Abstracts of the 21st International Myeloma Society Annual Meeting

ORAL PRESENTATIONS

OA-01

Talquetamab (tal) + Daratumumab (dara) + Pomalidomide (pom) in Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM): Results from the Phase 1b TRIMM-2 Study

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Introduction: Tal is the first approved GPRC5DxCD3 bispecific antibody (BsAb) for triple-class exposed RRMM. The immunomodulatory effects of dara+pom may potentiate the efficacy of tal. Initial TRIMM-2 results showed that dara + tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W) had promising efficacy, and a safety profile consistent with the respective monotherapies. We present results from pts who received tal+dara+pom in TRIMM-2. **Methods:** Pts had MM, ≥3 prior lines of therapy (LOT; including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double refractory to a PI and IMiD and had not received anti-CD38 therapy in ≤90 days. Pts received tal 0.4 mg/kg QW or 0.8 mg/kg Q2W + dara 1800 mg + pom 2 mg (starting cycle 2). AEs were graded per CTCAE v5.0; cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Responses were assessed per IMWG criteria. **Results:** As of April 10, 2024, 77 pts had received tal+dara+pom (median follow-up: 17.5 months [mo]). Median prior LOT was 6 over a median of 6.8 years since diagnosis. At baseline, 26.2% had high-risk cytogenetics and 23.4% had extramedullary disease. Most pts were penta-drug exposed (68.8%) and triple-class refractory (77.9%). Prior treatments included anti-CD38 (93.5% [83.1% refractory]; dara (90.9% [80.5%]), IMiD (100% [97.4%]; pom, 83.1% [75.3%]), chimeric antigen receptor-T cell (31.2%), and BsAb (39.0% [37.7%]) therapies. Median time since last exposure was 474 days (d) for dara and 385 d for pom. There were no dose-limiting toxicities. All pts had ≥1 AE (94.8% grade [gr] 3/4), most commonly dysgeusia (79.2%; NA gr 3/4), neutropenia (77.9%; 68.8% gr 3/4), CRS (74.0%; all gr 1/2), dry mouth (64.9%; 2.6% gr 3/4), and fatigue (57.1%; 5.2% gr 3/4). Median onset of CRS was 1 d after tal; median duration was 2 d. ICANS occurred in 3.9% (gr 3/4 1.3%). Infections occurred in 74.0% (29.9% gr 3/4); onset of most gr ≥3 infections occurred within the first 6 months (18/23 events). 5.8% of pts discontinued tal due to AEs. Two pts had gr 5 AEs (sepsis and hemorrhagic transformation stroke). ORR was 81.8%; 53.2% had a complete response or better. Median DOR was 22.1 mo (95% CI, 13.6–27.0). Median time to first response was 1.0 mo (range, 0.9–6.7). Median PFS was 15.5 mo (95% CI, 11.7–24.4). Responses were deep and durable in anti-CD38 refractory and prior T-cell redirection–exposed pts. Preliminary data showed that tal serum concentrations were generally within the same range as tal monotherapy. **Conclusions:** In heavily pretreated pts with RRMM who were mostly dara and pom refractory, tal+dara+pom showed promising depth and durability of response. The safety profile was consistent with the known safety profiles of each respective agent. Results support the versatility of tal as a combination partner and warrant further investigation of tal in combination with dara or pom.

OA-02

Multiplex CRISPR/Cas9 Genome Editing of Cord Blood-derived CAR NK Cells to Improve Their Persistence and Antitumoral Potential Against Multiple Myeloma

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Introduction: CAR NK immunotherapy has emerged as a cost-effective and safer therapeutic alternative in relapse/refractory cancer patients suitable in allogeneic context, constituting an off-the-shelf therapy against different tumors. However, despite their demonstrated antitumoral efficacy against multiple myeloma (MM), CAR NK cell cytotoxic potential may be compromised by their limited in vivo persistence or dominant immunosuppressive signals mediated by soluble factors as well as inhibitory immune checkpoints in the tumor microenvironment (TME), like TGF-β or NKG2A-HLA-E axis. To outperform all these limitations simultaneously, we aimed to develop a next generation cord blood (CB)-derived CAR NK product using CRISPR/Cas9 technology. **Methods:** NK cells were isolated from CB samples and expanded in vitro with irradiated feeder cells, IL-2 and IL-15. Activated CB-NK cells were then transduced with a 41BB-BCMA CAR lentiviral vector and nucleofected with sgRNA-Cas9 complexes. Knock-out (KO) efficiency was measured by Sanger Sequencing and multiparametric flow cytometry (M-FACS). Proliferative potential, immunophenotype and CAR expression was analyzed by M-FACS. Edited CAR CB-NK cell cytotoxic activity was measured in vitro against different MM cell lines and healthy PBMCs by calcein-release assays and primary MM by M-FACS analysis. Chromosomal structure aberrations in edited cells were analyzed at 19 days after nucleofection using Bionano's optical genome mapping Stratys™ System. In vivo CAR NK persistence and efficacy is being evaluated in a U266 ffLuc-GFP NSG-IL15 MM mouse model. **Results:** Simultaneous disruption of KLRC1 (gene that encodes NKG2A) and TGFBR2 genes in CAR CB-NK cells showed KO efficiency of 76.5% (68.3-85.5%) for NKG2A and 71.4% (62.7-76.0%) for TGFβ-RII measured by FACS, being consistent with insertion-deletion events observed by sequencing. Unselected double KO (DKO) CB-CAR NK cells showed increased cytotoxic capacity in vitro against MM cell lines compared to control cells (RPMI-8226 2:1 E:T; 86.2% vs 53.6% specific lysis; p< 0.001), even in the presence of TGF-β. However, DKO gene editing of CAR NK cells lessens their proliferative capacity. To circumvent this limitation PRDM1 was also targeted with 92.8% (84-96%) KO efficiency confirmed by sequencing and western blot analysis. Importantly, triple KO CAR CB-NK cells showed increased proliferative capacity compared to non-edited cells (5.2-fold) and maintained antitumoral potential of DKO cells against MM cell lines and primary MM cell. Furthermore, multi-edited TKO CAR NK cells did not show toxicity against healthy PBMCs nor contain chromosomal translocations. In vivo persistence, efficacy and potential oncogenesis of these effector cells is being tested in a long-term immunodeficient MM mouse model. **Conclusions:** Multiplex genome editing of CAR CB-NK cells using CRISPR/Cas9 technology constitutes a feasible and safe platform to increase their cytotoxic potential overcoming TME-derived therapy resistance in MM.

OA-03

Talquetamab (tal) + Teclistamab (tec) in Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM): Updated Phase 1B Results from RedirecTT-1 With >1 Year of Follow-Up

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Introduction: Tal (anti-GPRC5D) and tec (anti-BCMA) are the first bispecific antibodies approved as monotherapies for triple-class exposed (TCE) RRMM. Tal+tec may improve outcomes by redirecting T cells to 2 validated myeloma antigens. In the phase 1b RedirecTT-1 trial (NCT04586426), all dose levels (DLs), including the recommended phase 2 regimen (RP2R; tal 0.8 mg/kg + tec 3.0 mg/kg every other week [Q2W]), demonstrated promising efficacy and a safety profile consistent with each agent alone in pts with RRMM. We report updated results from RedirecTT-1 with longer median follow-up (mFU). **Methods:** Pts had TCE RRMM with measurable disease per IMWG criteria and were refractory, relapsed, or intolerant to the last line of therapy (LOT). Primary objectives were to evaluate safety and identify phase 2 expansion dosing. Confirmed response was reported in all treated pts with ≥1 postbaseline disease assessment or those ending study participation without postbaseline assessments. Adverse events (AEs) were graded per CTCAE v5.0. Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded per ASTCT criteria. **Results:** As of Mar 15, 2024, 94 pts received tal+tec (44 pts at the RP2R), with a mFU of 20.3 months

(18.2 months at the RP2R). Median age was 64.5 years. Median prior LOT was 4; 86.2% were triple-class refractory and 64.9% were penta-drug exposed. In total, 41.2% (21/51) pts had high-risk cytogenetics and 34 (36.2%) had extramedullary disease (EMD; ≥1 bone-independent lesion of ≥2 cm). Dose-limiting toxicities occurred in 3 pts across all DLs (grade [gr] 3 oral herpes and gr 3 elevated alanine aminotransferase/aspartate aminotransferase; gr 4 thrombocytopenia at the RP2R). The most common AEs were CRS (78.7%; gr 3, 2.1%; no gr 4/5), neutropenia (73.4%; gr 3/4, 68.1%), taste changes (64.9%; gr 3/4, not applicable), and non-rash skin AEs (60.6%; no gr 3/4). Gr 3/4 infections occurred in 63.8% of pts. ICANS occurred in 3.2% of pts (no gr 4/5). In total, 15 (16.0%) pts discontinued either tal or tec due to AEs, of which 7 (7.4%) were drug-related (5 due to infections). In total, 14 (14.9%) pts died due to AEs (11 due to infection), of which 6 (6.4%) were drug related. At the RP2R, responses occurred in 79.5% (61.1% with EMD) of pts and in 77.7% across all DLs. The probability of patients remaining in response at 18 months was 85.9% at the RP2R (81.8% with EMD) and 76.6% across all DLs. PFS at 18 months was 69.8% at the RP2R (52.9% with EMD) and 62.2% across all DLs. **Conclusions:** This is the first dual-targeting bispecific antibody combination in RRMM. Tal+tec had a safety profile that was similar with each agent as monotherapy. Reponses to tal+tec were consistent across DLs, with robust durability of response at the RP2R. Efficacy in pts with EMD closely approximates outcomes in all pts, potentially overcoming the poor prognosis in high-risk populations. These results support phase 2 investigation.

OA-04

A Phase 1 Study of P-BCMA- ALLO1, a Non-viral, Allogeneic BCMA Directed CAR-T in Relapsed/ Refractory Multiple Myeloma (RRMM)

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Introduction: Despite therapeutic advances, multiple myeloma (MM) remains incurable. BCMA targeting immunotherapies, such as bispecific T-cell engagers (TCE) and autologous CAR-T, provide clinical benefit, but relapses are common. TCE require chronic therapy and are complicated by a high rate of infections. Autologous CAR-T require apheresis, are hampered by prolonged manufacturing times, including manufacturing failures, bridging therapy and as a result potential adverse events. Therefore, patient (pt) focused, safe and off the shelf therapies are needed for MM pts. P-BCMA-ALLO1 is an allogeneic BCMA targeting CAR-T manufactured from healthy donor T-cells with non-viral transposon-based integration (piggyBac®) to express a human anti-BCMA VH-based CAR to produce a T stem cell memory-rich product. Cas-CLOVER™ Site-Specific Gene Editing eliminates endogenous T cell receptor expression to prevent graft-vs-host disease (GvHD), as well as the beta-2 microglobulin gene, to reduce MHC class I expression and potential host-vs-graft response. P-BCMA-ALLO1 is available as an "off-the-shelf" CAR-T and is being evaluated in a phase 1 clinical trial (NCT04960579) in RRMM pts. **Methods:** The primary objective is to determine the maximum tolerated dose of P-BCMA-ALLO1. The key secondary objective is to evaluate the anti-myeloma activity. Eligible pts (aged ≥18 y) were diagnosed with MM per IMWG criteria, had measurable disease, and have received prior treatment with a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody. The study is exploring escalating P-BCMA-ALLO1 doses and evaluating deeper lymphodepletion (LD) regimens. These "P" LD arms include: P1 - cyclophosphamide (cy) 500 mg/m^2/day + fludarabine (flu) 30 mg/m^2/day, P1.5 - cy 750 mg/m^2/day + flu 30 mg/m^2/day, and P2 - cy 1000 mg/m^2/day + flu 30 mg/m^2/day, for 3 days. **Results:** A total of 34 pts have been dosed with P-BCMA-ALLO1 in P LD arms and have completed the DLT evaluation period. 17 pts received treatment in arm P1, 7 pts in P1.5, and 10 pts in P2 with a P-BCMA-ALLO1 cell dose of >2 × 10^6 to <6 × 10^6 cells/kg on day 0. The median pt age is 66 years and median prior lines of therapy is 5. The median time from enrollment to study treatment was just 2 days and 100% of the intent to treat (ITT) population received P-BCMA-ALLO1. None of the pts required bridging therapy, highlighting the rapid accessibility of an off-the-shelf product. P-BCMA-ALLO1 was well tolerated with no DLT or GvHD. Most common grade (G) ≥ 3 TEAEs were neutropenia (61%), leukopenia (55%), lymphopenia (45%), thrombocytopenia (39%), anemia (30%) and febrile neutropenia (24%). Ten of the 34 pts (29%) developed CRS (G≤2) and one pt (2.9%) developed G2 ICANS. **Conclusions:** In summary, P-BCMA-ALLO1 is a well-tolerated allogeneic CAR-T that is available "on-demand" and demonstrates low rates of CRS and ICANS. Enrollment is ongoing and updated safety and efficacy data will be presented at the meeting.

