date selection, staff education, and patient awareness, modifications to existing regimens can be launched efficiently. Future direction includes: earlier use of the 30-minute infusion and removing ongoing pre-medications if no IRR. Hematology pharmacists are well-situated to navigate smooth and successful transitions in therapy modifications to benefit patients and optimize healthcare resources.

NSP-14

An Examination of Perceived Gaps in Multiple Myeloma Education for Nurses

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Introduction: Significant strides have been made in the survival rates of patients (pts) with multiple myeloma (MM). Now, with new drugs and refined treatment regimens, MM patients have the potential for deeper responses and significantly improved outcomes. Nurses play a crucial role in realizing and maximizing these advancements. As treatments in MM are rapidly evolving across the disease spectrum, the availability of engaging and effective education is critical. We created a live, continuing education symposium at an annual nursing meeting to provide education on MM topics and identify opportunities for future learning. **Methods:** To identify both perceived and unrecognized educational gaps among oncology nurses, we enacted a two-step process. First, all registrants were asked to submit questions in advance of the symposium. Secondly, four pre- and post-test questions were asked during the symposium to assess educational gaps and learning opportunities. **Results:** 683 oncology nurses registered, and 601 attended this live event. 44% identified as academic, 55% as community, and 1% both. Collectively, nurses reported seeing over 6,700 MM pts per month, resulting in more than 80,000 interactions with MM pts annually. Fifty-six questions were submitted prior to the meeting, covering 83 topics, which were then categorized according to common themes: Advancements in treatment (n = 15), side effects (n = 10), cellular therapy (n = 12), laboratory testing (n = 8), prognosis (n = 8), and patient education (n = 4). Notably, only two questions mentioned bispecific antibodies (BsAb). Four pre- and post-test questions were asked during the live meeting to assess knowledge gained on the following topics: cytokine release syndrome, transitions of care, the importance of quadruplet therapies, and disparities. Knowledge was gained with each question, most notably in understanding the impact of quadruplet therapy in achieving MRD negativity, with a 36.6% improvement in correct responses. Gaps remain regarding disparities in MM, with an observed gain of 42.5% and a remaining gap of 51.2%, providing an opportunity for further education. **Conclusions:** The questions submitted by nurses highlight evolving educational needs. Interestingly, there were few questions submitted about BsAb despite its increasing use in community settings, where over half of the symposium's attendees are in practice, which may indicate a lag in awareness of newer treatments. Nurses requested the latest updates

but were unable to formulate specific questions regarding disparities or BsAb. Finally, pre- and post-questions helped verify the continued need for education regarding effective treatment strategies and disparities in MM. Our findings are consistent with other publications, which highlight the need for ongoing education on various MM topics.

NSP-15

Supportive Clinical Care Pathways for Patients Receiving Bispecific Antibody and CAR T-Cell Therapy for Multiple Myeloma

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Introduction: A clinical care pathway (CCP), also known as a care path, aims to incorporate best practices and guidelines into a standardized approach to care. Additionally, when integrated into the electronic medical record (EMR), pathways create institutional "best practices" for continuity of care and, when shared, promote these to referring centers. Patients (pts) with multiple myeloma (MM) represent an increasing population due to innovative therapies, including bispecific antibodies (BsAb) and chimeric antigen receptor T-cell (CART) therapies, which improve survival rates; yet, pts face unique care challenges such as infection complications, risk of relapse, and survivorship concerns. Thus, we aim to create and integrate a CCP into the EMR that incorporates international guidelines and best practices for the long-term management of pts on BsAb or after CART. **Methods:** Our MM disease group identified the need for a standardized CCP for pts on BsAb or CART. To determine existing guidelines and practice patterns for a CCP, we conducted an extensive review of the literature, utilizing a search of electronic databases (CINAHL, Medline, Cochrane, and PubMed) that restricted publications to those in English between January 2020 and May 2025. We used the terms "clinical, care, path, pathway, myeloma." Articles would be included if they proposed or reported the use of a supportive care model for MM pts receiving BsAb or after CART. Since the definition of pathway-directed therapy in MM examines genetic aberrations in tumor cells, these papers were excluded, and the search yielded no results. We then expanded the search to include a Google Scholar website search to find relevant papers. **Results:** The search identified 3 treatment pathways, including 2 in the US and 1 in Australia, but no supportive CCP in MM pts receiving BsAb or after CART. Three international guidelines published in the last 12 mos on immunotherapy and CART from the IMWG, NCCN, and TCT were reviewed. Best-practice recommendations from 1 collaborative pharmacy group and one international nurse leadership group were also considered. Consistent themes identified for pts receiving BsAb and after CART include the prevention and early detection of infection, monitoring for relapse, and the importance of survivorship strategies to support the physical, financial, and social aspects of immunotherapy delivery. **Conclusions:** International guidelines and best practices exist for the treatment of pts receiving BsAb or CART with MM. However, standardized guidelines and EMR integration is lacking. If CCPs exist, they are not widely disseminated. No published supportive CCPs for patients receiving BsAb and after CART were identified in this review. As effective care coordination is critical to ensure pts receive the correct infection prophylaxis, disease monitoring, and survivorship care, we aim to finalize a CCP and integrate it into the EMR for consistent coordination of care in pts undergoing therapy with BsAB and after CART.

NSP-16

The Psychological and Quality-of-Life Impact of Haematological Malignancies in Young Adults: A Comparative Study of Myeloma, Lymphoma, and Leukaemia in a Private Healthcare Setting in UK

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Introduction: Haematological malignancies such as multiple myeloma (MM), lymphoma, and leukaemia are predominantly diagnosed in older adults. However, patients face distinct challenges, including psychological distress, long-term health complications, and concerns related to career, family, and fertility. These experiences are underexplored, particularly within private healthcare where access to treatment and support structures. It compares the psychological burden, quality-of-life concerns, and long-term care needs of young patients diagnosed with MM, lymphoma, or leukaemia within a private healthcare system. By identifying gaps in care provision and assessing coping mechanisms across different malignancies, the study aims to inform tailored support interventions for this underserved patient population. **Methods:** A cross-sectional survey was conducted among young adults diagnosed with MM, lymphoma, or leukaemia in a London based private healthcare facility. Inclusion criteria included: (1) diagnosis at age ≤55, (2) at least six months post-diagnosis, and (3) treatment received in a private setting. The questionnaire covered key areas such as anxiety, emotional well-being, support needs, fertility discussions, and secondary health conditions. Data were analysed using descriptive statistics and visual data representations. **Results:** This study, involving 92 younger patients (average age 41) with lymphoma, leukemia, or myeloma, reveals

significant long-term challenges. Patients experienced initial anxiety about their future and families, which, while persistent, evolved to include more physical side effects over time. While psychological distress often stemmed from survival uncertainty, acceptance of illness grew, though fears of recurrence remained. The research highlights the critical need for personalized support, with varying preferences for coping mechanisms like financial planning, peer mentorship, or nutritional advice. Fertility preservation emerged as a major concern, often requiring earlier and more structured counseling. Furthermore, patients commonly developed diverse secondary health complications, necessitating ongoing, tailored monitoring and rehabilitation. The findings strongly advocate for private healthcare systems to enhance long-term care through integrated mental health support, accessible fertility preservation, expanded post-treatment rehabilitation, and routine long-term health monitoring. **Conclusions:** Young adults diagnosed with MM, lymphoma, and leukaemia in private healthcare settings face distinct yet overlapping challenges. This study highlights the importance of tailored psychological support, improved fertility preservation strategies, and comprehensive long-term health monitoring. Addressing these gaps through integrated, patient-centred care plans can significantly enhance quality of life and long-term health outcomes. Future research should explore the comparative impact of private versus public healthcare models in supporting young haematology patients.

NSP-17

The Power of Partnership: Supporting Patient Adherence to Treatment Through a Unique Collaboration of Healthcare Professional and Patient Organisations

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Introduction: The development of new myeloma treatments in the past 20 years has increased treatment options and the complexity of regimens. Patients commonly receive quadruplet myeloma therapy, in addition to supportive medications. Treatments are largely outpatient-based and healthcare professionals (HCPs) are required to help patients understand complex regimens, including provision of written medication schedules. To aid and standardise production of treatment schedules, an Australian/New Zealand haematology society developed an online tool (MyeTxScheduler https://rego.interact.technology/myetx/) pre-populated with standard myeloma protocols. The tool allows HCPs to create printed, point-of-care, myeloma treatment schedules that patients use to tick off medications as taken. Treatments can be individualised as clinically indicated. The schedule also includes dates for appointments and links to patient information. Following successful implementation in Australia and New Zealand, a baseline survey by United Kingdom (UK) nurses and pharmacists revealed variation in practices related to myeloma medicine aids and identified a gap. A proposal was made to adapt MyeTxScheduler for UK use. **Methods:** A working group of UK myeloma pharmacist and nurse groups, Australian HCPs, and a UK patient organisation, partnered to expand the tool to include UK-specific regimens and information. Collaboration with the UK patient organisation, and an Australian patient support group, provided necessary funding to support the work. Following adaptation, MyeTxScheduler now includes 32 approved myeloma treatment protocols. HCPs from 11 UK hospitals were invited to pilot its use and HCPs and patients were asked to feedback on their experience using the tool. **Results:** Early results indicate two-thirds of schedules required no modifications. Most modifications were related to steroid dosing, reflecting individual hospital practice. The age of patients in the pilot ranged from 50 to >90 years, indicating the tool can be used across a wide age range. Initial evaluation shows its efficacy in assisting myeloma patients' comprehension of intricate treatment regimens to support treatment adherence. One patient described the tool as 'the greatest thing that ever happened to me with managing medications, the scheduler makes sure I do the right thing every day'. Average completion time by HCPs was five minutes, demonstrating the tool is user-friendly within busy clinic settings. Uptake of a standardised tool across the UK could reduce the potential inefficiencies and risks involved with HCPs creating different compliance charts in their regions. **Conclusions:** This unique international collaboration has successfully facilitated the wider use of a treatment scheduling tool to enhance patient understanding of and adherence to myeloma treatment. This, in turn, supports optimised patient outcomes. Further work involves extended piloting to widen dissemination.

NSP-18

Describing the Impact on Patients Starting Myeloma Therapy by a Myeloma Care Pharmacist in a Specialized Community Oncology Pharmacy Setting

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Introduction: Oral therapies have improved overall survival for patients with multiple myeloma (MM) in recent decades, and MM can be considered a chronic disease.1 Most MM care is provided in the outpatient setting and patients and care partners need to take on a larger responsibility in disease management. Triple and quadruple MM therapies have moved to earlier lines due to their efficacy, meaning patients are taking complex treatments for the majority of their care, which often includes oral and injectable therapies. Additionally, most patients with MM are diagnosed at 65 years or

older and manage other co-morbidities and medications. In the community, a specialized myeloma care pharmacy program provides early patient assessment during prescription verification, medication reviews, and patient counselling. At treatment start, pharmacists with expertise in myeloma can identify drug therapy problems (DTPs) early and make necessary interventions. A DTP is any undesirable event or risk of an event experienced by the patient involving their drug therapy and interferes with their goals of therapy. DTPs require professional judgment to resolve and prevent further clinical consequences. In 2021, 14 ambulatory oncology clinical pharmacy key performance indicators (AOcpKPIs) were identified by Canadian oncology pharmacist expert consensus as evidence-based services that oncology pharmacists perform that impact patient care and outcomes in the outpatient setting.2 Cancer Care Ontario (CCO) has published a reference on best practices for delivery of take home cancer drugs (THCDs).3 These recommendations and the 14 AOcpKPIs have been integrated into the pharmacy workflow. The study aim is to show the impact of early pharmacist involvement in a community specialty oncology pharmacy for patients with MM and to describe the quality of patient care through measurement of DTPs and AOcpKPIs identified during the initial patient interaction. **Methods:** A retrospective descriptive cohort study will be completed. Patients with MM initiated on lenalidomide, pomalidomide, and selinexor from April 28, 2025 to August 31, 2025 will be included in data collection and analysis. Outcomes to measure include: Number of DTPs identified and number of AOcpKPIs identified during initial patient counseling. **Results:** Total of 16 patients (30 interactions) were included in the study to date. Total number of DTPs identified and resolved during the initial dispense and patient counseling session was 67, with a mean of 4 per patient. For the 16 patients, pharmacists completed a total of 121 AOcpKPIs during initial dispense and patient counseling (84 during initial dispense, 37 during the counsels), with a mean of 5 per initial dispense and 2 per counsel. **Conclusions:** Following evidence-based practice by incorporating CCO recommendations and AOcpKPIs into the pharmacy workflow, specialized myeloma care pharmacists in a community specialty oncology pharmacy were able to make an impact on patient care by identifying and resolving DTPs.

NSP-19

Diagnostic Journeys in Myeloma: A Qualitative Exploration of Barriers and Facilitators

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Introduction: Multiple myeloma (MM) is considered one of the most challenging cancers to diagnose leading to frequent diagnostic delays. Delays are associated with increased complications due to more aggressive disease at diagnosis, end organ damage and reduced disease-free survival. Reviews of medical records and claims data estimate a median of 163 (IQR 84–306) days from symptom presentation to diagnosis and report half of patients have 3 or more primary care visits before specialist referral. These studies have demonstrated and quantified delayed diagnosis but give us limited insight into why delays are happening. Qualitative research is well suited to address this question by capturing the processes, context and perspective of patients' diagnostic journeys. Our objective was to conduct in depth semi-structured interviews of adults with MM to better understand their journeys to MM diagnosis. **Methods:** A purposive sample of MM patients (age 18+, diagnosed within the last 10 years, English or Spanish speaking) were recruited to participate in a 60-minute interview. Our semi-structured interview guide, informed by the Models of Pathways to Treatment, focused on understanding patients' diagnostic journeys and barriers and facilitators to MM diagnosis. Audio recorded interviews were transcribed and analyzed using thematic analysis using ATLAS.ti (v.25.0.1). **Results:** Among 30 participants, 16 were female, 6 identified as Hispanic or Latino, 12 as Black/African American, 10 as White and 2 as Asian. Mean age was 69 years old. Patients' diagnostic journey began with, new or prolonged symptoms, critical medical events (traumatic fall, kidney failure) or abnormal test results. We identified several themes that describe barriers and facilitators that influenced patients' journeys to a myeloma diagnosis. Facilitators to diagnosis included: 1) Encouragement from social support networks to seek care for new or worsening symptoms, 2) Existing primary care provider relationships and rapport leading to timely evaluation and specialists and 3) Self-advocacy in the face of persistent symptoms. Barriers to diagnosis included 1) Conservative management in the face of persistent symptoms, 2) Dismissal of myeloma symptoms due to age and/or preexisting comorbidities, and 3) Limited knowledge of MM presentation delaying initial testing and diagnosis. **Conclusions:** Our findings indicate that, earlier diagnosis of MM may have been possible for some patients and suggest several strategies for improvement. Most patients were entirely unaware of MM prior to their diagnosis, highlighting the opportunity for public education campaigns about the symptoms of MM. We identified instances of continued conservative management in the face of symptoms (pain, anemia) that were not improving, resulting in missed opportunities for quicker MM diagnosis. Targeted education could help clinicians identify opportunities for further diagnostic workup (SPEP) when managing symptoms that are not improving

LATE BREAKING ABSTRACTS

OA-61

A Randomized Phase 2 Study of Daratumumab, Lenalidomide, Ixazomib, and Dexamethasone in Transplant-Ineligible/Deferred Patients with Newly Diagnosed Multiple Myeloma: Alliance Foundation Trial 41

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Introduction: The treatment of newly diagnosed multiple myeloma (NDMM) has rapidly evolved, and induction combining an anti-CD38 monoclonal antibody, lenalidomide, a proteasome inhibitor, and dexamethasone has become a standard of care. In this prospective randomized phase 2 trial, we evaluated the efficacy and safety of induction with a 4-drug combination of daratumumab (Dara), lenalidomide (R), ixazomib (I), and dexamethasone (d) (Dara-RId) in transplant ineligible or deferred patients (pts), followed by maintenance with Dara RI versus R for up to 2 years. We hypothesized that this quadruplet would improve tolerability with less peripheral neuropathy in this older population. Here, we present the results of the induction phase **Methods:** Transplant-ineligible or deferred pts with NDMM were eligible. This was a multicenter trial sponsored by the Alliance Foundation Trials, LLC, AFT-41 (NCT04009109). Each cycle was 28 days. All pts received 12 cycles with daratumumab 1800 mg s.c. on the conventional schedule, lenalidomide 15 mg p.o. on days 1–21, ixazomib 4 mg p.o. on days 1, 8, 15, and dexamethasone weekly. After 12 cycles, pts received maintenance based on prior randomization to Dara-RI or R for up to 2 years. In maintenance, R was reduced to 10 mg and I was reduced to 3 mg. Randomization occurred before starting induction. Stratification was based on presence of high-risk features: ISS stage III or high-risk FISH cytogenetics (del 17, t (14;16), t (14;20), t (4;14), del (1p), or gain (1q)). The primary endpoint was progression-free survival (PFS). **Results:** We enrolled 79 pts across 7 sites from October 2020 until December 2023. Accrual was affected by the COVID19 pandemic, leading to early closure to accrual in December 2023. Median age was 74 years (range 63–86); ≥75 years of age (45.6%); female (59.5%); white (83.5%), African American (7.6%), Asian (1.3%), and Hispanic ethnicity (6.3%). Additional baseline characteristics included ISS staging I (41.8%), II (35.4%), and III (22.8%) with high-risk features in 37% by ISS stage III and/or high-risk FISH. The 12-month PFS was 92% (95% CI 86.1–98.4%). The ORR during induction was 92.4% (PR 22.8%; VGPR 46.8%; CR 15.2%; sCR 7.6%). Grade ≥3 adverse events included neutropenia (16.5%), infections (11.4%), anemia (10.1%), thrombocytopenia (8.9%), and syncope (7.6%). There was no grade ≥3 neuropathy (grade 1, 15%; grade 2, 14%). There was no treatment-related mortality reported; 61 pts went on to maintenance therapy and 7 pts discontinued treatment for adverse events during induction. **Conclusions:** Dara-RId offers a regimen that has the efficacy of a 4 drug combination with the convenience of oral ixazomib and minimizes the risk of peripheral neuropathy for older, transplant ineligible NDMM. There is ongoing follow up to determine the benefit of maintenance with dara RI v. R alone. Support: AFT, Celgene, Janssen, Takeda.

OA-62

Dynamic Prediction of Progression Based on Minimal Residual Disease (MRD) in Patients with Newly Diagnosed Transplant Eligible Multiple Myeloma

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Introduction: Flow cytometry and next-generation sequencing (NGS) have enabled sensitive monitoring of minimal residual disease (MRD) in multiple myeloma (MM). Recent studies have shown a strong association between landmark and sustained MRD negativity with improved progression-free survival (PFS). However, the predictive value of long-term MRD dynamics, including conversion from MRD negativity to MRD positivity, is not well explored. In the current study, we addressed whether and to what extent MRD conversion from MRD negativity to MRD positivity using NGS with a sensitivity of 10^{-5} would predict for clinical progression in newly

diagnosed MM (NDMM). **Methods:** This study used data of the CASSIOPEIA IFM 2015-01/HOVON131 trial, which enrolled 1085 transplant-eligible NDMM patients aged 18–65 years, who were randomized for induction and consolidation with or without daratumumab in combination with VTd (D-VTd, n = 543; VTd, n = 542), followed by a second randomization between daratumumab maintenance or observation. MRD by NGS was assessed at multiple timepoints after induction and consolidation, and yearly during maintenance and long-term follow up. Longitudinal MRD measurements (NGS 10^{-5}) were analyzed using a joint model by combining a negative binomial mixed model for the longitudinal MRD data and a Cox proportional hazards model for time-to-progression, calculated from the first MRD negative measurement. International Staging System (ISS) score, cytogenetic risk, treatment with or without daratumumab, and time to first MRD negative sample were included as covariates in the model. **Results:** 583 (54%) NDMM patients achieved MRD negativity (by NGS at 10-5, regardless of response) at any phase of the trial and were included in the current analysis. Patients had a median number of 4 (range 1–9) longitudinal MRD measurements. Median follow-up from first randomization was 79.7 ([IQR] 75.1–85.5) months. MRD increase measured with NGS was associated with an increased risk of progression (hazard ratio [HR] log-scale MRD 1.53; 95% CI [1.42–1.70], $p < 0.001$). The joint model including MRD dynamics for prediction of clinical progression showed high discrimination (C-index 0.87). The model further enabled an individualized prediction, by dynamically updating the risk of progression after each MRD measurement. The median time from MRD conversion to clinical progression was 17.7 months (95% CI 13.4–24.0). **Conclusions:** Dynamic assessment of MRD conversion from negative to positive measured with NGS (sensitivity of 10-5) is a strong predictor for clinical progression in MM patients who have achieved MRD negativity upon treatment. Integration of sequential MRD measurements with other predictive factors yielded a robust prediction model. These results show the potential of continued MRD monitoring for individual-patient risk prediction in clinical practice and MRD-guided decision making.

OA-63

Efficacy and Safety of Iberdomide, Daratumumab, and Dexamethasone, in Transplant-Ineligible Newly Diagnosed Multiple Myeloma Patients: Initial Analysis of the GEM-IBERDARAX trial

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Introduction: In elderly transplant-ineligible newly diagnosed multiple myeloma (TIE NDMM) patients, daratumumab, lenalidomide, and dexamethasone (DRd) is a standard of care. Iberdomide, an oral novel CELMoD, has shown promising efficacy. The Spanish Myeloma Group (GEM) planned a multicenter phase II clinical trial to evaluate Iberdomide plus dexamethasone (Iberdex) alone (cohort 1-previously reported), or in combination with daratumumab (cohort 2) in TIE NDMM patients. The study aimed to include ≥30% of frail patients. This abstract focuses on the cohort 2. **Methods:** Cohort 2 (Iberdaradex) included TIE NDMM patients treated with iberdomide (1.6 mg orally on days 1–21, q4w; reduced to 1 mg after protocol amendment), weekly dexamehasone (40 mg or 20 mg if ≥75 years), and daratumumab (1800 mg, per standard schedule), until progression, toxicity, or death. An interim analysis was planned after all patients completed 6 cycles. Primary endpoint: overall response rate (ORR), and complete response (CR). Secondary endpoints: safety, minimal residual disease (MRD) by next-generation flow (sensitivity ≥10^{-5}), progression-free (PFS) and overall survival (OS). Frailty was assessed using the IFM frailty score. **Results:** 77 patients were enrolled in the cohort 2. Median age was 77 (67–88) and 51.9% were female. ISS III 28.6%. 23 patients (31.1%) were fit, and 51 (68.9%) frail, of whom 30 (58.8%) were ultra frail.

After 6 cycles, in the efficacy-evaluable population (n = 73), 91.8% of patients responded, 20.5% achieved CR or better and 75.3% VGPR or better. MRD negativity was observed in 20 patients (27.3%). Overall, and after a median follow-up of 11.1 months (3.5–29.2), best ORR was 93.1%, CR or better was 34.2% and VGPR or better was 83.5%. No response differences based on frailty.