OA-05

Assessing the Effect of Previous Antibiotic Usage on Bispecific Monoclonal Antibody Therapy in Multiple Myeloma Patients

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Introduction: Bispecific monoclonal antibodies (BsAbs) offer a promising new treatment option for Multiple Myeloma (MM), yet addressing relapse concerns demands further investigation. Given its crucial role in immunology, the gut microbiota emerges as a key factor influencing the effectiveness of immunotherapy. This study explores the impact of antibiotics, acknowledged as primary regulators of the gut microbiota, on treatment involving BsAbs. **Methods:** This retrospective analysis encompassed 164 MM patients treated with BsAbs across five medical centers. Patients were classified as "antibiotic" if they received non-prophylactic antibiotics 30 days before treatment, while others as "non-antibiotic". For validation, samples were collected from 24 patients before the initiation of priming doses. T cells were characterized in peripheral blood using a FACSCantoII. Gut microbiota was assessed via 16S rRNA gene sequencing with the Ion 16S Metagenomics kit from stool samples. Serum bacterial-derived metabolites were measured via GC-MS. **Results:** 76.8% of the patients enrolled belonged to the non-antibiotic group and 23.2% to the antibiotic group. Antibiotic patients had higher ISS stages; while other baseline characteristics were similar. Response rates (65% vs. 62%, p=0.8) and complete response rates (31% vs. 19%, p=0.14) showed no significant intergroup difference. At a median follow-up of 13.9 months for the non-antibiotic group and 22.3 months for the antibiotic group, the 2-year overall survival (OS) rates were 61% (95% CI 51-73) and 27% (95% CI 14-52), respectively (p=0.002). Age, ECOG, and ISS were additionally incorporated into a multivariable Cox regression model, indicating a non-significant trend towards poorer OS in the "antibiotic" group (HR 1.73 [95% CI 0.96-3.09], p=0.066). The antibiotic group displayed reduced T cell proportions (p=0.04), impacting both CD4 and CD8 populations. Specifically, alterations were observed in T helper subpopulations as Th2 (p=0.02). Through gut microbiota sequencing, we observed a trend towards lower bacterial α-diversity and evenness in patients receiving antibiotics. Interestingly, patients with lower index values had worse PFS (p=0.04 and p=0.03, respectively). The taxonomic comparison revealed significant changes in the composition. Three of the genus with a higher differential abundance in the non-antibiotic group (Eubacterium ventriosum, Roseburia and Limosilactobacillus) exhibit the property of producing the microbiota-derived metabolites short-chain fatty acids (SCFAs). Consistent with this, patients labeled as "antibiotic" exhibited lower circulating concentrations of SCFAs such as acetate, whose concentration revealed a potential prognostic value (p=0.01). **Conclusions:** This study underscores the significant reduction in MM patient survival treated with BsAbs when non-prophylactic antibiotics precede priming doses. Preliminary findings suggest antibiotic-induced microbiota alterations could affect survival outcomes and effector cell functionality.

OA-06

Impact of Clonal Hematopoiesis on Clinical Outcomes to BCMA-Directed CAR T-Cell Therapy in Multiple Myeloma

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Introduction: Chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen (BCMA) is highly effective in multiple myeloma (MM), but is associated with immune-mediated toxicities and cytopenias. MM patients commonly have co-existing clonal hematopoiesis of indeterminate potential (CHIP), which is associated with a hyperinflammatory phenotype and decreased treatment efficacy with autologous stem cell transplantation. However, the impact of CHIP on outcomes to BCMA-directed CAR T-cell therapy in MM is unknown. **Methods:** We identified consecutive MM patients treated with BCMA-directed CAR T-cell therapy between 2017-2023 at our institution who had targeted gene sequencing for CHIP. CHIP was defined by the presence of a leukemia-associated somatic mutation with a variant allele fraction of >2% in unselected bone marrow aspirate. Treatment responses were assessed per the International Myeloma Working Group. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS) were graded according to the ASTCT guidelines, and cytopenias were graded according to CTCAE version 5. **Results:** A total of 104 patients were included, of whom 57 patients (55%) had CHIP. There were no differences in baseline clinical characteristics at the time of CAR-T infusion between patients with and without CHIP (p >0.05 for all comparisons). CHIP was not associated with treatment response rates, progression-free survival, or overall survival (p >0.05 for all comparisons). CHIP was also not associated with the incidence, severity, or management of CRS and ICANS (p >0.05 for all comparisons). However, the presence of CHIP did impact the risk of prolonged cytopenias. Patients with CHIP had a significantly higher incidence of transfusion dependence after CAR-T for both packed red blood cells (day +100: 15% vs. 0%; day +365: 14% vs. 0%; p=0.01) and granulocyte colony stimulating factor (day +100: 30 vs. 9%; day +365: 15% vs. 0%; p< 0.001). There was also a trend for higher transfusion dependence for platelets (day +100 and +365:

13% vs. 0%; p=0.06), and thrombopoietin receptor agonist use was significantly higher in patients with CHIP (8% vs. 1%; p=0.04). On multivariate modeling, CHIP was independently associated with a delayed time to transfusion independence for both packed red blood cells (HR 0.56; p=0.008) and granulocyte colony stimulating factor (HR 0.45; p<0.001). **Conclusions:** The presence of CHIP in MM patients did not impact treatment efficacy or the risk of immune-mediated toxicities (CRS/ICANS) to BCMA-directed CAR T-cell therapy, but was associated with prolonged transfusion-dependent cytopenias.

OA-07

A Comparison of Standard of Care Idecabtagene Vicleucel and Ciltacabtagene Autoleucel CAR T-cell Therapy in Relapsed or Refractory Multiple Myeloma

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Introduction: Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), two anti-B-cell maturation antigen CAR T-cell therapies, have demonstrated marked responses and improved survival among patients with relapsed/refractory multiple myeloma (RRMM) in the clinical trial and standard of care (SOC) setting. Here, we compare safety, efficacy, and survival for patients treated with SOC ide- and cilta-cel. **Methods:** Data were from a retrospective chart review of RRMM patients leukapheresed by 12/31/2022 with the intent to receive SOC ide- or cilta-cel at 19 institutions in the US Multiple Myeloma Immunotherapy Consortium. An inverse probability of treatment weighting (IPTW) approach was used to compare outcomes by type of therapy (cilta- vs. ide-cel), balancing on age, sex, race and ethnicity, extramedullary disease, high-risk cytogenetics, prior BCMA therapy, bone marrow plasma cells, penta-refractory status, ECOG performance status, lymphodepleting chemotherapy, baseline ferritin, low cell dose, and bridging therapy response. Logistic regression and Cox proportional hazard models were used to examine the association of treatment type with safety, efficacy, and survival accordingly, while adjusting for IPTW weights. **Results:** A total of 641 patients were apheresed by 12/31/2022 with ide-cel (n=386) and cilta-cel (n=255). 586 patients were infused (n=350 for ide-cel; n=236 for cilta-cel) with a median follow-up of 13.0 and 12.6 months, respectively. After IPTW, patient characteristics were well-balanced. Patients treated with cilta-cel were more likely to have grade ≥ 3 CRS (OR=6.19, 95% CI=2.10-18.24), infections (OR=2.04, 95% CI=1.42-2.93), and delayed NT (OR=33.01, 95% CI=4.38-248.48) compared to patients treated with ide-cel. Of note, only 1 ide-cel treated patient had delayed NT. Patients treated with cilta- vs ide-cel were more likely to have second primary malignancies, although not statistically significant (OR=1.79, 95% CI=0.78-4.12). Compared to treatment with ide-cel, cilta-cel was associated with better treatment responses of CR or better (OR=2.49, 95% CI=1.68-3.69) and PR or better (OR=1.66, 95% CI=0.95-2.92), although the latter was not statistically significant. Patients treated with cilta-cel had a longer PFS and OS than ide-cel (HR=0.47, 95% CI=0.36-0.63 and HR=0.66, 95% CI=0.46-0.95, respectively). Consistent findings were observed in the ITT cohort (PFS: HR=0.44, 95% CI=0.34-0.57; OS: HR=0.52, 95% CI=0.37-0.72, respectively). No association was observed for type of therapy with any or severe ICANS, any CRS, and non-relapse mortality. We observed consistent findings when repeating the analyses restricting the ide-cel cohort to patients infused during the same time-period as FDA approval for cilta-cel (≥ March 2022). **Conclusions:** Our results suggest a less favorable safety profile but higher efficacy and better survival for cilta-cel compared to ide-cel in the SOC setting.