Safety analysis included the first 6 cycles. Iberdomide was started at 1.6 mg in 55 patients (71.4%), at 1.3 mg in 1 patient, and at 1 mg in 21 patients (27.2%). Most frequent AEs were neutropenia (any grade: 74.0%, and G3–4: 67.5%, only 5.2% febrile neutropenia) and

infections (48.1% and G3–4: 16.9%), mainly respiratory (39%, G3–4: 9.1%, pneumonia 5.2%). Skin rash occurred in 23.4% (G3–4 in 2 patients) and fatigue in 16.9% (G3–4 in 3).

At data cut-off, 3 patients had progressed at 4.7, 8.9 and 13.7 months, 6-month PFS: 92.2% and 12-m PFS: 80.8%. Five deaths occurred within the first 6 months: 2 from pneumonia, 1 biliary sepsis, 1 sudden death and 1 status epilepticus- all ultra frail, and all but one had started at 1.6 mg iberdomide. Six-m OS: 93.5% and 12-m OS: 81.1%. **Conclusions:** This initial analysis demonstrates that Iberdaradex is effective in TIE NDMM patients, and it is remarkable that most of this population was frail or ultra frail. The VGPR and CR or better rates of 83.5% and 34.2% are encouraging. The safety profile after 6 cycles was acceptable and manageable in this particularly frail population.

OA-64

Evidence for Pre-Existing Myeloma Cells with a Gene Expression Pattern Associated with Resistance to BCMA CAR T Cells

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Introduction: Targeting BCMA has shown promise in multiple myeloma (MM), but the durability of responses remains limited. To identify mechanisms of resistance to BCMA CAR T cells, we performed Spatiotemporal Genomic Analysis (SaGA) on myeloma cells engaged by CAR T cells but not killed in culture, followed by RNAseq. **Methods:** We introduced Dendra2 into KMS12PE, KMS18, KMS26, KMS27, RPMI8226 and cultured them with BCMA- or CD19-CAR T cells (1:1) for up to 20 h. Cells that were engaged for 16 hours and alive, were photoconverted and sorted for RNAseq. Differentially expressed gene gene sets from these data as well as from differentially expressed genes on day 28 post CAR T infusion (Dhodapkar, BCD, 2022) were then used to find pre-existing cells. **Results:** Engagement times leading to cell death in the 5 cell lines ranged from 5.48–9.42 h, but a proportion of cells survived (24.7% on average, range 3.8–42.9%). We repeated the experiment with CD19 CAR T cells in KMS18 and KMS12PE and the total time of engagement of live cells was reduced from 12.49 and 14.63 h to 5.39 and 2.74 h respectively. Importantly with BCMA CAR T the average and total time of engagement was nearly identical for all cells, indicating stable engagement. In contrast for CD19 CAR T the average time of engagement was less than 30 min. To explore the role of resistance in engagement time, KMS18 cells lacking CD95 and overexpressing Serpin B9 were tested and showed increased viability (28.8% to 88.3%) and longer engagement (53.3% to 83.0% engaged for 16 h). RNAseq of photoconverted cells from KMS12PE and KMS26 revealed 1101 commonly upregulated genes (padj<0.01, FC >2), and top gene ontology hits included "integrin signaling" and "inflammation by chemokine and cytokine signaling." The latter was related to upregulation of IFNg-responsive genes (e.g., CXCL10, GBP4, IL6). Down-regulated genes were associated with cell death (e.g., TNFRSF10B, PMAIP1, BBC3) and unfolded protein response (e.g., ATF4, ERN1, DDIT3). This is consistent with reports of residual cells post-BCMA CAR T (Dhodapkar, BCD, 2022) and in vitro selection of resistance to BCMA T cell engagers (Lee, ASH, 2024). In these studies, the selection time was 4 weeks, in this present study it was 16 h, suggesting selection of pre-existing cells. To determine if similar cells existed in patients pre-CAR T infusion, we determined the top 100 down-regulated genes 28 days post-CAR T and if there were cells at day 0 where gene expression correlated (>0.8). We found that a subset of day 0 cells in each patient had a day 28-like expression pattern. We performed a similar analysis using the top 100 down-regulated genes from the resistant KMS12PE (correlation >0.85) and the findings reflected the day 28 signature. **Conclusions:** These data suggest that MM cells resistant to BCMA-targeted therapies are pre-existing in patients. These cells can be detected by single cell analysis and could be used to inform treatment decisions.

OA-65

Farorable Outcome of Relapsed/Refractory Multiple Myeloma Treated with Idecabtagene Vicleucel (Ide-cel) Chimeric Antigen Receptor (CAR) T-Cell Therapy; IFM Experience from the Descar-T Registry

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Introduction: Ide-cel was first available in France since 04/2021 through the Early Access Program for treatment of patients (pts) with relapsed/refractory multiple myeloma (RRMM) having received at least 3 therapies including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody and then via commercial access from 11/2024. Here we present an update of characteristics and outcomes of pts enrolled in this program. **Methods:** All consecutive pts with RRMM registered in the DESCAR-T database treated with Ide-cel from 04/2021 to 02/2025 were enrolled. Main objective was to analyze efficacy (response rates, PFS and OS, according to two periods: cohort A (04/2021 to 04/2023, n = 175) with limited open center (n = 11) and cohort B (05/2023 to 02/2025, n = 596) with unlimited access. Secondary objective was safety including CRS, ICAN, cytopenia, infection, and SPM. **Results:** 915 pts were included of whom 115 (13%) were not infused. Median age of the 771 infused pts (58% male) was 66 years (range: 29–85) and was superior in cohort B (66.9 y) as compared to cohort A (61.7 y). Median Nb of prior lines of therapies was 3 (range: 0–13). More pts had received <2 lines in cohort B (122/596 [20%] vs 5/175 [3%], p < 0.0001). Revised International Staging System (R-ISS) stage 3 was noted in 21% of pts, 37% had high risk cytogenetic abnormalities defined by del(17p) or t(4;14), and high tumor burden (>30% BMPCs) was present in 53%, in both cohorts. Triple- (73%) and penta-refractory pts (22%) were lower in cohort B (69% vs. 83%, p < 0.0001 and 19% vs. 31%, p = 0.01, respectively). Extramedullary disease (EMD) was observed 10% of pts 8% in cohort B vs. 16% in cohort A). 162 pts (21%) did not meet at least one of the KarMMa inclusion criteria. 630 pts (82%) had bridging therapy of which 188 (34%) responded. Median vein-to-vein time was 56 days (range: 39–357), (61 d in cohort A vs 55 d in B, p < 0.0001). In both cohorts, best ORR at M3 post Ide-cel was 89% (n = 638), including CR in 42%. 264 pts (34%) progressed after Ide-cel and 139 pts (18%) died, mostly of disease progression (73%). With a median follow-up of 11.8 m, median PFS was 14.8 m (95% CI, 12.6–16.8), similar in both cohorts (HR: 0.85, p = 0.19). Median OS was 38.9 m (95% CI, 34.2 – NR). EMD, ISS, prior bispecific and penta-refractoriness were negative factors for PFS and OS. CRS occurred in 677 (88%) pts (3% gr ≥3). ICAN occurred in 81 (11%) pts (2% with gr ≥3). Persistent grade ≥3 toxicities at M1 were noted in 28% to 49% of pts. Infections in the first 6 m after Ide-cel occurred in 187 (24%) pts (grade ≥3: 33 [18%]). 24 pts developed SPM. **Conclusions:** This study confirms safety and efficacy of Ide-cel in pts with RRMM in real- world settings across the 4-year period. Response rates, PFS and safety compares favorably to those reported in the registration trial and the real-world studies in the US. During both periods, selection of less advanced pts leads to a prolonged PFS and OS, never reported to date outside of clinical trial.

OA-66

Maintenance Therapy with Belantamab, Pomalidomide and Dexamethasone in High-risk Myeloma Patients: A Phase 2 Study with a Safety Run-in - Interim Analysis

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Introduction: Disease control among high-risk myeloma patients with combination maintenance strategies have resulted in improved outcomes. We have evaluated the safety and efficacy of BCMA ADC (belantamab) and IMiD (pomalidomide) in combination with dexamethasone in high-risk myeloma (NCT05208307). **Methods:** Newly diagnosed high-risk myeloma pts that have achieved ≥PR post-ASCT were included. High-risk myeloma was defined by the presence of t(4;14) in 31.6%, t(14;16) in 10.5%, del17p in 57.9% pts by FISH or CTG or presence of ≥20% circulating cells (pPCL) in 21.1%. Double-hit myeloma (as defined by presence of ≥2 high-risk cytogenetic abnormalities including gain of 1q was seen in 73.7% of pts. Each cycle is 28 days. Belantamab 1.9 mg/m^2 intravenously (IV) was given every 56 days and pomalidomide 4 mg PO on days 1 to 21 and dexamethasone 40 mg PO weekly. After the safety run in the first 6 pts, one DLT occurred and the DSMC recommendation was to continue 1.9 mg/kg of Belantamab administered IV every other cycle. A protocol amendment was made to administer belantamab 1.9 mg/kg every 12 weeks in the MTD group, after the first 2 doses received 8 weeks apart (56 days). In such case the ophthalmological evaluations can happen prior to the belantamab dosing q 12 weeks. **Results:** 12 additional pts were enrolled. Median age was 59 (32–75). 52.6% male and 36.8% black. Median time from diagnosis and from transplant to study entry was 8.0 (range, 3.9–11.0) and 2.4 (range, 1.9–4.6) months, respectively. At study entry, ≥CR and ≥VGPR rates were 31.6% and 52.6%, respectively, which deepened to 68.4% and 15.8% while on study. The median time to best response was 1 months (range, 0.43–13.8). Of the 14 pts with available MRD data, MRD (10^{-5}) and (10^{-6}) were achieved in 78.6% and 64.3%, respectively. After a median follow up of 6 months from study entry, and 15 months from diagnosis, none of the 17 evaluable patients for efficacy had progressed or died. In the MTD group, when patients receive belantamab 1.9 mg/kg every 12 weeks, there were no grade 3 or 4 events occurred. At data cut-off, all 17 pts were still receiving treatment. Most common (≥20%) TEAEs in the safety run in cohort (N = 6) were blurry vision (83.3% [G3/4, 16.67%], pneumonitis/hypoxia ([G3/4, 33.3%]), dizziness (33.3%), diarrhea (33.3%), cough (33.3%) and peripheral neuropathy (33.3%) and a thromboembolic event occurred (G3/4, 16.66%). In the MTD group

evaluable for safety (N = 12) blurry vision (58.33%) and insomnia (33.33%) were the most common TEAEs. No grade 3 or 4 events occurred. **Conclusions:** In pts with high-risk myeloma, BPd maintenance deepened responses, with MRD negativity (10^{-5}) attained in 80% of pts. The extended dosing schedule of belantamab 1.9 mg/kg every 12 weeks is not associated with higher grade toxicities and had proven efficacy in this setting. The current results support the exploration of BPd maintenance in future high-risk studies. The current study will expand to include the new IMS-IMWG high-risk definition.

OA-67

Phase 2 Study of Cevostamab Consolidation Following BCMA CAR T Cell Therapy: Preliminary Safety and Efficacy Data from the "STEM" (Sequential T Cell-Engagement for Myeloma) Trial

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Introduction: BCMA-targeted CAR T cells have unprecedented activity in relapsed/refractory multiple myeloma (RRMM), but most patients (pts) relapse. FcRH5 is a MM antigen with expression independent of BCMA. Cevostamab (cevo) is an FcRH5-targeted, T cell-engaging bispecific antibody with activity in RRMM, including in pts with prior BCMA-directed therapies. We hypothesized that fixed-duration cevo following CAR T cells would be feasible, tolerable, and improve sustained MRD-negative complete response (CR) rates. **Methods:** This is an ongoing single-institution, investigator-initiated study (NCT05801939). RRMM pts who received standard of care CAR T cells (ide-cel or cilta-cel), with stable disease or better, receive cevo starting 10–12 weeks (wks) post-CART at step-up dose of 3.6 mg IV on Cycle 1 Day 1 (C1D1), followed by 132 mg starting C1D8, then q3wks for total of 8 cycles. If pts have MRD-negative CR after C8 (Adaptive Clonoseq, at 10-5 sensitivity), they stop therapy and are observed. If not, they get another 8 cycles, then stop. Primary endpoint is frequency of MRD-negative CR 1 year post-CAR T cells. All patients receive prophylactic IVIG. **Results:** 27 pts (20M and 7F; median age 64; 21 White, 6 Black) enrolled. 74% had high risk cytogenetics, with 41% having ≥2 high risk features; 19% had extramedullary disease. Median number of prior lines was 4 (2–10), with 74% triple-class refractory, 11% prior BCMA therapy, and 11% prior talquetamab. 93% received cilta-cel and 7% ide-cel. Reponses at enrollment were 63% CR/sCR, 15% VGPR, 18% PR, 4% SD; all 25 evaluable for MRD were MRD-negative. As of 6/27/25 data cut-off, no DLTs have been seen, including no ICANS or HLH; CRS was seen in 4 (15%) pts (3 G1, 1 G2) and infusion reactions in 19% (all G1/2). Median number of cycles is 8, and 6 (22%) pts had dose reductions to 90 mg. Most common TEAEs are lymphopenia (74%, G3/4 67%), neutropenia (74%, G3/4 44%), cough (59%, G3/4 0%), rash 44% (G3/4 0%), thrombocytopenia 41% (G3/4 22%), upper respiratory infection 37% (G3/4 0%), and AST increase 33% (G3/4 7%). Infections were seen in 52% (G3/4 in 15%). Immune-related AEs were seen in 4 pts (colitis G1, neuropathy with ataxia G3, ITP G4, autoimmune hepatitis G1) – all resolved. So far, 22 pts are response-evaluable after 8 cycles, with 81% in sCR, 9% VGPR, 5% SD; 21/22 (95%) were MRD-negative at 10^{-5}, and 20/22 (91%) at 10^{-6} (1 pt had PD after C4, counted as MRD+). 3 pts to date have required the 2nd 8 cycles of cevo. 14 pts are evaluable at 1 year post-CAR T cells, with 93% in MRD-negative (at 10^{-5}) sCR, 79% at 10^{-6}. With median follow-up of 12 months (range 3–25) post-CAR T cells, estimated 12-month PFS and OS are both 95%. **Conclusions:** To date, cevostamab consolidation post-CAR T cell infusion appears feasible and well-tolerated in late-line RRMM, with low rates of non-hematologic G3/4 TEAEs, including infections. Preliminary efficacy appears promising, with over 90% showing sustained MRD-negative sCR at 1 year.

OA-68

Safety and Efficacy of Linvoseltamab (LINVO) in Patients (Pts) with High-risk Smoldering Multiple Myeloma (HR-SMM): First Results from the Phase 2 LINKER-SMM1 Trial

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Introduction: LINVO, a BCMA × CD3 bispecific antibody, is approved for triple-class exposed relapsed/refractory multiple myeloma (RRMM) after ≥3 therapies (EU) or ≥4 prior lines of therapy (US).

Early intervention in HR-SMM when the immune system is more functional could significantly delay or prevent progression to active MM. Here we report the preliminary safety and efficacy of LINVO in pts with HR-SMM from the LINKER-SMM1 study (NCT05955508). **Methods:** LINKER-SMM1 is an open-label study of LINVO monotherapy in adults with HR-SMM, defined as SMM diagnosis within 5 yrs of study entry and high-risk features by Mayo 2018 "20-2-20" or PETHEMA criteria. Treatment (tx) began with a 3-week step-up schedule of 1 mg (week [W]1), 4 mg (W2), and 25 mg (W3), followed by LINVO 200 mg in 28-day cycles: weekly for Cycle (C)1, every 2 wks for C2–5, and every 4 wks for C6–24.

Part 1 (P1) was a safety run-in of 6 pts. Primary endpoints were frequency of AEs of special interest, including Grade (Gr) ≥2 CRS and ICANS, and frequency and severity of tx-emergent AEs (TEAEs). In the ongoing Part 2 (P2) expansion, primary endpoints are complete response (CR) rate and MRD negativity at 12 and 24 months (mos). Key secondary endpoints for P1 and P2 include overall response rate (ORR), MRD negativity rate, and duration of response (DOR). **Results:** As of May 28, 2025, 24 pts were enrolled (Mayo criteria, n = 18; PETHEMA criteria, n = 6). Median age was 63 yrs (range 39–79), 29% male, and 92% ECOG PS 0. Median duration of exposure was 16.6 wks (range 1–57). Median duration of follow-up was 12.7 mos (P1) and 3.3 mos (P2). No safety concerns were observed in P1. Overall, 92% of pts experienced ≥1 TEAE, and 38% (n = 9) experienced a Gr ≥3 TEAE (all Gr 3 except neutropenia). Neutropenia was the only Gr ≥3 hematologic toxicity (Gr 3, n = 4; Gr 4, n = 2). Infections occurred in 79% of pts (n = 19) and consisted of mostly low-grade respiratory tract infections ([RTI], n = 6; upper RTI, n = 3). Gr 3 infections were reported in 3 pts: COVID-19, Salmonella gastroenteritis, and Staphylococcus epidermidis bacteremia; the latter 2 were assessed as tx-related and rapidly resolved with IV antibiotics. Ig replacement was given to 95% of pts who received ≥1 cycle of therapy. CRS occurred in 10 pts (42%), and all events were Gr 1 except a single Gr 2 event after the 1 mg step-up dose. Tocilizumab was used in 2 pts. No ICANS events were observed. No pts discontinued tx. After ≥1 cycle of LINVO (n = 19), investigator-assessed ORR per IMWG criteria was 100% (≥VGPR 74%; ≥CR 37%). Among P1 pts with longer follow-up, 100% achieved ≥VGPR (1 VGPR; 5 ≥CR) and 100% achieved MRD negativity at 10^{-6}. All responses were ongoing at the time of data cutoff and showed evidence of deepening over time. **Conclusions:** LINVO in HR-SMM was highly active with 100% ORR, and the safety profile appeared more favorable compared to RRMM. These data support further investigation of LINVO as an early intervention for SMM.

OA-69

The Role of Philanthropy in Accelerating the Understanding and Treatment of Multiple Myeloma

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Introduction: Grants, primarily from government agencies, have long provided the resources for scientific research to advance knowledge and understanding of diseases. Multiple myeloma is no exception. However, philanthropy can also play an important role in accelerating the understanding of a disease and its potential treatments. The Paula and Rodger Riney Foundation (Foundation) was created to advance the understanding of multiple myeloma (MM) and to support research that might lead to a cure. **Methods:** The Foundation began their efforts in late 2019 by soliciting research projects from leading investigators in the field of MM research. As of May 2025, the Foundation has supported research programs in 21 institutions (over 170 unique research projects) totaling over $214 M in grants. To measure the success of the Foundation's effort, an accounting of the following output measures were collected; number of manuscripts or presentations, manuscripts under review or in preparation, additional grants or applications derived from the research, patents and applications, spin offs or new companies formed, doctoral thesis/trainees and clinical/therapeutic/diagnostic drug candidates. Data collection was limited to those institutions with at least one year of financial support (16 of the 21 institutions). In addition, the Foundation has provided the IMS with resources (> $16 M) to manage Translational and Career Development Awards (T&CDA). **Results:** At the time of this abstract 12 of the 16 institutions had provided the requested information. Each recipient of the T&CDA from 2021 to 2024 were contacted and asked the same questions (2025 recipients were not contacted as they recently received their awards). At the time of this abstract 22 of the 75 had responded. Table 1 lists the totals for each of the criteria used to assess the impact of the support provided by the Foundation. In addition,

Table 1 (abstract OA-69)

	Manuscripts or Presentations*	Manuscripts under review/ preparations	Grants/ applications	Patents/ applications	Spin outs/new company formation	Doctoral thesis/ trainee	Clinical/ therapeutic/ diagnostic candidates
Institutions n = 12 of 16	225	17	74	40	6	22	10**
IMS Awards n = 22 of 75	106*	8	2	4	1		1

*Includes many high impact journals like Cancer Cell, Nature Medicine, Nature Cancer, Journal of Clinical Oncology and an few book chapters.
**Hem/onc and MM related therapies.

these investigations have led to the identification of 10 new MM targets and 8 new drugs/delivery approaches. **Conclusions:** It is difficult to determine the direct impact of philanthropy on advancing scientific understanding of a disease. However, the wide range of support to many institutions by the Foundation has led to numerous publications, grants, patents, and new therapies all of which could be an indication of the importance of philanthropy in advancing the understanding and treatment of multiple myeloma.

OA-70

Patient-Reported Outcomes (PROs) and Safety in Patients (Pts) With NDMM Achieving MRD Negativity and ≥CR (MRDneg) in the Phase 3 PERSEUS and CEPHEUS Trials

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Introduction: The Phase 3 PERSEUS and CEPHEUS trials showed daratumumab (Dara) plus bortezomib, lenalidomide, and dexamethasone (DVRd) improved MRDneg rate and PFS in both transplant-eligible (TE; PERSEUS) and -ineligible (TIE)/-deferred (TD; CEPHEUS) pts with NDMM. To understand the impact of achieving MRDneg on health-related quality of life (HRQoL), we assessed PROs and safety in pts from PERSEUS/CEPHEUS who achieved MRDneg vs those who remained MRDpos (or not in CR). **Methods:** Pts were randomized 1:1 to receive Dara + VRd induction/consolidation + DR maintenance vs VRd induction/consolidation + R maintenance (PERSEUS) or to receive DVRd vs VRd (CEPHEUS). MRDneg rate (10^{-5} and ≥CR) was a key secondary (PERSEUS) or primary (CEPHEUS) endpoint. PROs were evaluated at baseline and D1 Cycles [C] 1–8 and every 3rd C (CEPHEUS) or D1 C1–C3, pre-ASCT, C5, C7 and then Q12W (PERSEUS). PROs included concepts from the European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 (EORTC QLQ-C30). TEAE were graded with NCI-CTCAE v.5. **Results:** Median follow-up was 47.5 months (mo) in PERSEUS (median age 60 [range 31–70] y) and 58.7 mo in CEPHEUS (70 [31–80] y); 355/354 and 197/198 pts were assigned to DVRd/VRd, respectively. In PERSEUS, 267 (75.2%, D-VRd) and 168 (47.5%, VRd) pts, and in CEPHEUS 120 (60.9%, D-VRd) and 78 (39.4%, VRd) pts achieved MRDneg. Median treatment duration was longer in pts who achieved MRDneg vs MRDpos pts in PERSEUS (DVRd, 46.0 vs 41.3 mo; VRd, 45.9 vs 30.9 mo) and CEPHEUS (DVRd, 57.5 vs 22.5 mo; VRd, 56.6 vs 21.7 mo).

The TEAE exposure-adjusted incidence rates (EAIR) per 100 pt-mo consistently favored pts who achieved MRDneg vs MRDpos pts in the DVRd arm across analyses in both PERSEUS (any TEAE, 156.82 vs 165.12; grade 3/4 TEAE, 11.89 vs 17.65; serious TEAE, 2.21 vs 3.21; TEAE leading to discontinuation, 0.19 vs 0.35; TEAE with outcome of death, 0.07 vs 0.19) and CEPHEUS (119.64 vs 235.78; 11.34 vs 13.15; 2.99 vs 3.99; 0.10 vs 0.38; 0.25 vs 0.76, respectively). EAIR for grade 3/4 infections/infestations and grade 3/4 neutropenia were lower in pts who achieved MRDneg vs MRDpos pts in PERSEUS (1.03 vs 1.67; 3.06 vs 4.39, respectively) and CEPHEUS (0.98 vs 1.92; 1.51 vs 2.15).