OA-08

Safety and Preliminary Efficacy of BMS-986393, a GPRC5D CAR T Cell Therapy, in Patients (pts) With Relapsed/Refractory (RR) Multiple Myeloma (MM) and 1–3 Prior Regimens: Results From a Phase 1 Study

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Introduction: MM often becomes refractory early in its course, emphasizing a need for novel therapies. BMS-986393, a potential first-in-class autologous chimeric antigen receptor (CAR) T cell therapy targeting G protein-coupled receptor, class C, group 5, member D (GPRC5D), was safe and efficacious in pts with heavily pretreated RRMM (median 5 prior regimens) in the phase 1 CC-95266-MM-001 study (NCT04674813). At 150 × 106 CAR T cells, the overall response rate (ORR) was 91% (complete response rate [CRR] 48%; Bal et al, ASH 2023). Here we present initial results in pts with RRMM and 1–3 prior anti-MM regimens from CC-95266-MM-001. **Methods:** Pts had 1–3 prior anti-MM regimens including proteasome inhibitor and immunomodulatory agents; prior anti-CD38 therapy was not required. After screening and leukapheresis, pts received lymphodepleting chemotherapy followed by a single infusion of BMS-986393 150 × 106 CAR T cells. The primary objective was safety. Secondary objectives included clinical activity per IMWG Uniform Response Criteria and pharmacokinetics (PK). **Results:** As of Mar 18, 2024, 31 pts had received BMS-986393. Median age was 62 y (range 31–78); 19% were Black or African American; 29% had extramedullary disease. High-risk cytogenetics (del[17p], t[4;14], and/or t[14;16]) were seen in 26%, and 65% had 1q21 gain/amp. Pts had received a median of 2 prior regimens; 29% had 3 prior regimens. Around half (52%) had prior stem cell transplantation; 71% had received anti-CD38 therapy; 90% were lenalidomide-refractory; 55% were triple-class refractory; 90% had MM refractory to the last regimen, and 3% had prior B-cell maturation antigen (BCMA)-targeted therapy. Median follow-up was 4.9 mo. Treatment-emergent adverse events (TEAEs) occurred in 97%, 81% experienced a grade (G) 3/4 TEAE; there were no deaths. Treatment-related AEs (TRAEs) occurred in 94%; 42% had a G3/4 TRAE. Cytokine release syndrome was reported in 81% (all G1/2; all resolved); no pts had macrophage activation syndrome/hemophagocytic lymphohistiocytosis. Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 10% (all resolved; all G1/2), 10% had a non-ICANS neurotoxicity TRAE (n = 2 dizziness, n = 1 ataxia; all G1/2), and 48% had an on-target/off-tumor TRAE of the mouth, nails, or skin (all G1/2). Of 24 pts evaluable for efficacy, 23 achieved a response for an ORR of 96%. The CRR was 42%. Of 23 responses, 87% were ongoing. PK analyses showed fast and robust cellular expansion. Pharmacodynamic longitudinal assessment of soluble BCMA indicated BMS-986393 led to deep tumor clearance post-infusion. **Conclusions:** Initial results suggest that a single infusion of BMS-986393 is safe and has promising preliminary efficacy in pts with RRMM and 1–3 prior regimens. While follow-up is limited, the safety profile of BMS-986393 at 150 x 106 CAR T cells was favorable with no new safety signals. High response rates were achieved. These data support BMS-986393 as a potential early-line treatment in RRMM. The trial is ongoing.

OA-09

Mezigdomide Enhances Activity of BCMA-Targeted Cellular and T-Cell Engager Therapies and Mitigates Immune Toxicity in Preclinical Models of Multiple Myeloma

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Introduction: Mezigdomide (MEZI) is a cereblon E3 ligase modulator (CELMoD) under clinical investigation in patients with multiple myeloma (MM). Preclinically, MEZI exhibits potent cereblon-dependent Ikaros/Aiolos degradation leading to MM cell killing along with immune-stimulatory effects, synergizing with antimyeloma drugs in IMID-resistant MM cell lines and mouse xenografts. Early-phase clinical trials indicate notable activity and tolerable safety profile in relapsed/refractory MM. However, the impact of MEZI on BCMA-targeted agents remains undetermined. **Methods:** MEZI combination with second-generation murine BCMA CAR T cells or a BCMAxCD3 T-cell engager (TCE) was investigated in fully immunocompetent syngeneic and genetically engineered mouse MM models with humanized CRBNI391V in vivo. Therapy responses and mechanisms underlying potential synergisms were sequentially evaluated by multidimensional flow cytometry in MM and immune cell samples from blood and tibial bone marrow (BM) aspirates obtained from mice before, during and after treatment. **Results:** BCMA CAR T cells from CRBNI391V mice were infused following lymphodepletion in MM5080CRBN-I391V syngeneic or MIcγ1CRBN-I391V transgenic mice once MM was developed. CAR T cells induced dose-dependent responses defined by reduction of serum immunoglobulin levels, decline in BM MM cells, and increase in mouse survival. Sub-optimal BCMA CAR T cells and MEZI doses were then combined. MEZI doubled depth and duration of responses of CAR T cells, leading to complete remission (CR) and survival extension in comparison to CAR T cells alone (median overall survival, mOS: 273 vs 323 days; p=0.03). Mechanistically, MEZI expanded PD1+CD8 CAR T cells in the BM at day +7 after cell infusion, and prolonged persistence of PD1+CAR T cells with effector-memory and non-exhausted phenotypes. Next, BCMAxCD3 was administered at different doses to MM5080CRBN-I391V syngeneic or MIcγ1CRBN-I391V mice once MM was established. Dose-dependent responses were observed

in both models, leading to CR and survival extension with 1 mg/kg dose (p< 0.01) that correlated with expansion of BM-exhausted CD8 T cells. Then, TCE at a suboptimal dose (0.1 mg/kg) was combined with low-dose MEZI, which significantly induced four times deeper and sustained responses leading to extended survival in comparison to monotherapy arms (mOS: 263 days vs not reached; p< 0.0001). MEZI and BCMAxCD3 combination stimulated the expansion of BM PD1+CD8 T cells with effector-memory phenotypes and low expression of exhaustion markers (TIM3+, LAG3+). Finally, an increased ratio between CD8 T cells and regulatory Treg cells in the BM before treatment initiation correlated with better response to MEZI and TCE combination. **Conclusions:** MEZI enhances the activity of BCMA-targeted agents by expanding active CAR or endogenous T cells with effector-memory phenotypes without signs of exhaustion, potentially preventing therapy-related antigenic loss and mitigating T cell-mediated toxicity.

OA-10

Impaired Membrane Trafficking of GPRC5D Mediates Resistance to Anti-GPRC5D TCE

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Introduction: Bispecific T cell engagers (TCEs) and chimeric antigen receptor T cells (CAR T) directed against GPRC5D have demonstrated efficacy in relapsed multiple myeloma (MM). However, patients invariably relapse with the emergence of mutant GPRC5D clones. Whether these identified GPRC5D mutants, in particular non-truncating SNVs involving non-extracellular domain residues, confer resistance to anti-GPRC5D therapies remain to be defined. **Methods:** Serially collected bone marrow aspirates pre- and post- GPRC5D TCE therapy were subjected to magnetic beads CD138+ sorting followed by whole genome sequencing (100x), scCNV, and scRNA. Identified GPRC5D SNVs were cloned and stably transduced in K562 cells for functional characterization. **Results:** Study cohort included 12 patients who received talquetamab. 11/12 had ≥VGPR and mPFS of 13.5 months. Among 5/12 with progressive disease, all had newly detected GPRC5D mutations. Patient MM-19 had clonal GPRC5D biallelic deletion, while MM-18 had a major subclone (90%) harboring biallelic GPRC5D deletion and a minor subclone (5%) with SNV leading to a frameshift mutation (p. Leu174Trpfs180ter). MM-03 progressed with GPRC5D monoallelic loss coupled with clonal p.Asp239Asn (p.D239N). MM-31 at progression harbored 4 subclones with either GPRC5D biallelic deletion (12%), p.Arg233ter (45%), p.Tyr257Ser (28%), or rearrangement between chr 2 and GPRC5D locus on chr 12 (15%). Similarly, MM-32 demonstrated convergent evolution of mutant subclones harboring biallelic deletion 12p (7%) and another subclone with monoallelic loss coupled with GPRC5D p.Glu146ter (35%). Among the GPRC5D SNVs, 3 mapped to its extracellular domain and 2 to its transmembrane domain. Notably, all GPRC5D SNVs clustered within conserved motifs across GPCR family of proteins known to be implicated in protein trafficking across golgi/ endoplasmic reticulum (ER) and cell membrane. Indeed, confocal microscopy and flow cytometry assays of K562 cells stably expressing WT or mutant GPRC5D demonstrated that the identified GPRC5D mutants, except p.D239N, were retained in the ER (co-localizing with calnexin), abolishing GPRC5D surface expression. Meanwhile, GPRC5D p.D239N was detectable on the cell surface with its expression level comparable to WT GPRC5D. We evaluated the binding of talquetamab (monovalent GPRC5D binding) and forimtamig (bivalent) on p.D239N expressing clones. While forimtamig demonstrated dose dependent linear binding to D239N, talquetamab binding to p.D239N was only detectable at high concentrations ≥ 10 nM. Consistent with their binding, forimtamig demonstrated enhanced cytolytic activity against GPRC5D p.D239N. **Conclusions:** GPRC5D antigen escape predominantly involve convergence of multiple clones harboring monoallelic chr.12p deletions coupled with GPRC5D mutations. GPRC5D mutations cluster within GPCR conserved motifs involved in protein trafficking and hence prevent its membrane localization.

OA-11

Safety and Efficacy of Standard of Care Ciltacabtagene Autoleucel (Cilta-cel) for Relapsed/Refractory Multiple Myeloma (RRMM): Real World Experience With Updated Follow-up

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Introduction: We present updated outcomes of patients with relapsed/refractory multiple myeloma (RRMM) treated with standard of care ciltacabtagene autoleucel (cilta-cel), with longer follow-up and expanded patient cohort. **Methods:** Patients at 16 US academic centers who underwent apheresis with intention to manufacture standard of care cilta-cel by 12/31/2022 were included. **Results:** 255 patients underwent apheresis and 236 (92.5%) received cilta-cel infusion. 19 patients did not get cilta-cel due to progression/death (11), manufacturing failure (3), other cancer (2) or other reasons (3). Median CAR-T cell dose (106/kg) was 0.6 (0.1-1); cell dose < 0.4 x 106/kg: n=7. 19% of patients received a non-conforming product. The median follow-up after CAR-T was 13 months (range: 0.3-21.8). Amongst patients receiving cilta-cel (N=236), median age was 64 years (26% ≥ 70 years), 57% were male, 30% had penta-refractory disease, 34% had extramedullary disease (EMD), 39% had high-risk cytogenetics, and 6% had plasma cell leukemia. Median prior lines of therapy were 6, 14% had prior BCMA therapy and 4% had prior bispecific antibodies. 54% of the patients would not have met eligibility criteria for CARTITUDE-1. 78% of the patients received bridging chemotherapy (overall response rate, ORR: 27%). Lymphodepletion (LD) included fludarabine (Flu) + cyclophosphamide (Cy): 81%, bendamustine: 13%, others: 6%. Cytokine release syndrome occurred in 75% (≥ grade 3: 5%), immune effector cell-associated neurotoxicity syndrome in 14% (≥ grade 3: 4%) and HLH-like syndrome in 2% of patients. Delayed neurotoxicity (DNT) occurred in 10% of patients with median time to onset of 24 days, with most common finding being 7th nerve palsy (4%, n=11) and Parkinsonism seen in 2% (n=5) patients. DNT resolved in 54% of patients by last follow-up, while 21% patients died with ongoing symptoms. Severe infections were seen in 21% of patients. Second primary malignancies (SPMs) were seen in 8.5%. SPMs excluding non-melanoma skin cancers were seen in 5.5% and myeloid malignancies/acute leukemia in 1.7%. Overall response rate (ORR) and complete response (CR) rates were 89% and 70% in all infused patients, and 95% and 76% in patients receiving a conforming product with Flu/Cy lymphodepletion. Median progression free survival was not reached, with a 12-month survival estimate of 68% (95% CI: 62-74) in all patients and 73% (95% CI: 66-81) in patients with conforming product and Flu/Cy LD. Patients with prior BCMA therapy, high-risk cytogenetics, and extramedullary disease had inferior PFS on multivariable analysis. 50 patients died by data cut-off, including 10% (n=23) due to non-relapse mortality. **Conclusions:** Patients treated with SOC cilta-cel had a favorable ORR (89%), CR rate (70%) and PFS with longer follow-up (12 month estimate: 68%) despite a large proportion of patients having high-risk features. Long-term monitoring for SPMs is recommended.