PRO scores were similar for pts who achieved MRDneg vs MRDpos. With DVRd, mean change from BL (SE) in EORTC QLQ-C30 global health status in pts who achieved MRDneg vs MRDpos pts in PERSEUS (maintenance C34) was 7.6 (2.0) vs 3.3 (3.2), and in CEPHEUS (C36) was 8.5 (2.8) vs 4.2 (4.3). Similar safety and PRO trends were seen with VRd in both studies. **Conclusions:** In both TE and TIE/TD pts with NDMM, MRDneg achievement was associated with favorable PROs and exposure-adjusted safety outcomes vs MRDpos pts treated with DVRd or VRd. Pts achieving MRDneg stayed on treatment longer and maintained HRQoL despite this prolonged exposure. These data help reassure physicians that MRDneg pursuit in NDMM pts does not adversely impact safety or HRQoL.

PA-516

A Multi-omics Approach to Understanding Extramedullary Multiple Myeloma

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Introduction: Multiple Myeloma (MM) is usually restricted to the bone marrow (BM). However, in a subset of patients, MM cells form lesions outside of the BM which is known as extramedullary multiple myeloma (EMM). These represent up to 8% of patients at primary diagnosis and up to 40% of patients with relapsed disease. EMM is a poor prognosis factor, with no therapeutic approaches specifically developed for EMM and inferior outcomes for these patients even after receiving new treatment modalities, such as bispecific antibodies and CARTs. Understanding the unique biology

of EMM is critical for the development of novel EMM therapeutics. In this project we aimed to profile the genetic clonal evolution in the development of EMM, identify signatures of transcriptional plasticity in EMM, and understand how EMM cells interact with the tumour microenvironment. **Methods:** We generated matched whole exome sequencing of BM and EMM samples, and matched spatial transcriptomics data, specifically, Nanostring GeoMX gene expression data from BM samples and Visium HD data from EMM samples from a retrospective cohort of 6 EMM patients treated at the Peter MacCallum Cancer Centre in Melbourne, Australia. **Results:** We observed both shared and unique mutations in the EMM samples compared to matched BM samples, suggesting clonal evolution in EMM. There was significant diversity in the microenvironments and the transcriptional composition of EMM disease, with EMM cells within a single sample often showing a diversity of gene expression signatures. MM cells had differential patterns of interactions with cells of the microenvironment, with a subset of patients showing more homogeneous spatial patterns of cell interactions, while others showed a diversity of cellular niches of communication. These features were shared between BM and EMM sites, suggesting that interactions with the microenvironment were tied to the unique biology of each MM patient. There was significant heterogeneity in the expression of BCMA, CD38, FCRL5, SLAMF7, GPRC5D. **Conclusions:** Our study showcases the unique biology of EMM and will enable the identification of EMM-specific evolutionary changes and targets.

PA-517

BCMA CAR-T Therapy with Radiotherapy Bridging and Maintenance Achieves Unprecedented Complete Response in Extramedullary Myeloma

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Introduction: Extramedullary disease (EMD) in relapsed/refractory multiple myeloma (RRMM) presents a significant clinical challenge due to its aggressive nature, rapid progression, and resistance to conventional treatments. Despite promising improvements observed with BCMA-CAR T therapy, outcomes for EMD-MM patients remain suboptimal, characterized by significantly lower overall response rates (ORRs) and shorter median progression-free survival (PFS). **Methods:** To address this critical unmet need, this study retrospectively evaluated the clinical efficacy and safety of a novel tri-modal strategy, which integrates radiotherapy bridging, BCMA CAR-T cell therapy, and post-CAR-T maintenance, specifically designed to overcome EMD resistance. We retrospectively analyzed 10 consecutive R/R EMD-MM patients from three centers who received fully humanized BCMA-CAR T therapy (equecabtagene autoleucel) with bridging radiotherapy (10–30 Gy) and maintenance therapy with IMiDs or Chidamide (CAR-T group). This cohort was compared to 10 retrospecitively propensity-matched patients who received standard of care (SOC) treatments during the same period (SOC group). All patients in both groups had progressed after more than two lines of previous treatments. **Results:** CAR-T group demonstrated 100% ORR at six months, significantly higher than the 10.0%(1/10) ORR observed in the control group ($p < 0.001$). There was 100% CR rate at six months and Kaplan-Meier analysis revealed significantly superior PFS in the CAR-T cohort, with the median PFS not reached, compared to just 3.0 months in the SOC group (HR = 0.03, 95% CI: 0.01–0.15, $p < 0.001$). All CAR-T recipients maintained continuous CR throughout the follow-up period (median 14.5 months, range 6–24 months), whereas 90% of SOC patients progressed within 12 months. The 12-month PFS rate was 100% for the CAR-T group versus 10% for the SOC group ($p < 0.001$ by log-rank test). Median OS was not reached in CAR-T group (0% mortality at median follow-up of 14 months) versus 5.5 months (IQR: 3.0–12 months; 90% mortality within 12 months). **Conclusions:** This retrospective analysis of fully humanized BCMA-CAR T therapy in high-risk RRMM patients with EMD confirms profound efficacy, including extramedullary disease clearance and sustained remissions. Despite predictable and manageable toxicities (e.g., mild CRS, hematologic events), patients prognosis markedly improved. Future research will be needed to prioritize optimized bridging/maintenance strategies—including drug sequencing, dosing, and response-adapted regimens to maximize durable efficacy while minimizing risks through personalization.

PA-518

Case Report: BCMA-targeting CAR T-cell Therapy Induces Complete and Durable Remission in Relapsed Extramedullary Plasmablastic Multiple Myeloma

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Introduction: Plasmablastic multiple myeloma (PBM) is an aggressive multiple myeloma (MM) form, identied by a high risk of

recurrence and poor prognosis, with limited effective treatment options. **Methods:** Present study reports a case initially diagnosed with IgG-kappa MM with double-hit genetics. Following induction chemotherapy with bortezomib, doxorubicin and dexamethasone (VAD), and subsequent consolidation therapy with ixazomib, lenalidomide, and dexamethasone, the disease progressed, manifesting as a plasmoblastic tumor in the right pelvic cavity. After two cycles of carfezomib, daratumumab, cyclophosphamide, cisplatin, etoposide and dexamethasone (KD-DECP), the patient achieved partial response. She declined autologous stem cell transplantation (ASCT) and instead received radiotherapy as bridging therapy, followed by B-cell maturation antigen (BCMA)-targeting chimeric antigen receptor (CAR) T-cell therapy with pomalidomide as maintenance therapy. **Results:** She achieved complete response (CR) at 3 months and has remained disease-free for over 18 months based on the latest follow-up. Although grade 2 cytokine release syndrome (CRS) and other adverse events were observed, they were manageable. **Conclusions:** BCMA CAR-T cell accompanied with bridging radiotherapy and pomalidomide as maintenance therapy provided a promising therapy treatment for PBM, which is more aggressive and with shorter survival. Further studies are demanded to assess the effciency and long-term bene ts for this challenging subtype.

PA-519

Daratumumab-based Salvage Treatment for Multiple Myeloma: Experience from a Peruvian Institution

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Introduction: Daratumumab is a human IgGκ monoclonal antibody that targets CD38 and induces direct and indirect antimyeloma activity. Castor, Pollux and Apollo clinical trials have demonstrated efficacy in patients with relapsed/refractory myeloma patients. The aim of the study was to evaluate the efficacy and the survival of the daratumumab-based treatment in our institution. **Methods:** This is a retrospective study where the information was abstracted from electronic medical records (EMR) for relapsed/refractory multiple myeloma patients >18 years treated at AUNA from January 2017 to July 2025. The inclusion of the patients was regardless of the eligibility for stem cell transplant. Patients with amyloidosis were excluded. The survival rates were analyzed with Kaplan Meier method and the difference was computed by the log-rank test. Stata program was used for calculation. **Results:** A total of 49 patients were included, mostly were male (59%). The median age was 63 years (range 45–82). The clinical stage was reported as I, II and III in 37%, 28% and 28% of cases, respectively. Ig G, IgA and light chain myeloma were reported in 47%, 29% and 24%, respectively. 69% had kappa light chains. All patients received daratumumab only or in combination. 81% and 14% received one and two lines of previous therapy. 14% underwent autologous transplant before the use of daratumumab. 96% and 88% were exposed to proteosome inhibitors and immunomodulators as part of front-line therapies. 41% and 71% were refractory to proteosome inhibitors and immunomodulators. 67% were refractory to the last therapy. Daratumumab-based regimen was used as a bridge for transplant in 16% of cases. The most common combination was daratumumab-pomalidomide-dexamethasone with 31%, followed by daratumumab-lenalidomide-dexamethasone and daratumumab-bortezomib-dexamethasone in 29% and 20% respectively. Daratumumab monotherapy was used in 14%. The overall response rate was 79% (55% complete response, 14% very good partial response, 10% partial response). At a median follow-up of 48 months, the median progression-free survival (PFS) was 16months (IQR 7–45 m), the 12-month PFS was 58.5% (95% CI, 42.9%–71.2%). The median overall survival (OS) was 74 months (IQR 48–102), the 5 y-OS was 66.6% (95% CI, 49.2–79.2). No differences were found in terms of progression-free survival or overall survival when these were evaluated according to regimen type. **Conclusions:** The daratumumab-based regimen was highly effective in terms of overall response rate similar to international trials as Castor trial although slightly higher in term of complete response rate even compared to Pollux trial. The progression-free survival was similar to Castor trial but lower than Pollux trial. However, the PFS was better than Apollo trial. The overall survival rate was higher than the Pollux, Castor and Apollo trials.

PA-520

Efficacy and Safety of Low-frequency Daratumumab in Systemic Light-chain Amyloidosis

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Introduction: In recent years, daratumumab has been widely applied in the treatment of systemic light-chain (AL) amyloidosis, significantly improving the prognosis of patients. As the number of CD38+ plasma cells and tumor burden in patients with AL amyloidosis is significantly lower compared to those in patients with multiple myeloma, it is crucial to determine the appropriate dose and frequency tailored for these patients. Therefore, in the present prospective, multicenter clinical trial (ChiCTR2100049253), we evaluated the efficacy and safety of low-frequency daratumumab in AL amyloidosis. **Methods:** This study enrolled 48 patients with AL amyloidosis who received low-frequency daratumumab in multiple

hospitals from July 2021 to May 2024. Among them, 38 were newly diagnosed patients and 10 were relapsed and refractory patients.
The dosage frequency of daratumumab was once every 2 weeks for weeks 1–8 and once every 4 weeks for weeks 9–24, with a treatment cycle of 4 weeks. After week 25, daratumumab monotherapy was maintained every 8 weeks for at most 2 years. **Results:** Among the 48 patients, 60.4% had kidney involvement, 81.3% had heart involvement, and 22 (45.8%) had Mayo 2004 stage III AL amyloidosis. The percentage of patients with hematologic response ≥ very good partial response (VGPR) at 3 months was 72.1%, including 37.2% complete response (CR) and 34.9% VGPR, with an overall response rate (ORR) of 86.0%. The percentage of hematologic response ≥VGPR at 6 months was 82.1%, including 56.4% CR and 25.6% VGPR, with an ORR of 87.2%. The best hematologic ORR was 93.8%, with 56.3% (27/48) of patients achieving CR. The median time to first hematologic response was 15 days. The percentage of patients who had a cardiac response and a renal response at 6 months was 53.8% and 47.1%, respectively, and the best cardiac and renal response rates were 64.1% and 73.9%, respectively. With a median follow-up of 26.0 months (range, 1.6–39.4 months), the median overall survival (OS) and progression-free survival (PFS) were not reached in either newly diagnosed patients or relapsed and refractory patients. The 2-year OS and PFS rates of all patients were 89.6% and 83.3%, respectively. Considering the safety endpoints, 83.3% of patients experienced at least one treatment-related adverse event (AE). The most common AEs in this group were infection (23/48, 47.9%), fatigue (22/48, 45.8%), and fever (18/48, 37.5%). Constipation occurred in 12 patients (25.0%), infusion reactions in 9 patients (18.8%), and peripheral neuropathy in 8 patients (16.7%). **Conclusions:** Low-frequency daratumumab regimen is an effective and safe treatment strategy for AL amyloidosis.

PA-521

Evolution of Age and Causes of Death in Patients with Multiple Myeloma in the Era of Novel Agents

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Introduction: Survival in multiple myeloma (MM) has improved markedly in recent years thanks to therapeutic advances. Our group previously reported an increase in overall survival (OS) among 420 patients diagnosed between 2000 and 2022, from 50.7 months to >100 months in the most recent 8-year interval. As patients live longer, deaths from causes other than MM are becoming more frequent and must be recognised and, where possible, prevented by treating clinicians. **Objective:** To analyse temporal changes in age at death and causes of death in MM during the era of novel agents. **Methods:** We performed a retrospective, observational study that included all deaths recorded between January 2009 and April 2025 among 464 MM patients treated at our centre. Two independent reviewers examined medical records and classified each death into four categories—MM progression, treatment-related toxicity, MM-unrelated, or unknown while also recording the involved organ system. Deaths were analysed in two 8.5-year periods (Jan 2009–Jun 2017 and Jul 2017–Apr 2025). The study was approved by the local ethics committee. **Results:** Median age at death increased from 71 years (range 41–91) in the first period to 75 years (45–97) in the second ($p = 0.001$), with no change in age at diagnosis. Consequently, the gap between age at death and life expectancy in Spain narrowed (life expectancy 83.2 years vs 83.8 years for the two periods, respectively). Causes of death are summarised in Table 1. Although MM progression remained the leading cause, its proportion fell from 70.1% to 58.5% of deaths with a known cause. Conversely, MM-unrelated deaths rose from 27.6% to 33%. Overall, infections accounted for 26.9% of organ-specific deaths, followed by cardiovascular events (11.5%), the latter showing a progressive increase over time. Treatment-related mortality remained ≤9% throughout the study period. **Conclusions:** Recent therapeutic advances appear to have delayed death in MM, bringing patients' lifespan closer to that of the general population. Over the last years, the mortality profile has shifted: while disease progression is still pivotal, infections and cardiovascular events constitute a growing—and often preventable—share of deaths. These findings underscore the importance of truly comprehensive patient care—including, but not limited to, infection prevention and cardiovascular risk management—to fully realise the potential of modern therapies.

PA-522

Glycosylation Single-Cell Transcriptomic Profiling Decodes Driver Mechanism and Genetic Characteristics of Circulating Plasma Cells in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a hematologic malignancy involving clonal plasma cells in the bone marrow (BM). Circulating plasma cells (CPCs) in peripheral blood (PB) are detectable in newly diagnosed MM (NDMM) patients and serve as a prognostic marker. However, the biological mechanisms behind CPC formation remain unclear. This study explored CPC heterogeneity, genetic features, and migration mechanisms. **Methods:** We comprehensively analyzed transcriptomes and glycoproteomics in paired BM and PB samples from 4 NDMM patients using glycosylation single-cell RNA sequencing (scRNA-seq). Subsequently, we included paired samples from an additional 10 NDMM patients for further analysis by CyTOF. **Results:** Single cell

RNA-seq revealed distinct transcriptomic and glycan profiles in CPCs versus BM plasma cells (BMPCs). CPCs overexpressed genes linked to migration (EMP3, AHNAK), adhesion (TYROBP, CD44), angiogenesis (LGALS1), and osteoclastogenesis (ANXA2), while BMPCs upregulated MPO. CPCs showed lower therapeutic target (BCMA, FcRH5) but higher drug-resistance gene expression. Glycosylation was more abundant in BMPCs.

We categorized BMPCs and CPCs into 14 distinct cell clusters (C1-C14). Only the C12 subcluster was present in BM and PB with a relatively higher glycosylation burden. RNA velocity analysis revealed C12 exhibited a strong directional flow toward other subclusters. Survival analysis based on the MMRF CoMMpass dataset (n = 858) showed that patients with high C12 had an inferior OS compared to low C12 ($p < 0.0001$). These findings indicate that C12 is the CPC-initiating cell cluster, essential for CPC production and a prognostic factor for survival. Next, we identified a total of 11 gene modules by hotspot analysis. We found that module 9, which highly expressed 21 genes (including PTTG1, CDC20, STMN1, RRM2, and HMGB1), was shared by both BMPCs and CPCs. KEGG enrichment analysis showed genes in module 9 were enriched for the cell cycle. Differentially expressed gene analysis between C12 in BM and PB showed that SPP1 was upregulated in medullary CPC-initiating cells. The high expression of module 9 gene set in BM is a prerequisite for the production of CPCs, and on this basis, upregulation of SPP1 is the key to PB migration of MM cells. Furthermore, CyTOF analysis substantiated the presence of a subpopulation in CPC-initiating cells, which exhibited a characteristic MM stem cell-like phenotype of CD19+CD27-CD138-.

Mean Spearman correlation analysis revealed MM cells positively correlated with T/NK cells ($R = 0.87$, $p < 0.001$). Proliferating T cells exhibited metabolic activation and communicated with CPC-initiating cells via SPP1 signaling. **Conclusions:** In this study, we employed multi-omics techniques to precisely analyze the heterogeneity of CPCs from multiple perspectives of the transcriptome and proteome. Our results demonstrated that the circulation of MM was driven by specific CPC-initiating cells with unique genetic profiles and interaction with immune microenvironment cells.

PA-523

HDAC and CDK Inhibitor Combinations Synergize in Limiting Myeloma

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Introduction: A recent high-throughput screen in multiple myeloma (MM) cell lines revealed ~40 potentially synergistic combinations. Secondary screening to down-regulate MYC and upregulate the RB/p16 pathway identified three synergistic combinations effective in both proteasome inhibitor-sensitive and resistant cell lines. HDAC/CDK inhibition was the most effective combination. **Methods:** Human MM cell lines treated with dinaciclib (CDK inhibitor), entinostat (HDAC inhibitor), or the combination, were assessed for viability (MTS assay), apoptosis (Annexin V/PI staining), protein expression (Western blotting), and proliferation (Incucyte). Primary $CD138^+$ MM cells were isolated from patient bone marrow aspirates and tested ex vivo with single agents and the combination. In vivo efficacy was evaluated in NSG xenografts and Bcl-xL spontaneous tumor models (caliper, bioluminescense). RNA-seq was performed on treated L363 cells, followed by differential expression analysis (GSEA and DAVID). **Results:** Combined CDK/HDAC inhibition with dinaciclib and entinostat in MM cells reduced MYC expression, increased p16, induced apoptosis, and suppressed RNA Pol II phosphorylation more effectively than single agents. Target engagement was confirmed by downregulation of CDK1/2/5 and HDAC1/3 in both parental and proteasome inhibitor–resistant LP1 cells. Viability, proliferation, and synergy analyses revealed that the combination is more effective than either drug alone and was potent in drug-resistant MM models. Combined CDK/HDAC inhibition was well tolerated in NSG and Bcl-xL mice at optimized dosing regimens without significant toxicity. In NSG mice bearing L363 MM xenografts, the combination reduced MYC, increased p16, delayed tumor growth, and significantly improved survival compared to single agents. In the Bcl-xL immunocompetent model, survival improvement was achieved, though combination therapy was not superior to single agents. Combined CDK/HDAC inhibition with dinaciclib and entinostat selectively reduced the viability of $CD138^+$ SMM patient cells more effectively than single agents, while sparing $CD138^-$ non-neoplastic cells. RNA-seq analysis of L363 myeloma cells treated with dinaciclib and/or entinostat revealed potential biomarkers and master regulators of CDKi/HDACi synergy, with downregulation of replication proteins suggesting a mechanism involving replication stress, DNA damage, and apoptosis. To address translational limitations of dinaciclib and entinostat, we tested next-generation agents: the selective oral CDK9 inhibitor KB0742 combined with the HDAC inhibitors quisinostat or zabadinostat, which have improved pharmacokinetics and safety. The synergistic action of these combinations was validated. **Conclusions:** Further investigation into a combined genetic signature will aid in discovering mechanisms of drug synergy and provide biomarkers for a combined response that may translate to the clinic.

PA-524

Iberdomide Maintenance after Autologous Hematopoietic Cell Transplant for Patients who Previously Received Lenalidomide Maintenance

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Introduction: Delaying autologous hematopoietic cell transplantation (aHCT) consolidation and proceeding straight to lenalidomide maintenance has become more common as patients derive deeper remissions from initial therapy for multiple myeloma (MM). Therefore, a maintenance strategy is needed after melphalan and salvage aHCT. Iberdomide (iber) is a next-generation CELMoD with higher potency than lenalidomide, and we aimed to determine its benefit as maintenance. **Methods:** Cohort 2 of this phase II trial (NCT05354557) enrolled patients who previously had lenalidomide maintenance and received a salvage aHCT after progressing on 2–3 prior lines of therapy (LOT) counted by progressions. Iber was given as 1 mg orally on days 1–21 of 28-day cycles for up to 12 cycles, with continuation of treatment if patients had not progressed. **Results:** Cohort 2 enrolled 15 patients (median age 61 years [47–74], 67% female) after a median of 2 prior LOT (2–3). 73% were triple-class refractory and 66% had high-risk cytogenetics. The majority (80%) had deferred aHCT consolidation, while 20% had a second aHCT. Median time from MM diagnosis to salvage aHCT was 42 mo (30–164), and median time from aHCT to starting iber was 3.4 mo (2.8–4.9). Disease status prior to salvage aHCT was 27% untreated progressive disease (PD), 13% stable disease (SD), 33% partial response (PR), and 27% very good PR (VGPR). When starting iber, patients had SD, PR, VGPR, CR with positive measurable residual disease by 10^{-5} flow (MRD+), and CR without measurable residual disease (MRD-) in 13%, 33%, 13%, 33% and 7% of cases, respectively. All patients are alive with a median follow-up of 15.4 months from starting iber, and 30% (n = 4) remain on treatment with iber with sustained responses past the 12-mo mark. Patients not assessed at the 3-mo mark included those who withdrew from the study due to grade 1 rash (n = 1), travel plans (n = 1) and early progression (n = 1). 8 patients discontinued iber due to PD. Median time to progression post iber was 7.4 mo (3–18.6). Median time to best response to iber was 3.5 mo (3.2–7) with 25% (n = 3), 25% (n = 3), 25% (n = 3) and 25% (n = 3) achieving SD, PR, VGPR, and MRD neg CR, respectively. Median PFS from starting iber was 9.3 mo (6.7–NR), median OS was not reached. CTCAE grade 3 toxicities included neutropenia (n = 1), rash (n = 2), and infections (n = 3). No grade 4/5 toxicities occurred. **Conclusions:** Iber maintenance after salvage aHCT in patients with MM who had prior lenalidomide maintenance was overall well tolerated without unexpected or high-grade adverse events. Changes in immune function over time will also be reported. Iber allowed for a prolonged benefit in a high-risk population, as initiation of maintenance around 3 months post salvage aHCT resulted in a median of more than one year before requiring further LOT. These results support further investigation of iber as a maintenance strategy in patients who have progressed on lenalidomide maintenance.