OA-12

Interim Phase 2 Study Results of Durcabtagene Autoleucel (PHE885), a T-Charge™ Manufactured BCMA-Directed CAR-T Cell Therapy in Patients (pts) with r/r Multiple Myeloma (RRMM)

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Introduction: Durcabtagene autoleucel (PHE885) is a novel BCMA-directed CAR-T cell product manufactured using the T-Charge™ platform that preserves T-cell stemness and reduces manufacturing time to < 2 d, allowing for short door-to-door times. A phase 1 trial reported high response rates (ORR=98%) with no unexpected safety findings in heavily pretreated pts with aggressive RRMM. Here we report the interim analyses from the open-label, single-arm, multicenter phase 2 trial of PHE885 in pts with RRMM (NCT05172596). **Methods:** Eligible pts had RRMM, were ≥18 y old, and had received ≥3 prior lines of therapy. The primary endpoint was ORR. Secondary outcomes included CRR, PFS, OS, and safety. Efficacy analysis set (EAS) consisted of pts infused with in-specification PHE885 at 10e6 cells and with ≥6 mo postinfusion follow-up (or discontinued early). The safety and full analysis set (FAS) included all infused pts regardless of disease measurability, dose, or follow-up. **Results:** As of Jan 9, 2024, 161 pts were enrolled and 145 pts were infused: 34 pts at the 5e6 target dose and 111 pts at the 10e6 target dose. Robust cellular expansion was observed by qPCR. Among infused pts, median (range) age at enrollment was 61 y (35-78); 63% of pts were male. 27% of pts had ≥5 prior lines of therapy; 77% of pts were triple-class refractory. At study entry, 45% of pts had stage II disease (R-ISS), 18% had stage III. 16% of pts had high-risk cytogenetics. 33% of pts had ≥50% bone marrow plasma cells at baseline. 55% of pts required bridging chemotherapy prior to infusion; all pts received lymphodepletion. With median follow-up of 8.3 mo (6.0-13.4), ORR (≥PR) by IRC assessment in the EAS (N=62) was 92%, 95% CI [82.2-97.3%], meeting the primary endpoint (P< 0.001); CRR (CR+sCR) was 53% [40.1-66.0%]. 6-mo PFS probability was 82% [69.0-90.1%]. In the FAS for pts with ≥6 mo follow-up (N=107), ORR (≥PR) was 97% [92.0-

99.4%]; CRR was 53% [43.4-63.0%]. 6-mo PFS probability was 86% [78.1- 91.7%]. In the safety set (N=145), all pts experienced at least 1 AE. The most common gr ≥3 AEs occurring in ≥20% of pts were neutropenia, anemia, and thrombocytopenia. Any-gr CRS was reported in 96% of pts; 6% had gr ≥3. Median time to CRS onset was 8 d (1-15), and median duration was 4 d. ICANS occurred in 13% of pts; 4% had gr ≥3. HLH, MAS, or IEC-HS was reported in 10% of pts; 6% had gr ≥3. In total 14 pts died of any cause; among them 4 pts died within 30 d of infusion. Cause of death was AE in 10 pts (9 pts at the 10e6 dose, among them 5 due to infections) and MM progression in 4 pts (3 at the 10e6 dose). First results of the primary efficacy analysis will be presented at the meeting. **Conclusions:** T-Charge™-manufactured PHE885 produces high response rates with a manageable safety profile in RRMM. Efficacy thus far has appeared comparable between doses, with a trend toward better safety at the 5e6 dose. Longer follow-up is needed to fully assess durability and response rates as late conversions to CR/sCR have been observed.

OA-13

Belantamab Mafodotin, Pomalidomide, and Dexamethasone vs Pomalidomide, Bortezomib, and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: Patient-Reported Outcomes from DREAMM-8

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Introduction: Belantamab mafodotin (belamaf) is a first-in-class antibody-drug conjugate targeting B-cell maturation antigen and acts through a multimodal mechanism. The phase 3, open-label, randomized DREAMM-8 trial (NCT04484623) met its primary endpoint of a statistically significant progression-free survival (PFS) benefit favoring belamaf, pomalidomide, and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd) in patients with relapsed/refractory multiple myeloma (RRMM) who had received ≥1 prior therapy, including lenalidomide. Here, we present patient-reported outcomes (PROs) with BPd vs PVd. **Methods:** Patients were randomized (1:1) to BPd or PVd. Patients completed PRO assessments at baseline and every 4 weeks (Q4W) during treatment, and at a reduced frequency beyond this. PRO measures included EORTC QLQ-C30, EORTC QLQ-MY20/IL52 disease symptoms/pain, PRO-CTCAE patient-reported tolerability, FACT-GP5 side effects, and OSDI (Q8W after week 21). Based on the median PFS of 12.7 months with PVd, this analysis focused on the time points within the first year of data collection (up to week 53). Each domain was summarized using descriptive statistics. **Results:** Among 302 patients (BPd, n=155; PVd, n=147), adherence to PRO assessments until treatment discontinuation was >90% for most visits up to week 53. EORTC QLQ-C30 global health status/quality of life (GHS/QOL), role and physical functioning, fatigue, and pain were maintained over time in both the BPd and PVd arms overall. Between weeks 5 and 53, patients receiving BPd or PVd maintained overall QOL (< 10-point change from baseline), as measured by the EORTC QLQ-C30 GHS/QOL domain, and there were no differences (≥10 points) between treatment arms. Similarly, there were no differences (≥10 points) between treatment arms for physical functioning, fatigue, role functioning, or disease symptoms/pain. A higher proportion of patients reported vision-related function (≥12.5-point increase from baseline) and ocular symptom (≥16.67-point increase from baseline) worsening on BPd vs PVd as reported on the OSDI measure. However, this improved for most patients; median time to improvement in vision-related function from the first meaningful worsening was 57.0 days. Most symptomatic adverse events evaluated by PRO-CTCAE were reported as no to low severity, frequency, and interference (PRO-CTCAE ratings ≤2) in both arms throughout the study. Blurred vision and fatigue were reported at higher levels (PRO-CTCAE ratings ≥3) in the BPd arm. As measured by the FACT-GP5, most patients in the BPd arm (generally 84%-98%) reported feeling "not at all," "a little bit," or "somewhat" bothered by treatment side effects; a similar pattern was observed in the PVd arm (89%-100%). **Conclusions:** Treatment with BPd or PVd in patients with RRMM resulted in stable health-related QOL over time and was generally well tolerated by patients.

OA-14

Prospective Functional Bone Disease Evaluation of Newly Diagnosed Multiple Myeloma with Combined Use of (18)F-FDG-PET/CT and Whole-Body Diffusion Weighted Magnetic Resonance

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Introduction: FDG-PET/CT is the most widely used imaging technique to detect bone and extramedullary disease (EMD) in multiple myeloma (MM) and is recommended for response assessment by IMWG. In clinical practice, PET/CT is usually associated to magnetic resonance imaging (MRI); addition of diffusion-weighted imaging sequences in the recently introduced whole body-MRI (WB-MRI) has further increased sensitivity and has been lately proposed for response assessment by MY-RADS guidelines. **Methods:** We herein present a prospective single-center study aimed at comparing PET/CT and WB-MRI during diagnosis/staging of smoldering MM (SMM) and newly diagnosed MM (NDMM) and in defining treatment response in transplant-eligible (TE) and ineligible (TI) patients (pts). Pts undergo both imaging techniques at baseline (B) and prior to maintenance therapy (TE) or after 1 year of treatment (TI). Secondary aims are to define the prognostic role of the two techniques and to compare and validate imaging criteria (IMPeTuS and MY-RADS) in clinical practice. **Results:** Between October 2022 and March 2024, 79 pts (25 SMM and 54 NDMM) underwent PET/CT and WB-MRI at B. Among NDMM pts with CT-assessed bone disease (61%), WB-MRI was positive in 100% and FDG-PET in 88%; in the remaining 39% pts, WB-MRI was negative in 43% (none with PET-assessed focal lesions, FLs) and positive in 57% (half with positive FDG-PET). WB-MRI detected FLs and paraskeletal disease (PSD) in more pts than FDG-PET (FLs:76% vs 54%, p=0.04; PSD:30% vs 20%, p=0.01); a slight concordance resulted in detecting diffuse disease (DD) (30% vs 46%, p=0.11, k=0.35). Presence of DD in WB-MRI and PET/CT was related to R-ISS III (p=0.048 and 0.04); DD in WB-MRI was also related to higher monoclonal protein concentration (p=0.048) and higher percentage of marrow plasma cells (p=0.02). Among SMM pts, FLs and DD detected by PET and WB-MRI were similar (FLs:12% vs 4%, p=0.99; DD:16%). To March 2024, 11 pts had imaging re-evaluation, with a concordance of 87.5% between techniques. **Conclusions:** Our data support combined use of PET/CT and WB-MRI for MM staging at B; preliminary data also show a good concordance in response assessment. Further expansion of study population and larger number of pts who have reached the post-treatment timepoint are needed to properly define the role of WB-MRI vs PET/CT at diagnosis and response assessment. Updated data with extended follow-up and regarding response assessment will be presented at the meeting.

OA-15

Maintenance Therapy Cessation for Multiple Myeloma Patients with Three-Year Sustained MRD Negative Remissions

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Introduction: Lenalidomide maintenance (LM) therapy is a cornerstone therapeutic strategy in multiple myeloma (MM) patients (pts), prolonging remissions and extending overall survival. Long-term analysis of the UK Myeloma XI trial has suggested that the benefit of continuing maintenance in pts with sustained minimal residual disease (MRD) negative (neg) status beyond 3 years, is unclear (Pawlyn et al. ASH 2022. Abs# 570). We present updated results from a prospective phase II study of LM discontinuation in MM patients after >3-years of sustained MRD neg remission while on LM. **Methods:** This phase II study (n=50) evaluates MRD dynamics following LM discontinuation in pts who have demonstrated >3 years of durable MRD neg responses. Enrolled pts stop LM and undergo surveillance with serum and clinical follow-up (f/up) every 3 months, bone marrow MRD testing by multiparametric flow cytometry (single 10-color tube with limit of detection of at least 6x106 with at least 3 million cell acquisitions, meeting IMWG criteria) every 6 months, and annual PET-CTs for 3 years. Primary endpoint is sustained MRD neg rate after 1 year, while secondary endpoints are sustained MRD neg rate at 3 years of cessation, re-treatment responses, microbiome and immune studies, health-related quality of life outcomes, and progression-free survival (PFS). **Results:** From February 2020 to March 2024, a total of 43 pts enrolled onto the study. The median f/up is 21.2 mo (17-32). Median time since diagnosis is 8.1 years (4-20), and median duration of maintenance therapy is 56.3 mo (33-161). Pts enrolled included 31(72%) ISS-I, 9(21%) ISS-II, 2(5%) ISS-III, 1(2%) stage not reported (NR), 6(14%) high-risk (HR) cytogenetics [t(4,14), t(14,16), +gain 1q21.3], and 4(9%) cytogenetics NR. After stopping LM, 26/31(84%) remained MRD neg at 12 months. Patients with a durable MRD neg response at 24 mo was 82% (95% CI 69-96%), and PFS at 24 mo was 91% (95% CI 81-100%). Durable MRD

neg response at 24 mo for standard risk (SR) vs. HR or NR pts was 87% (95%CI 74-100%) vs. 66% (95% CI 40-100%) (p=0.058). Among MRD pos convertors, 4/9 had clinical progression requiring alternative therapy than LM, while 5/9 remained asymptomatic with MRD conversion. Three asymptomatic MRD convertors restarted LM; subsequent testing demonstrated 1 pt remained MRD pos while 1 pt recaptured MRD neg. **Conclusions:** Current results suggest LM cessation among SR patients who have sustained MRD neg remissions for >3 years is feasible and associated with low rates of clinical progression. Ongoing efforts, studying MRD dynamics, immune biomarkers, and patient quality of life are underway with the potential to guide earlier treatment discontinuation and thereby define functional cure in MM.

OA-16

Long-Term Evaluation of Minimal Residual Disease Dynamics in Multiple Myeloma Patients Achieving Complete Response After First Line Treatment

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Introduction: Minimal residual disease (MRD) negativity is a powerful biomarker in Multiple Myeloma (MM) associated with prolonged PFS and OS. However, MRD negativity at a single timepoint cannot guarantee for its sustainability overtime; hence, relapses may also occur. The bone marrow (BM) niche has a critical role in supporting myeloma cells, but little is known about its dynamic changes during disease progression. The aim of this study was to evaluate the frequency and prognostic value of MRD over time and highlight possible associating alterations in the BM microenvironment. **Methods:** MRD and BM profiling were evaluated with Next-Generation Flow (NGF) cytometry in 313 MM patients (pts) who achieved complete remission (CR) after first-line therapy. Pts were divided in two groups based on the timing of the first MRD evaluation: Group A (n=240) examined for MRD at their first evidence of CR and Group B (n=73) in sustained CR >24 months after first MRD testing. Median follow-up was 35 months. A second, third and fourth consecutive MRD assessment was performed for 52%, 34% and 18% pts, respectively (median interval: 6 months). The BM profiling was examined per patient with the surface panel of NGF, allowing for the construction of an individualized patient immune profile, based on the levels of 17 BM subsets. **Results:** 106/313 (33.9%) pts were MRD positive (+) in their first examination (same frequency in Groups A and B), and had a shorter PFS than MRD negative (-) pts (HR:0.36, 95% CI:0.22-0.61, p< 0.0001). MRD+ pts in Group B had a 2-fold higher risk of subsequent progression compared to Group A (HR:0.51, 95% CI:0.24–1.05, p=0.03), probably due to their higher tumor burden (median: 3x10-4 vs. 3x10-5, p< 0.001). Indeed, the tumor burden increase per log scale conferred a worse outcome among MRD+ pts of both groups. The presence of high-risk cytogenetics or ISS III did not affect the favorable prognosis of MRD-negativity achievement. 34% of pts changed their MRD status over time, with those changing from MRD- to MRD+ (n=27) showing a 2.2-fold higher risk for relapse than those with persistent MRD+ (HR:2.2, 95% CI:1.1-3.9, p=0.04). Surprisingly, pts changing from MRD+ to MRD- (n=28) had a more favorable prognosis when compared to continuously MRD- pts. Changes in the MRD status were accompanied by alterations in the BM composition; the alteration of MRD-negativity to an MRD+ status between two consecutive MRD assessments was accompanied with a relevant increase of NK cells and of the ratio of memory/naïve B cells among total BM nucleated cells. **Conclusions:** MRD prognostication stands irrespective of CR durability, while tumor burden can further stratify MRD+ pts with different risk of progression. MRD should be periodically re-evaluated, since MRD dynamics may confer a distinct prognostication than a persisting MRD status. MRD dynamics are accompanied by alterations in the BM immune profile, which may shed light in the underlying biology of MRD.

OA-17

Liquid Chromatography Mass Spectrometry (LC-MS) for Identification of Exceptional Responders in Newly Diagnosed Multiple Myeloma (NDMM)

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Introduction: MS allows for sensitive detection of monoclonal protein in peripheral blood. Currently, MALDI-TOF MS is most frequently used due to the method's high-throughput and cost-effectiveness. However, we hypothesized that for the identification of exceptional responders, more sensitive methods should be utilized. Samples that are negative by MALDI-TOF MS can also be tested by LC-MS, a method approximately 10 times more sensitive. **Methods:** We pooled data from two prospective phase 2 studies in NDMM, wherein exploratory analyses included response evaluation with MS. Patients were treated either with carfilzomib, lenalidomide, and dexamethasone plus autologous stem cell transplant (KRd-ASCT, NCT01816971) or with daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd, NCT03500445). Samples for MS assessments were collected after 18 cycles and one year later in the KRd-ASCT, and after cycles 8, 12, and 24 in the Dara-KRd. MALDI-TOF MS evaluation was performed using the EXENT platform (The Binding Site, part of Thermo Fisher Scientific). Negative samples were reflexed for LC-MS testing.

Bone marrow (BM) MRD by NGS (sensitivity threshold 10-6, clonoSEQ, Adaptive Biotechnologies) was performed at the same timepoints. **Results:** A total of 74 patients with samples available for MS evaluation, out of 118 patients enrolled in both studies, were included in this analysis: 36 from the KRd-ASCT trial and 38 from the Dara-KRd. Median follow-up was 50.2 months (range: 7.1-128.9). According to the standard IMWG criteria, best overall responses were sCR in 63 (85%) patients, CR in 3 (4%) patients and VGPR in 8 (11%) patients. EXENT(-) as a best response was reached in 45 patients (61%), all but one EXENT(-) patients were in sCR or CR. LC-MS(-) was achieved by 22 (30%) patients. There were two PFS events in the LC-MS(-) group, one caused by death due to secondary malignancy; the only MM progression occurred more than 7 years after diagnosis in a patient with t(4:14). Hazard ratio for progression or death between LC-MS(-) and EXENT(+) patients equaled 0.12 (0.05-0.31, p=0.0007), between LC-MS(+)/EXENT(-) and EXENT(+) equaled 0.49 (0.21-1.15, p=0.12), and between LC-MS(-) and LC-MS(+)/EXENT(-) equaled 0.30 (0.07-1.19, p=0.12). For the 44 patients who had BM MRD evaluable at the 10-6 threshold, the agreement between LC-MS and BM MRD was 68%. Among the discordant cases, the proportion of LC-MS(+)/BM MRD(-) patients was higher (25%). Notably, for the 32 LC-MS(-) OR 10-6 BM MRD(-) patients, the 5-year PFS rate was 96%. None of the 9 'double-negative' patients have experienced disease progression. **Conclusions:** In addition to the prognostic significance of MS(-) at any level, the depth of MS negativity is associated with longer PFS. LC-MS(-) and/or 10-6 MRD(-) patients experience long term disease control. The potential of LC-MS to enhance the prognostic potential of MRD at 10-6 for predicting longer disease control is currently under evaluation in a larger sample set.

OA-18

Association of Cardiac Biomarkers and Adverse Events with a Carfilzomib-Containing Quadruplet in High-Risk Newly Diagnosed Multiple Myeloma Patients: Correlative Program of the GMMG-CONCEPT Trial

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Introduction: Cardiovascular adverse events (CVAE) are clinically relevant side effects of the proteasome inhibitor carfilzomib (K). In the GMMG-CONCEPT study (NCT03104842), K-based quadruplet is given as first-line treatment with isatuximab, lenalidomide, and dexamethasone (Isa-KRd) in induction (IND) and consolidation (CONS) of high-risk (HR) multiple myeloma (MM) patients (pts). Transplant-eligible pts undergo high-dose melphalan intensification (INTENS), all pts receive 2 years Isa-KR maintenance (MAIN). **Methods:** Pts were eligible for this correlative study if a serum sample from inclusion and ≥1 later time point were available. High sensitive Troponin I (hs-TnI) indicating myocardial injury and N-terminal pro-b-type natriuretic peptide (NT-proBNP) reflecting hemodynamic stress were measured using immunoassays (Abbott) and are reported as medians with interquartile ranges. Time-to-event analyses were performed using Kaplan-Meier estimators; log-rank test was used for statistical analysis. The primary aim was to evaluate if NT-proBNP or hs-TnI were predictive of CVAE. **Results:** In total, 126 pts (median age 60 years) were included with 2-11 samples per pt. Overall, 48 (Kaplan-Meier estimator 42.3%) pts experienced any CVAE while on study; arterial hypertension was the most common (n=24, 19%). Most CVAEs occurred during the first 3 IND cycles and during MAIN. The majority of pts (96/126,

76%) showed increased NT-proBNP levels (>125 ng/l) before treatment initiation (median 229 ng/L [IQR, 129-503]). Pts with preexisting cardiovascular comorbidities (CVM; n=64) showed higher levels of NT-proBNP after INTENS (122 [92-353] vs 87 [62-136] ng/l, p=0.007) and during CONS (171 [84-574] vs 111 [58-190] ng/l, p=0.016) and MAIN (224 [115-379] vs 131 [56-186] ng/l, p=0.016) but not before treatment initiation or during IND compared to pts without CVM. Increased NT-proBNP levels at any time point were not predictive for occurrence of CVAE. NTproBNP levels during MAIN (224 [115-379] vs 131 [56-186] ng/l, p=0.008) were higher in pts who experienced a CVAE (n=48) compared to pts without. In contrast to NT-proBNP, hsTropI levels were low at baseline (median 3.7 ng/L [IQR, 2.2-7.0]) and elevated above normal limits (>26.2 ng/L) in only 4/126 pts (3%). Time-to-event analysis showed that pts with baseline hsTropI levels of ≥2.9 ng/L had a significantly higher risk of developing a CVAE during treatment vs pts with hsTropI levels < 2.9 ng/L (p=0.0059). In Cox regression analysis, an early change from baseline was associated with a slightly, but significantly elevated risk for new onset CVAE (hazard ratio 1.13 [1.02-1.24], p=0.017). **Conclusions:** Elevated levels of NT-proBNP are common in newly diagnosed HR MM pts, but neither the baseline value nor an early change from baseline within the first 3 IND cycles are predictive for CVAEs. In contrast, hsTropI is rarely elevated, but baseline levels below < 2.9 ng/L were negative predictive for the occurrence of CVAE during Isa-KRd quadruplet treatment for high-risk MM.

OA-19

Marrow Immune Features Are Most Informative of Early MRD Negative Treatment Response in Newly Diagnosed TE Patients: Insights from the UKMRA Phase 3 RADAR Study

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Introduction: Response depth, especially post-ASCT, may relate to host immune function as well as disease biology and drug sensitivity. We hypothesise that the bone marrow (BM) immune microenvironment at baseline is predictive of early MRD response following induction and ASCT in newly diagnosed MM. **Methods:** In RADAR, standard risk (SR) patients (pts) [defined as < 2 of t(4;14), t(14;16), del(17p), 1q+,1p-)] receive R-CyBorD induction followed by high dose melphalan and ASCT. Baseline immune profiles were analysed in fresh BM using a 10-marker flow panel. Flow-based MRD (10-5) was assessed in BM at day 100 post-ASCT. Combining with clinical data, we aimed to predict early MRD response using an Elastic Net penalised logistic regression model. We used a 36-marker CyTOF panel on thawed BM samples for detailed study of T-cell states. **Results:** 251 SR-enriched pts (MRD positive=152, MRD negative=99; median age 61.5y, male 58.6%, White 86.5%; SR=230, HR=21) were included. We predicted MRD outcome with ~65% accuracy (assessed repeatedly on 20:80 test/train splits). The importance of variables was assessed both independently through univariate analysis and by ranking their coefficient within the whole Elastic Net model. Clinical parameters (B2M, albumin and paraprotein), had little prognostic value for early MRD response. Intriguingly, the IgG isotype was enriched in MRD positive patients (66% vs 51%, Chi-square p=0.021). The most significant markers and highest ranking coefficients in our model were BM immune biomarkers. CD4+T-cells were amongst the strongest predictors of MRD negativity (OR 1.33, 95%CI 1.03-1.73, p=0.032). Higher frequency of CD138+ tumour cells (OR 0.79, 95%CI 0.61-1.02, p=0.069), CD56Bright NK-cells (OR 0.73, 95%CI 0.52-0.98, p=0.047) and double negative (DN)T-Cells (CD3+CD4-CD8-) (OR 0.66, 95%CI 0.50-0.85, p=0.002) were correlated with MRD positivity. Using CyTOF from 18 patients (MRD positive=8, negative=10), we resolved 50 T-cell clusters across a range of differentiation states from naïve (CCR7+CD27+) to terminally differentiated (GranzymeB+CD57+) CD4+ and CD8+ T-cells. In line with our Elastic Net model, CD4+T-cells were enriched in MRD negative pts (t-test, p=0.074). However, a rare subset of CD4+T-cells with a phenotype of early activated effector memory cells (CD28+KLRG1+GranzymeB+CD57-) was highly enriched in MRD positive pts (t-test, p=0.0021), highlighting how deeper phenotyping elucidates immune biomarkers of MRD status. Furthermore, DN(CD3+CD4-CD8-) T-cell clusters enriched in MRD positive pts (t-test, p=0.009) were CD57+GZMB+ indicating these cells that lack canonical T-cell co-receptor expression possessed hallmarks of terminal differentiation at baseline in MRD positive pts. **Conclusions:** In summary, variables indicative of the pt's own immune system are the most informative of early treatment response after R-CyBorD induction and ASCT. Follow up analysis will reveal if these associations hold with later and sustained MRD responses.