PA-526

Patterns of Use of Free Light Chain Testing in Patients with Multiple Myeloma in Colombia

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Introduction: Serum free light chain (FLC) assay is recommended for diagnosis and monitoring of multiple myeloma (MM). However, the extent to which these recommendations are implemented in clinical practice in Latin American countries, such as Colombia, is not well documented. Real-world data can help assess testing patterns and identify potential gaps in care. This study aimed to describe the use of FLC testing in MM patients in Colombia using a national healthcare claims data. **Methods:** We conducted a retrospective, population-based analysis using SISPRO, Colombia's national health information system, from 2015 to 2024. All individuals aged ≥18 years with at least one medical attention (including consultations, hospitalizations, emergency room visits, and procedures) during the period were included. MM cases were identified using ICD-10 codes. Laboratory tests were identified using CUPS codes, Colombia's standardized procedure classification. We included all prevalent cases of MM and assessed yearly FLC test volumes and proportion of MM patients tested. Trends in the use of total light chain (TLC) test use were analyzed in parallel for comparison. **Results:** Between 2015 and 2024, the yearly number of adult patients attended with a main diagnosis of MM increased from 2,938 to 6,373. The total number of medical attentions for these patients rose from 59,047 in 2015 to 173,707 in 2024. Since 2015, 75,779 κFLC and 63,560 λFLC tests were performed on 47,841 and 37,615 individuals in Colombia, respectively, averaging 1.54 and 1.57 tests per patient per year. When considering all FLC tests, regardless of the associated diagnosis, the number of individuals tested annually increased, from 3 in 2015 to 18,741 in 2024 for κFLC, and from 3 in 2015 to 11,080 in 2024 for λFLC. Among all FLC tests, 6% (κFLC) and 7% (λFLC) were related to an MM diagnosis. The proportion of MM patients attended each year who received at least one FLC test increased during the period, reaching 13.1% for κFLC and 12.3% for λFLC by 2024. Despite the increase in FLC utilization, TLC testing remained in use, increasing from 3,937 total tests in 2015 to 10,141 in 2024. Among all TLC tests performed, 8% were associated with an MM diagnosis. The annual proportion of MM patients receiving at least one TLC test remained relatively stable, ranging from 4.7% to 5.8% during the period. **Conclusions:** Despite guideline recommendations, FLCs remain underutilized in Colombia, whereas TLCs, which are not recommended for MM diagnosis or monitoring, continue to be widely used. This indicates a gap between clinical guidelines and real-world practice, possibly driven by insufficient interdisciplinary coordination. Strengthening collaboration between clinicians and

laboratory teams may improve appropriate utilization and alignment with guidelines' recommendations.

PA-527

Population Pharmacokinetic Model-Based Melphalan Dosing with Siltuximab Interleukin-6 Blockade in Older Multiple Myeloma Patients Undergoing AHCT: Phase II Run-In Results

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Introduction: High-dose melphalan followed by autologous hematopoietic cell transplantation (AHCT) is a standard consolidation strategy in multiple myeloma (MM), but dose-related toxicities limit its tolerability, particularly in older adults. Based on our 2 prior pilot studies, we hypothesized that population pharmacokinetic (pop PK) model-based melphalan dosing coupled with interleukin-6 (IL-6) blockade using siltuximab, would optimize anti-myeloma efficacy while minimizing transplant-related symptom burden. **Methods:** We conducted a single-center phase II 15-patient run-in trial (NCT06679829) to evaluate the feasibility of targeting a goal cumulative melphalan area under the curve (AUC) of 13 ± 1.5 mg*h/L using our pop PK model (Shah et al Clin Pharmacokinet. 2022). Patients aged ≥60 years with newly diagnosed MM undergoing AHCT received 70 mg/m^2 melphalan on day −2, followed by individualized pop PK model-based dosing on day −1 (InsightRX, Inc.). Siltuximab (11 mg/kg IV) was administered on days −7 and +14. Primary endpoints for the run-in included safety and feasibility of achieving the AUC target in ≥10 of 15 patients. Secondary endpoints included MM response rates, minimal residual disease (MRD) by next-generation flow and engraftment kinetics. **Results:** To date, 14 of the 15 patients have been treated (median age 68 [61–73], 50% male, 71% standard-risk cytogenetics). All patients received quadruplet therapy as induction for MM, with a median of 1 prior line of treatment (range 1–2). Pre-AHCT disease status was complete response (CR) without measurable residual disease (MRD-) (n = 1), very good partial response (VGPR) (n = 9), partial response (PR) (n = 3) and stable disease (SD) (n = 1). Median melphalan AUC was 12.9 mg*h/L (range 11.3–14.4), with 13 of 14 (93%) patients achieving the target AUC. Nine patients have had day +100 restaging with 4 achieving a CR (2 MRD-negative) and 3 achieving a VGPR. No relapses or deaths have occurred. Median time to neutrophil engraftment was 12 days (range 9–16). Engraftment syndrome occurred in 2 patients. CTCAE grade 3 toxicities included neutropenic fever (n = 5) and mucositis (n = 3), with no observed grade 4–5 toxicities. **Conclusions:** In this first prospective study of its kind, we demonstrate the safety and feasibility of using individualized pop PK model-based melphalan dosing to achieve a target AUC, along with IL-6 blockade to decrease symptom burden in older adults with MM undergoing AHCT. The upcoming randomized phase II portion of the study will evaluate efficacy and patient-reported outcomes compared to standard BSA-based dosing.

PA-528

Real-World Management of Relapsed/Refractory Multiple Myeloma Following Early Anti-CD38 Exposure

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Introduction: Multiple myeloma (MM) remains an incurable disease despite significant advances in its treatment, with inevitable relapses over time. Patients with relapsed and/or refractory MM who are triple-exposed (to PIs, IMiDs, and anti-CD38 antibodies) have a poor prognosis, with a median progression-free survival (PFS) of 4.1 months and a median overall survival (OS) of 13.3 months, as reported in the LOCOMMOTION and MOMMENT studies conducted in patients with more than four prior lines of therapy. The widespread use of anti-CD38 agents has increased the proportion of patients who become refractory to this therapy in earlier treatment lines, although limited data are available on salvage treatments in this setting. The aim of our study is to evaluate the real-world effectiveness of salvage therapies in MM patients experiencing first or second relapse who were previously exposed to anti-CD38, in order to support clinical decision-making and provide context for the use of emerging therapies such as immunotherapy. **Methods:** This was a retrospective, observational, single-center study that included all patients diagnosed with multiple myeloma who were refractory to anti-CD38 therapy in either the first or second line of treatment. All patients were treated at the University Hospital of Jerez de la Frontera and initiated anti-CD38 therapy between 2019 and 2024. Baseline characteristics, induction and salvage treatment regimens, treatment durations, and responses to each regimen were collected. Statistical analysis was performed using R software. **Results:** Eighteen patients were included, with a median age of 73.5 years. Anti-CD38 therapy was used in the first line in 38.9% and in the second line in 61.1% of cases. All patients were refractory to anti-CD38. In total, 72.2% were triple-exposed, and 50% were triple-refractory. With a median follow-up of 12.35 months (95% CI: 4.53–13.53), the median PFS following anti-CD38 refractoriness was 6.08 months (95% CI: 3.97–7.32), and the median OS was 11.4 months (95% CI: 1.6–33.3). In patients treated in second line, PFS was 6.44 months (95% CI: 3.45–7.32), and in third line 6.08 months (95% CI: 3.32–8.67). Among

salvage therapies, bispecific antibodies—particularly teclistamab—showed the most promising results: all treated patients achieved complete response (CR) and the 6-month PFS was 100%. The KD regimen also demonstrated efficacy, with one CR and a median PFS of 11.5 months (95% CI: 2.73–36.29). Other regimens such as PoCyDex or belantamab mafodotin showed lower effectiveness. **Conclusions:** This real-world study highlights the clinical challenges of managing triple-refractory MM patients in a non-trial setting. Our findings support the role of bispecific antibodies as a promising treatment option and emphasize the importance of real-world evidence to guide clinical decisions in comparable healthcare settings. Additional figures, survival curves, and detailed data will be presented in the final poster.

PA-529

Risk of Infections after Bispecific Antibodies Targeting Anti-B-cell Maturation Antigen (BCMA) in Multiple Myeloma-intravenous Immunoglobulin (IVIG) Significantly Lowers the Risk of Infection

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Introduction: Elranatamab and teclistamab are bispecific antibodies (BsAb) against B-cell maturation antigen (BCMA) and are highly effective in treatment of multiple myeloma (MM). Due to lowered humoral immunity, infections are common with BsAb and Intravenous Immunoglobulin (IVIG) is recommended for infection prophylaxis. Here, we report the incidence of infections, utilization patterns and effect of IVIG use among patients with MM receiving elranatamab and teclistamab using large-scale real-world data. **Methods:** We conducted a retrospective analysis of de-identified electronic health records from Epic Cosmos, which covers more than 1700 hospitals and 40000 clinics in the United States. Adult patients (>18 years old) diagnosed with MM, with >2 doses of elranatamab or teclistamab and with >6 months of data collected in Epic Cosmos were included. Patients were followed from first to last administration of BsAb. International Classification of Disease-Clinical Modification (ICD-CM)-10 codes were used. Infection episodes were considered distinct if consecutive ICD codes indicating infection were more than 56 days apart or if a new ICD code was used. Proportion of patients with each type of toxicity, rate of toxicities and time to first toxicity were quantified. Rate of infections before and after IVIG was compared using paired t-test. **Results:** A total of 1646 MM patients (1491 received teclistamab and 155 received elranatamab) met study eligibility and had a median follow-up of 7.1 months (interquartile range [IQR], 1.8–13.0). Median age at the time of initiation of BsAb was 70 years (IQR, 63–76) and 881 (53.5%) were male. Majority (n = 1402, 86%) lived in urban areas, 1042 (63.3%) identified as white and 808 (49.1%) were anti-CD38 exposed. Median time from diagnosis to BsAb initiation was 4.7 years (IQR, 2.3–7.5). During treatment with BsAb, 493 patients (30%) were documented to have at least 1 infection with an infection rate of 0.06 (standard deviation [SD], 0.27) episode/patient-month and median time to first infection was 2 months (IQR, 0.7–5.1). Bacterial sepsis was the most common type of infection (n = 200, 12.2%), followed by febrile neutropenia (n = 126, 7.7%) and viral pneumonia (n = 89, 5.4%). The risk of infection was higher amongst those who received teclistamab (n = 458, 30.7%) compared to those who received elranatamab (n = 35, 22.6%), p = 0.03. Almost half of patients (n = 826, 50.2%) received IVIG while on BsAb and among these patients, infection rate decreased from 0.09 (SD, 0.27) episode/patient-month prior to IVIG use to 0.03 (SD, 0.15) episode/patient-month after IVIG use ($p < 0.001$). **Conclusions:** In this largest nationwide cohort of MM patients treated with anti-BCMA BsAb, only half of the patients received IVIG and use of IVIG was associated with a 67% decrease in infections. More awareness is needed to expand the use of IVIG to prevent infections in patients receiving BsAbs and prospective studies would be crucial to establish its optimal dosing schedules.