OA-20

A New Circulating Tumor Cell-Based Prognostic System To Refine Patient Stratification Status of Newly Diagnosed Multiple Myeloma Patients

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Introduction: The evaluation of circulating tumor cells (CTCs) has been suggested as a new biomarker with an independent prognostic value for newly diagnosed Multiple Myeloma (NDMM) patients (pts). Recently, we highlighted a CTC value of 0.02% as an optimal prognostic cutoff for NDMM pts, independent from other established prognostic features. Herein, we aimed at defining a novel CTC-based prognostic algorithm to refine current stratification systems. **Methods:** NDMM pts (n=535) with median follow-up monitoring of 45 months (range 12-71 months) were included in the study. All pts had available clinical data regarding demographics, cytogenetics, heavy/light chain restriction, bone marrow (BM) infiltration, white blood cell and platelet counts, levels of serum albumin, creatinine, calcium, LDH and β2-microglobulin. R-ISS stage and phenotypic classification system (PCS) were also available, the latter estimated using the relevant frequencies of normal, clonal and total BM plasma cells as assessed with flow cytometry, based on the available online MGUS-like calculator. **Results:** The CTC-cutoff was used in subgroup analyses of PFS and OS over other parameters, showing a significantly lower risk of subsequent progression and/or death for pts with CTCs< 0.02% in all cases. The same impact of CTCs was observed on PFS, both for transplant eligible (TE) and transplant ineligible (TI) pts (HR:0.38, 95% CI:0.22-0.59 for TE, p< 0.001; HR:0.43, 95% CI:0.31-0.64, p< 0.0001 for TI). The effect on OS was mainly retained in TI pts (HR:0.4, 95% CI:0.22-0.71, p=0.004), probably due to the low number of deaths during the monitoring period. The lack of interaction between CTCs and R-ISS and/or PCS, allowed us to incorporate data of all three systems in an effort to refine patient stratification. Pts were assigned one point per increased risk status in each individual system (i.e., 1-3 points for R-ISS; 1-3 points for PCS; 1-2 points for CTCs) and thus, the final score ranged between 3-8 points. A total of 3.5%, 17.4%, 22.3%, 22.1%, 20.3% and 14.4% of pts achieved scores of 3,4,5,6,7 and 8, respectively. PFS and OS worsened gradually between each increasing score, but the optimal efficacy of the model was attained by segregating pts to 3 groups; group A (score 3-5), group B (score 6-7) and group C (score 8). Median PFS was not reached, 42months, and 25 months for groups A, B and C, respectively; p< 0.0001), and OS was not reached in all groups (p< 0.001), showing a superior stratification efficacy (C-index 0.65) when compared to R-ISS, PCS and CTC classification individually or in any dual combination thereof. **Conclusions:** Elevated CTC numbers worsen the prognostic status of NDMM pts irrespective of other clinical features. The incorporation of the 0.02% CTC-cutoff with R-ISS and PCS, results in a new stratification system with improved prognostic value, able to better define NDMM patient subgroups that could benefit from different therapeutic strategies.

OA-21

Clinical Implications of Residual Immunophenotypically Normal Plasma Cells Within Bone Marrow at Various Disease Stages in Multiple Myeloma

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Introduction: Residual normal plasma cells (NPCs) within bone marrow (BM) act as competitors of abnormal plasma cells, playing an important clinical role during the malignant transformation and disease aggressiveness in plasma cell disorders. Previous studies have described the relationship between the persistence of NPCs and survival outcomes at several timepoints, but its clinical significance remain to be fully elucidated across various disease courses. Following the clearance of tumor plasma cells post-treatment, the numerical or proportional alterations in NPCs during the minimal residual disease (MRD) phase could also indicate the evolution of response depth and changes in the immune microenvironment. To date, however, there has been a scarce of research specifically addressing residual NPCs at the MRD stage. **Methods:** In light of this, we conducted a comprehensive retrospective study utilizing a substantial flow cytometry dataset comprising 1363 MM patients and nearly 5000 MRD samples across all disease courses from the National Longitudinal Cohort of Hematological Diseases in China (NICHE, NCT04645199). **Results:** Our results revealed that 47 (4.5%) newly diagnosed myeloma patients with high NPC ratio (≥5%) within bone marrow (BM) exhibited distinct indolent features, characterized by lower tumor burden, reduced frequencies of cytopenia, immunoparesis, and high-risk cytogenetics. Importantly, high residual NPC ratio at diagnosis or relapse was independently associated with favorable survival outcomes. Furthermore, high absolute level of NPCs at undetectable MRD timepoint was also related with superior clinical benefit and immune reconstitution. Among MRD-positive patients, NPCs ratio within BMPCs was significantly negatively correlated with residual tumor cell levels post-treatment. In addition to MRD status, grouping based on NPC ratio (< 50%, 50-90%, ≥90%) at MRD phase demonstrated better risk stratification for detectable MRD patients compared to residual tumor log levels. The dynamic NPC ratio time-dependent model could classify patients into three groups with diverse longitudinal change trends, which lead to distinct survival outcomes. **Conclusions:** Collectively, the persistence of residual NPCS serves not only as a valuable complementary biomarker for risk stratification but also provides valuable insights on reclassifications and kinetics of MRD.

OA-22

A Single-Cell Atlas of Bone Marrow Immune Microenvironment Characterizes Dysregulation Associated With Multiple Myeloma Outcomes

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Introduction: Immune components of the bone marrow (BM) microenvironment in multiple myeloma (MM) have emerged as critical factors for disease progression and therapy responses. Identifying dysregulated immune populations associated with clinical outcomes has thus attracted significant attention. To this end, we profiled the BM microenvironment (BMME) of newly diagnosed MM (NDMM) patients to identify immune populations and signaling pathways associated with cytogenetic risk and disease progression. **Methods:** We established a harmonized consortium to generate an Immune Atlas of MM aimed at informing disease etiology, risk stratification, and potential therapeutic strategies. Together, we analyzed 361 CD138neg BM samples from 263 NDMM subjects enrolled in the CoMMpass clinical trial via scRNA-seq resulting in more than 1.1 million single cells representing immune subpopulations spanning myeloid, lymphoid, and erythroid lineages. These subpopulations were tested for significant association with cytogenetic risk and disease progression. Outcome-associated populations were characterized by differential expression, pathway enrichment, and intercellular communication analyses. Lastly, we developed risk stratification models incorporating cytogenetic events and immune signatures and assessed their performance. **Results:** Compositional analysis revealed multiple significant immune alterations associated with poor outcomes. This includes depletion of B cells, depletion of naïve T cells, enrichment of terminally differentiated, senescent CD8+ T cells, and general enrichment of cells of myeloid lineage. Empiric analyses suggest that NDMM patients with poor outcomes exhibited a shift toward immunosenescence and late-activated CD8+ T cells producing IFN-II. In contrast, MM patients with better outcomes displayed expanding naïve and central memory CD8+ T cell subsets. This could be in part due to observed differential signaling of BAFF by IFN-I-stimulated monocytes and APRIL by IFN-II-stimulated monocytes. Finally, we assessed if incorporating various cell abundance signatures could improve risk stratification over prevailing cytogenetic risk models using a bootstrap validation approach. Incorporating cell abundance signatures resulting in an increase in model AUC from 0.73 with only demographic and cytogenetic metrics, to 0.81 when adding the top 11 predictive cell clusters, to 0.96 using all immune clusters. **Conclusions:** Profiling the BMME of NDMM patients revealed dysregulated T cells and myeloid subpopulations associated with patient risk and disease progression. Key signaling pathways, namely IFN, APRIL, and BAFF, appear to drive these outcome-associated populations. Integrating these findings with cytogenetics and clinical characteristics improved the prediction of PFS. Collectively, this work underscores the importance of capturing the BMME as a prognostic marker for MM and may allow for rational optimization of treatment regimens.

OA-23

Differential Immunophenotypic and Genetic Landscapes of High-Risk and Standard-Risk Multiple Myeloma Patients

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Introduction: Specific cytogenetic abnormalities and copy number alterations are associated with high-risk (HR) for poor outcome in multiple myeloma (MM) patients. Immune therapies such as monoclonal antibodies and T cell redirection agents are a predominant theme in myeloma. Therefore, understanding the distinct immunophenotypic and genetic landscapes of HR and standard-risk (SR) MM patients is crucial for developing rationally designed therapeutic strategies and improving clinical outcomes. **Methods:** This study included 79 MM patients, comprising 54 HR and 25 SR cases. HR status was determined by the presence of translocations t(4;14), t(14;16), t(14;20), deletion of chromosome 17 (del17p), and gain/amplification of 1q (1q++/++). Both CD138-negative and CD138-positive fractions from the bone marrow of MM patients who had received 1-3 lines of therapy, including immunomodulatory drugs (IMiDs), were analyzed. The bone marrow microenvironment, focusing on immune cell populations and their functional states, was investigated using Mass Cytometry and single-cell RNA sequencing. Whole-exome sequencing (WES) was used for the analysis of CD138-positive fractions (MM cells). **Results:** The bone marrow microenvironment in HR MM exhibited

hallmarks of an activated and inflammatory state. Highly cytolytic CD4+ and CD8+ T cell subsets were prominent, alongside a distinct population of pre-dysfunctional GZMK+ CD8+ T cells, indicative of T cell exhaustion. Elevated frequencies of CD14+ monocytes, mast cells, and plasmacytoid dendritic cells further contributed to the inflammatory milieu. Notably, a subset of HR patients displayed prominent expression of interferon-stimulated genes (ISGs) (IFI6, IFI44L, OAS1, IFIT3, OASL, IFITM1, and IFITM3) in T cells and monocytes, independent of mutational status. This inflammatory landscape likely drives therapy resistance and disease progression in HR MM. Conversely, SR MM exhibited an immunosuppressive microenvironment dominated by naïve T cells and increased regulatory T cells (Tregs) with a strong Treg gene signature. Whole exome sequencing analysis showed no significant difference in single nucleotide variants within the RTK-RAS or cell cycle signaling pathways between SR and HR patients. However, TP53 mutations were exclusively observed in the HR group, affecting 23% of these patients. **Conclusions:** The distinct immunophenotypic and genetic landscapes between HR and SR MM patients have significant implications for disease progression and therapy resistance. HR MM patients exhibit a more activated and inflammatory bone marrow microenvironment, suggesting the need for targeted therapeutic interventions to enhance therapeutic efficacy. Additionally, TP53 mutations were exclusively found in HR patients, underscoring the importance of genetic profiling to refine risk stratification. Future research should focus on developing strategies to modulate the immune microenvironment in HR MM to improve outcomes.

OA-24

A Novel Mouse Model Engineered With Human Immune System Is a Translationally-Important Model for Studies Related to Immune-Microenvironment and Immunotherapies in Multiple Myeloma

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Introduction: Despite great efficacy observed in many preclinical in vivo models in multiple myeloma (MM), they are not mostly recapitulated in patients. The mouse models widely used for MM studies do not mimic the immunology in patients that allows a translationally relevant setting to interrogate MM biology associated with immune-microenvironment and immunotherapies. Previous immunocompetent models comprise of host immune system, which evidently differ from humans'. There is therefore an unmet need for a model that simulate human immune system for effective translational research. Here, we generated an immunocompetent mouse model humanized with human immune system (humice), interrogated its efficacy for MM engraftment and elucidated the molecular profile in this model vs. in the conventional NSG. **Methods:** Irradiated NSG pups were transplanted with fetal HSC to develop mature human immune system. Humice/NSG were engrafted with U266-Luc-GFP via tail vein. Bone marrow (BM) and liver (Liv) tumors were harvested at endpoint and processed for scRNA-seq. Molecular profiling was performed to compare: (a) tumors in humice vs NSG (b) tumors isolated from BM vs Liv. **Results:** While MM engraftment in NSG was expected, we observed that MM could also propagate efficiently in humice, at a rate significantly higher than in NSG, suggesting the role of human immune system in promoting MM growth and progression. At single cell level, transcriptomic clusters unique only for humice(Hu) had an enrichment of immune, defense and cytokine signaling, including important MM signature such as IL6-JAK-STAT and NFKB pathways, whilst, for NSG, transcriptional and chromatin activities predominated, suggesting that growth mechanisms in humice resembled the typical MM pathogenesis, whereas in NSG, epigenetic reorganization may be necessary to promote growth in a foreign microenvironment. Interestingly, apparent DEG also existed between tumors deriving from different compartments within the same animal group. HuBM showed upregulated Wnt signaling and resistance to apoptosis over HuLiv while NSGBM exhibited increased cell cycle and DNA replication processes over NSGLiv, implying that the transcriptomic heterogeneity in MM tumors may drive spatial diversity. Several genes were strikingly enriched in humice; most are cytokines or players of innate immunity, including CXCL9, CXCL10, STAT1 and IRF1 and importantly, they were all associated with poor survival in CoMMpass patients. Lastly, we observed that lenalidomide treatment in humice was efficacious. **Conclusions:** We showed differential growth profile and molecular alterations of MM cells populated in the presence vs. absence of human immune system, suggesting niche-specific mechanisms. We also provided proof-of-concept that humice responded well to an IMiD. Our model, therefore, provides an exciting tool for translationally-effective studies on functional interaction of MM with immune microenvironment and their complexity in responses to therapy involving the immune system.

OA-25

Impact of Clonal Hematopoiesis on the Carcinogenic Process of Multiple Myeloma

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Introduction: Clonal hematopoiesis (CH), an age-related phenomenon, is associated with the development of myeloid malignancies. Here, we explore the interaction of CH with terminally differentiated lymphoid malignancy, multiple myeloma (MM). **Methods:** Blood samples from MM patients (n = 194) at the time of diagnosis are sequenced for CH detection and compared with samples from a healthy population. UK Biobank data are analyzed over time for MM development according to CH status for validation. In vitro studies using a TET2 knock-out cell line are conducted to confirm functional consequences. Single-cell RNA sequencing and exosome RNA sequencing data are generated and analyzed to uncover underlying mechanisms. **Results:** Of the 194 patients, 79 (40.7%) harbor CH, significantly higher than the prevalence in the healthy population after adjusting for age and gender, with TET2 CH showing the most significant association among major CHs (odds ratio (OR): 3.4, $p < 0.001$). Patients with CH exhibit a lesser deep response to proteasome inhibitor-containing induction therapy (34.2% for CH patients vs. 74.5% for non-CH patients, $p < 0.001$). In UK Biobank analysis, CH carriers show increased risk with hazard ratio (HR) of 1.53 for MM development (95% confidence interval (CI): 1.15-2.0, $p = 0.003$), with TET2 displaying the most pronounced effect on MM risk (HR: 1.64, 95% CI: 1.01-2.7, $p < 0.047$). Single-cell transcriptomic data suggest that CH cells in the bone marrow frequently interact with MM cells through CCR10-CCL2, resulting in upregulation of the MAPK pathway and angiogenesis, findings supported by exosome RNA analysis. Conditioned media from TET2 knockdown macrophages significantly enhances MM cell proliferation compared to that from wild-type cells, an effect that could be reversed by an inhibitor for C-C chemokine receptor type 10 (CCR10) inhibitor. **Conclusions:** Here we show, CH is enriched in MM patients and is associated with therapy resistance. Particularly, TET2 CH plays a crucial role in CCR10-high myeloma progression through paracrine oncologic effects via exosomal interactions on CCR10, suggesting it may be a potential therapeutic target.

OA-26

Single Cell Whole Genome Measurement of Genomic Heterogeneity and Clonal Evolution in Multiple Myeloma

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Introduction: Bulk sequencing studies in multiple myeloma (MM) have defined key genomic processes contributing to development including single base substitution (SBS) signatures and complex structural variants (SV). However, they have limited sensitivity to define high-risk subclonal events which may lead to progression from precursor states to MM, or to relapse post-therapy. **Methods:** We applied single cell whole genome sequencing (scWGS) using direct library preparation (DLP+) to CD138+ plasma cells from the bone marrow of 14 patients with MM and precursor disease. Using new computational approaches, we characterized the single nucleotide variants (SNVs), copy number (CN) changes and complex SVs at a single cell (sc) level; reconstructing individualized evolutionary trajectories. For 8 patients we compared with bulk WGS on the same tumor sample, for the remainder with FISH and SNP-array. **Results:** We obtained 800-1600 scWG per patient, with all canonical IgH translocations identified by FISH recovered in the scWGS data. CN heterogeneity at the sc level was observed in all but 1; harboring t(11;14) with a simple genome. CN heterogeneity affected known MM genomic drivers, including convergent loss on 16q in multiple subclones, a complex amplification at TNFRSF17/BCMA and deletion in 8q bringing MYC next to a superenhancer. The number of subclones ranged from 1 to 21, with an average of 6 subclones per patient. This is in striking contrast with bulk WGS where we define no more than 1-2 subclones. Hyperdiploidy (HRD) was clonal in most patients when present, however HDR clones accrued additional events including both focal gains and deletions after the gains. 1 sample contained a major clone harboring t(14;20) and gain1q, together with a small HDR clone, suggesting separate populations with distinct underlying biological trajectories (i.e. MM and MGUS). Gain1q (3 copies) was observed as a clonal event in 8 samples, subclonal in 4 and absent in 2, with 2 patients exhibiting convergent subclonal amp1q (>3 copies). This was validated in a dataset of scWGS pre/post- T-cell redirecting therapy (Lee et al. Nature Med 2023), where either clonal or subclonal gain1q was detected 11/12 samples.SBS-signature analysis revealed APOBEC activity in some patients across distinct subclones, consistent with ongoing APOBEC mutagenesis, while in others APOBEC activity was restricted to individual subclones and not evident at the bulk WGS level. Considering a validation cohort of 421 bulk WGS, where we observe APOBEC- activity in 90% of patients, we propose that some degree of APOBEC activity is highly prevalent in MM pathogenesis. **Conclusions:** scWGS in MM reveals significant clonal heterogeneity, with multiple distinct clones exhibiting diverse genetic alterations. These findings underscore the genomic complexity and dynamic nature of MM; highlighting the capacity of highly sensitive scWGS to define the chronological order of genomic aberration and define high-risk subclones which may cause subsequent progression.

OA-27

Para-Medullary (PMD) and Extra-Medullary (EMD) Myeloma Demonstrate Increased Copy Number Aberration, Mutational Burden, Structural Variants and Genomic Complexity Compared to Marrow-Based Myeloma

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Introduction: Growth beyond the bone marrow (BM) represents clinically aggressive myeloma and is associated with inferior therapy response. We describe the largest PMD/EMD cohort to date, with comprehensive genomic characterization from combining SNP-array, extended targeted sequencing (MSK-IMPACT-Heme) and whole genome sequencing (WGS) data. **Methods:** We examined all available in-house PMD/EMD samples, comparing with paired BM where available, with our published WGS from NDMM BM (Maura et al. Nature Cancer 2023) and with WGS from PMD/EMD collected during autopsy (Landau et al. Nat Comm 2020). WGS data were processed via Isabl, MSK-IMPACT-Heme via cBioPortal, SNP-array by clinical pathology, all using in-house validated pipelines. **Results:** 148 plasmacytoma samples were assessed; 99 PMD, 49 EMD, with 53 pre-therapy and 95 post-therapy. 48 patients had paired BM samples (28 coincident and 23 distant in time), with 11 patients having > 1 PMD/EMD biopsy. Including our previously published data, the cohort comprised 258 samples from 176 patients: 105 WGS, 133 MSK-IMPACT-Heme, and 20 SNP-array. Within both the whole cohort and samples with paired BM, PMD/EMD had considerably more copy number aberration (CNA) than BM. GISTIC analysis for significant CNA detailed broad gains affecting 1q, 8q (MYC), 20p and 20q, with focal gains at 1q21, 6p25 and 18q21. Broad deletions affected 4p, 8p and 17p (TP53), and numerous focal deletions were detailed. Notably, gain/amp1q was observed in 78% of EMD overall, and in 83% of post-therapy EMD samples. Prevalent mutations in PMD/EMD affected KRAS, NRAS, and TP53, with KRAS being enriched in PMD (36%), while EMD was enriched for NRAS (38%) and TP53 (31%). Dndscv analysis revealed multiple genes to be positively selected as driver events, including epigenetic modifiers (KMT2A, KMT2C, TET2, SMARCA4), immune response (PRMD1, LTB), proliferation (STAT3, NF1, BTG1), adhesion (FAT1), and DNA-damage response (TP53, ATM, BRCA2).Paired BM-PMD/EMD showed 2 patterns; some had increased mutational burden, while others had retained mutations but increased CNA. Within those with > 1 PMD/EMD sample, diverging clones were defined by a variety of mutations (including KRAS, TP53, STAT3, IGF1R, DNMT3A), CNA affecting multiple chromosomes (including 8q; MYC, 17p; TP53), noncanonical translocations, and CNA consistent with chromothripsis. In the WGS data, we noted spatial divergence in mutational signature contribution and the emergence of complex structural variants. Several melphalan-exposed patients had SBS99 evident in the phylogenetic tree trunk of multiple biopsies, consistent with single cells surviving transplant and subsequently seeding in multiple sites. **Conclusions:** PMD and EMD demonstrate multiple features of genomic complexity when compared with BM-based myeloma, including emerging copy number aberration, mutational burden, and complex structural variants. Ongoing studies include expanding the WGS dataset, and correlation of genomic features with clinical response to therapy.