PA-530

Second Primary Tumor in Patients with Multiple Myeloma in Brazil: A Population-Based Study

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Introduction: Multiple myeloma (MM) is a hematological malignancy derived from post-germinal center B cells that have differentiated into plasma cells. These neoplastic plasma cells proliferate clonally within the bone marrow and produce a monoclonal immunoglobulin (M protein) [1–4]. In 2022, approximately 188,000 new cases and 121,000 deaths due to MM were estimated worldwide [5]. Advances in treatment options have significantly increased five-year survival rates, consequently elevating the number of patients at risk of developing second primary tumors (SPTs) [6–9]. The aim is to evaluate the occurrence and characteristics of second primary tumors among patients diagnosed with MM in Brazil. **Methods:** A time-series study was conducted using data from Brazilian Population-Based Cancer Registries (PBCR), coordinated by INCA/MS, including MM cases (ICD-O-3 codes 9731/3 and 9732/3) diagnosed between 1991 and 2021. SPTs were defined as all malignant neoplasms diagnosed on the same date or after the MM diagnosis, excluding non-melanoma skin cancers (basal cell and squamous cell carcinomas). Sociodemographic variables (sex, age, race/skin color, education, occupation, and geographic region) and clinical data (tumor site and diagnosis date) were analyzed. **Results:** Among 12,255 MM cases identified, 2.7% (n = 340) developed an SPT. Most were male (53.2%), aged 60–69 (31.8%) or 70–79 years (30.9%). Regarding race, 49.1% were White and 29.7% Brown. The most common SPTs were prostate (23.5%), breast (15.2%), lower

gastrointestinal tract (colon, rectum, anus; 8.2%), melanoma (7.6%), and extramedullary plasmacytoma (6.1%). Synchronous tumors were more frequent among younger patients: 55% occurred under 59 years old. Median age at diagnosis was 52 years for synchronous and 67–68 years for metachronous cases. Among synchronous tumors, extramedullary plasmacytoma accounted for 36%, followed by non-Hodgkin lymphoma, leukemia, breast cancer, and melanoma (each 9.1%). A decrease in SPT incidence was observed among women aged 40–59 years, from 0.40/100,000 (1991–2000) to 0.15/100,000 (2011–2021). Among men aged 60–69, incidence increased from 0.06/100,000 to 0.50/100,000 in the same periods. Breast (OR = 1.48; 95%CI: 0.67–3.39) and cervical cancers (OR = 1.80; 95%CI: 0.49–8.54) showed a higher chance of SPT among metachronous cases. **Conclusions:** In this national cohort of MM patients, the most frequent SPTs mirrored those of the general population (breast and prostate). However, synchronous tumors were more associated with rare hematologic neoplasms, particularly among younger individuals. Continuous surveillance for SPTs is recommended as part of MM patient care.

PA-531

Single-Cell Sequencing Reveals Transcriptional and Metabolic Divergence of Bone-Involved Multiple Myeloma

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Introduction: Multiple myeloma (MM) presents with heterogeneous clinical symptoms, commonly categorized as CRAB features—hypercalcemia, renal failure, anemia, and bone injuries. Notably, myeloma bone disease (MBD) is observed in up to 80% of newly diagnosed MM (NDMM) patients, highlighting its significant clinical burden. This study aims to systematically dissect the transcriptional, immunological, and metabolic distinctions between MM patients with and without bone involvement. **Methods:** We collected bone marrow specimens, bone marrow aspirates, and peripheral blood mononuclear cells (PBMCs) from 14 MM patients. According to their presenting symptoms at diagnosis, patients were classified into four groups: G1 (n = 4) with anemia, G2 (n = 4) with bone injuries, G3 (n = 2) with renal failure, and G4 (n = 4) presenting with all four CRAB features. Cellular subtypes were identified through clustering, followed by BCR sequencing, pseudotime analysis, inferCNV, and metabolic profiling to assess clonal evolution, immune dynamics, and transcriptional/metabolic heterogeneity across CRAB groups. **Results:** Distinct immune microenvironment alterations were observed across CRAB groups. Notably, bone disease groups (G2 and G4) displayed expanded monocyte populations, reduced T/NK cell proportions. B cell clonal diversity was markedly elevated in G2, with enriched unswitched memory B cells and disrupted differentiation trajectories. G4 showed enrichment of terminally differentiated subsets with upregulation of immunoglobulin-related genes, while G2 exhibited downregulation of bone remodeling pathways. Stage-specific expression of AHNAK, AREG, and BTG1 was observed along with cell differentiation. Plasma cells from G4 exhibited terminal differentiation and aggressive phenotypes, while those from G1 and G2 remained in earlier states. CNV analysis confirmed high genomic instability in malignant plasma cells, particularly in G3 and G4. Metabolically, each group demonstrated unique signatures: G2 showed glycation-related dysregulation linked to bone pathology, G3 featured enhanced TCA and BCAA metabolism. **Conclusions:** Our findings reveal symptom-specific transcriptional, immunological, and metabolic landscapes in MM. Bone injury groups are marked by immune suppression, clonal complexity, and metabolic reprogramming. Further research is needed to validate these findings.

PA-532

Targeting JAM-A to Prevent Multiple Myeloma Progression: Novel Peptide Inhibitors Block Proliferation and Offer a New Therapeutic Strategy for High-Risk Disease

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Introduction: Gain of chromosome 1q is a common high-risk (HR) abnormality in multiple myeloma (MM), linked to poor prognosis and extramedullary disease (EMD). F11R, which encodes Junctional Adhesion Molecule-A (JAM-A), is located on 1q and is frequently overexpressed in MM, especially in patients with adverse cytogenetics. JAM-A overexpression correlates with reduced progression-free and overall survival, and promotes proliferation, survival, motility, and invasion. Through cis-dimerization, JAM-A activates oncogenic signalling that drives early tumour growth. Given the incurable nature of MM, strategies that prevent progression in HR patients are urgently needed. This study aimed to develop second-generation peptide inhibitors that block JAM-A cis-dimerization and disrupt its oncogenic activity. **Methods:** F11R expression was analysed in patients using the CoMMpass dataset to assess correlations with cytogenetic risk and clinical outcome. JAM-A's role in proliferation was validated by siRNA knockdown in KMS18 cells. A computationally designed peptide library targeting the JAM-A cis-dimer interface was developed to improve upon the first-generation inhibitor, optimising binding affinity and stability. Lead peptides were evaluated in vitro using proliferation and β-galactosidase senescence assays. In vivo efficacy was evaluated using the chick chorioallantoic membrane (CAM) model, a rapid and cost-effective screening platform previously developed by our lab (PMID: 35267611). Tumour mass, Ki67 proliferation index, and $CD138^+$ plasma cell burden were assessed by IHC in pre-treated xenografts. **Results:** F11R expression was higher in MM patients with 1q gain

than those without (mean 9.610 vs 7.138, $p < 0.0001$), and progressively increased from healthy donors to relapsed MM (mean 48.4 vs 87.83, $p = 0.0425$). JAM-A expression above the median was linked to shorter progression-free survival (JAM-Alow 1106 days vs JAM-Ahigh 914 days, $p = 0.05$) and overall survival (JAM-Alow 2922 days vs JAM-Ahigh 2356 days, $p = 0.0009$). JAM-A overexpression in MM1.S enhanced proliferation (EV 115% vs JAM-A OE 169%, $p = 0.0152$). Knockdown in KMS18 cells confirmed JAM-A's role in proliferation. From the peptide library, P4 was the most potent, with an IC_{50} of 11.88 µM in KMS18 cells and efficacy in patient-derived $CD138^+$ cells. P4 induced senescence and reduced adhesion to HS5 stromal cells (untreated 34,081 RFU vs P4 24,473 RFU, $p = 0.0024$). JAM-A knockdown abrogated P4's effects (siNeg IC_{50} 14.53 µM vs siJAM-A IC_{50} not reached), confirming specificity. Strikingly, when tested in the CAM model, P4 pre-treatment significantly reduced tumour size and mass ($p < 0.0001$), as well as Ki67 index and $CD138^+$ content. **Conclusions:** This is the first in vivo demonstration of JAM-A inhibition via peptide therapy in MM. JAM-A is a key driver of MM proliferation, and P4 effectively disrupts its signalling in vivo. These findings support further development of P4 as a novel preventative strategy for HRMM, particularly in patients with 1q gain or EMD.

PA-533

Nutritional Status Indices on the Prognosis of Patients with Relapsed and Refractory Multiple Myeloma Treated with CAR-T Cell Immunotherapy

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Introduction: Chimeric antigen receptor (CAR) T-cell therapy shows remarkable efficacy against relapsed/refractory multiple myeloma (R/R MM). Nutritional status is an important factor affecting the prognosis of MM patients. Controlled nutritional status (CONUT) and prognostic nutritional index (PNI) are objective and practical tools for evaluating nutritional status. However, their predictive value for CAR-T therapy efficacy and prognosis in R/R MM remains poorly defined. **Methods:** We conducted a retrospective study of 181 patients with R/R MM who underwent CAR-T cell treatment. Optimal cutoff values were determined using receiver operating characteristic (ROC) curves, with patients stratified by CONUT (cutoff: 6.5) and PNI (cutoff: 42.75) scores. We investigated the effect of CONUT and PNI on CAR-T cell therapy outcomes in patients with R/R MM. **Results:** Before CAR-T therapy, patients with high tumor burden had lower PNI, while those with previous hematopoietic stem cell transplantation (HCT) had higher CONUT and lower PNI. After CAR-T infusion, the objective response rate (ORR) was 95.04% in the low CONUT group versus 88.75% in the high CONUT group; similarly, ORR was 89.16% in the low PNI group versus 94.9% in the high PNI group. Compared to patients with high CONUT or low PNI, those with low CONUT or high PNI showed improved progression-free survival (PFS) and overall survival (OS). No significant differences in cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) were observed between CONUT or PNI subgroups. Additionally, compared with the high CONUT and low PNI group, the low CONUT and high PNI groups demonstrated faster recovery of red blood cells, hemoglobin, platelets, white blood cells, neutrophils, CD4+ T cells, and CD8+ T cells; a lower incidence of prolonged hematologic toxicity (PHT); and higher peak levels of CAR transgene. **Conclusions:** Overall, this study found that CONUT and PNI are significant prognostic predictors for R/R MM patients receiving CAR-T cell therapy, with those in the low CONUT or high PNI group having better long-term prognosis.

NSP-20

Myeloma Patient Outcome Scale (MyPOS): Cross-cultural Adaptation and Evidence of Validity for Brazilian Population

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Introduction: The Myeloma Patient Outcome Scale (MyPOS) instrument was developed to monitor symptoms and improve the quality of life of people with multiple myeloma. This study intend to adapt to Brazilian culture and investigate psychometric properties of MyPOS. **Methods:** Methodological, cross-sectional, multicenter study. Stage 1: cross-cultural adaptation, which consisted of translation, back-translation and content validation of Portuguese version using the Delphi technique. Stage 2: search for evidence of the instrument's psychometric validity and its application to a population sample. Data factorability was assessed using the Kaiser-Meyer-Olkin (KMO) and Bartlett tests. The factor structure of the MyPOS was assessed using Exploratory Factor Analysis (EFA), with factor extraction using the Robust Diagonally Weighted Least Squares (RDWLS) method, a Robust Promin rotation method, and factor retention using parallel analysis with random data permutation. Internal consistency was measured by composite reliability and the stability of the extracted factor was assessed by the H index. To investigate evidence of validity through relationships with external measures, the EQ-5D-3L instrument was used, and to assess the stability of the instrument, the test-retest was performed at an interval of 10 to 14 days. **Results:** Content validity was obtained through the agreement of the expert committee, and the recommended Content Validity Index (≥ 0.9) was achieved in both rounds of analysis. The instrument was administered to 145 participants, predominantly female (57.93%), of mixed race and black (54.48%), with a median age of 68 years and a median time since diagnosis of 29 months. In the

psychometric analysis, EFA suggested the retention of two factors. Factor 1 (Symptoms and Functioning) and Factor 2 (Emotional Response) explained, respectively, 30.61% and 10.42% of data variance. The instrument presented a multidimensional character, good reliability (ω coefficient for the general questionnaire: 0.873), and replicability of the factorial structure (H-Latent >0.80). **Conclusions:** This study obtained evidence of validity and consistency for the Brazilian version of MyPOS, allowing its use in clinical practice and in other clinical trials that address this topic.