OA-28

MM Progression and Evolution of Refractory Disease Explained by Integrative Multiomics in Moffitt Cancer Center's Patient Cohort

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Introduction: We present Moffitt's MM cohort, consisting of 1,005 patients with 1,627 bone marrow biopsies with RNA-seq/WES data, including precursor stages (MGUS/SMOL,16%), therapy naïve (18%) and relapsed disease (66%). We have applied an integrative approach to identify mechanisms driving progression and emergence of multi-drug resistance. **Methods:** In addition to multivariate analysis on mutations, cytogenetic abnormalities and transcriptomic pathways associated with progression and refractory disease, we have conducted dNdS analysis to identify low-frequency mutated genes with imbalance between synonymous and non-synonymous mutations. Dimensionality reduction and clustering analysis recreated a transcriptional topology of MM. Geneset enrichment analysis identified biology associated with MM progression and refractory disease, as well as putative mechanisms driving aforementioned transcriptional dysregulation. Furthermore, we have conducted sc-multiomics in healthy donor plasma cells, primary MM cells from MGUS to refractory disease, as well as H3K27ac /CUT&TAG. shRNA-silencing of YY1, one of the identified putative drivers of multidrug resistance, in MM cell lines demonstrated in vitro re-sensitization to proteasome inhibitors (PI). **Results:** In addition to previously identified MM frequently mutated genes (e.g. KRAS, NRAS, DIS3, etc.) dNdS analysis identified new loss of function (e.g. SUZ12, etc.) and gain-of-function mutated genes. Transcriptional topology consisted of two mega-clusters of co-expressing genes (beta and alpha). Beta contained the hallmarks EMT, inflammatory response, TNFalpha signaling via NFkB, IL6/STAT3 signaling, apical junction, etc., and was under-expressed

in the transition from MGUS to SMOL. Alpha overlapped with hallmarks of oxidative phosphorylation, G2M checkpoint, MYC/E2F targets, etc. and was over-expressed in the transition from therapy naïve to refractory disease. Interestingly, no significant difference was observed in transcriptome between SMOL and therapy naïve MM. Enrichment analysis suggested that transcription of genes in beta and alpha were epigenetically regulated by H3K27me3 and H3K27ac, respectively. ScATAC/RNA-seq demonstrated correlation between differential expression and chromatin accessibility of genes from beta in precursor state transition (MGUS- >SMOL). CUT&TAG analysis confirmed H3K27ac signal in alpha genes, but not beta, as well as correlation between gene expression and H3K27ac signal. Genes in regular and super-enhancers in refractory disease, and genes involved in transcriptional activation domains (e.g. BRD4, CDK9, CTCF, and YY1) were over-expressed compared to therapy naïve MM. Functional validation by silencing YY1 in human MM cell line 8226 and a PI resistant lineage, led to re-sensitization of the latter. **Conclusions:** We demonstrate that MM progression and refractory disease are driven by a multifactorial dynamic, with multiple initiating genomic events causing genome-wide epigenetic and transcriptomic dysregulation.

OA-29

Mezigdomide (MEZI), Tazemetostat (TAZ), and Dexamethasone (DEX) in Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM): Preliminary Results From the CA057-003 Trial

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Introduction: The CA057-003 phase 1/2 trial (NCT05372354) is evaluating oral, novel-novel targeted triplet combinations using a MEZI+DEX backbone in pts with RRMM refractory to, intolerant to, or not candidates for established MM therapies. The third agent in each combination intervenes on a key oncogenic pathway upregulated in RRMM: 1) EZH2 inhibitor TAZ for PRC2 complex dysregulation; 2) BET inhibitor BMS-986158 for CKS1B (on chromosome 1q) amplification; 3) or MEK inhibitor trametinib for RAS-RAF-MEK-ERK activation. Here we report results from the dose-finding cohort of MEZI+TAZ+DEX in RRMM. **Methods:** Eligible pts had RRMM with progressive disease (PD) during or after the last regimen, ECOG PS score ≤1, absolute neutrophil count ≥1000/μL, and estimated glomerular filtration rate ≥45 mL/min/1.73 m2. Oral MEZI was given at 3 escalating doses (0.3, 0.6, and 1mg) on days (D) 1–21 of each 28-day cycle with oral TAZ (800mg) twice daily on D1–28 and weekly oral DEX (40mg; 20mg if ≥75 y of age). Primary objectives are to define the RP2D and dosing schedule, and to evaluate safety; secondary objectives are to assess efficacy and pharmacokinetics. **Results:** As of April 5, 2024, 13 pts received MEZI+TAZ+DEX (3 pts 0.3mg; 3 pts 0.6mg; 7 pts 1.0mg). Median (range) age was 67 (51–80) y and median time since initial diagnosis was 8.3 (2.4–13.3) y. Extramedullary plasmacytomas were present in 6 (46.2%) pts. Median number of prior regimens was 5 (3–14), 10 (76.9%) pts had triple-class refractory MM, and 9 (69.2%) had prior T-cell–redirecting therapy. Six (46.2%) pts continued treatment; 5 pts discontinued due to PD, 1 due to physician's decision, and 1 due to an adverse event (AE). Median number of cycles received was 4 (2–9). Median follow-up was 4.2 (1.6–9.2) mo; median MEZI treatment duration was 4.1 (1.6–8.5) mo. Grade (Gr) 3/4 treatment-emergent AEs (TEAEs) occurred in 9 (69.2%) pts; the most common hematologic TEAEs were neutropenia (46.2%) and anemia (15.4%). Most common (reported in >1 pt) non-hematologic Gr 3/4 TEAEs included infections (15.4%) and dyspnea (15.4%). No dose-limiting toxicities were observed. No TEAEs led to MEZI dose reduction or discontinuation. One pt died on study due to pulmonary sepsis. Overall response rate was 53.8% (95% CI, 25.1–80.8) with 1 stringent complete response, 2 very good partial responses, and 4 partial responses; median time to response was 0.95 (0.9–3.0) mo. There were responses among pts who had T-cell–redirecting therapies as their last line and deeper responses were observed at the highest MEZI dose. MEZI exposure increased in a more than dose-linear manner over the dose range. Coadministration of MEZI and TAZ did not alter MEZI exposure. MEZI remained pharmacodynamically active, inducing Ikaros/Aiolos degradation and B-cell reduction with TAZ at all dose levels (greatest effect observed at MEZI 1.0mg). **Conclusions:** MEZI+TAZ+DEX showed promising preliminary efficacy and safety in pts with RRMM, with no new safety concerns. Previously presented at EHA 2024.

OA-30

Phase 1 Study Of Anitocabtagene Autoleucel For The Treatment Of Patients With Relapsed And/Or Refractory Multiple Myeloma: Results From At Least 1-year Follow-up In All Patients

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Introduction: Anitocabtagene autoleucel (anito-cel, formerly CART-ddBCMA) is an autologous D-Domain BCMA-directed chimeric antigen receptor (CAR) T-cell therapy being studied in relapsed and/or refractory multiple myeloma (RRMM). **Methods:** Details of study have been previously reported (Frigault et al Blood Adv 2023). Patients (pts) with RRMM who had received ≥3 prior lines of therapy received a single infusion of anito-cel following lymphodepletion chemotherapy. Two doses (DL1 & DL2, respectively) of 100 and 300 (±20%) × 106 CAR+ cells were evaluated. The primary endpoints were incidence of adverse events and dose-limiting toxicities. Additional endpoints included quality & duration of clinical response assessed according to the IMWG Uniform Response Criteria for MM, evaluation of minimal residual disease (MRD), progression-free (PFS) & overall survival (OS). **Results:** At a median follow-up 26.5 months (range: 14 – 44), 40 pts (median age 66 years, range: 44-76) were enrolled and 38 received anito-cel (32, DL1; 6, DL2). Two pts not dosed had cell product manufactured but were not eligible for infusion due to medical complications. Pts had a median of 4 (range: 3-16) prior lines of therapy. All infused pts (100%) were triple-refractory, 26 (68%) were penta-refractory, 34 (89%) were refractory to last-line of treatment; 9 (24%) had high tumor burden, 13 (34%) had extramedullary disease, & 11 (29%) had high-risk cytogenetics (Del 17p, t(14;16), t(4;14)). CRS occurred in 36/38 (95%) pts; 1 pt in DL2 had grade (Gr) 3 CRS & all other cases were Gr≤2. ICANS occurred in 7 pts (5, Gr≤2; 2, Gr3), with 1 Gr3 case in each DL. All cases of CRS & ICANS resolved with management and without sequalae. No delayed neurotoxicities were observed through the follow-up period. All 38 pts demonstrated investigator-assessed response per 2016 IMWG criteria (ORR, 100%) with 22 sCR & 7 CR (≥CR rate, 76%), 6 VGPR (≥VGPR rate, 92%), & 3 PR. Conversions to sCR occurred from 1 to >12 months. Of those evaluable for MRD testing to date (n=28), 25 (89%) were MRD-neg at 10-5. Median duration of response, PFS, & OS were not reached; Kaplan-Meier estimated PFS rates for 6, 12, 18 & 24 months were 92%, 76%, 64%, and 56%, respectively. Durable responses in patients with high-risk features (EMD, BMPC ≥ 60%, or B2M ≥ 5.5mg/L), age >65 years, and high-risk cytogenetics were consistent with the overall study population. A dose of 115 ± 10 × 106 CAR+ cells was recommended for the ongoing phase 2 study, iMMagine-1. **Conclusions:** Adverse events with anito-cel, including CRS & ICANS, were manageable; no off-tumor tissue-targeted toxicity, delayed neurotoxicity nor Parkinsonian-like events were observed at time of data-cut. Efficacy analyses demonstrated 100% ORR, including 92% with VGPR or better & 76% with CR/sCR. Clinical responses were durable with an overall estimated 24-mo PFS rate of 56% with comparable responses seen in pts with 'high-risk' disease characteristics.

OA-31

TRIM28 Functions as a Key Protein Homeostasis Regulator and Mediates Proteasome Inhibitor Resistance in MM

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Introduction: The intracellular protein homeostasis represents a key biological process essential for the survival of multiple myeloma (MM) cells. Tripartite motif (TRIM) proteins are defined as a subfamily of the RING-type E3 ubiquitin ligase family and play key roles in protein quality control. Here, we investigated the function of TRIM28, a member of TRIM family, as a protein homeostasis regulator in MM. **Methods:** Bioinformatic analysis was used to clarify the correlation between TRIM28 with genes related to proteasome and autophagy mediated protein degradation pathway. shRNA knock-down (KD) and over-expression (OE) experiments were used to investigate the function of TRIM28. ChIP-seq and IP-MS were examined to clarify the potential downstream target of TRIM28. **Results:** Survival analysis revealed that the MM patients have poor outcome with high level of TRIM28 in MMRF-CoMMpass and in-house datasets, which were in the context of treatment with bortezomib. Bioinformatic analysis revealed a robust correlation between TRIM28 expression and the expression of proteasome subunits and autophagy-related genes in MM datasets. RNA-seq data showed that both the proteasome pathway and autophagy pathway were down-regulated after TRIM28 KD. TRIM28 KD led to significant decrease in chymotrypsin-like, caspase-like, and trypsin-like proteasome activities, along with ubiquitinated proteins accumulation. Meanwhile, we observed a decrease in autophagosome formation in TRIM28 KD cells, suggesting that TRIM28 activates autophagy. These results underscore TRIM28's critical function in maintaining protein homeostasis by regulating both proteasome and autophagy pathways. ChIP-seq and IP/MS analyses were employed to delve into TRIM28's mechanism in maintaining protein homeostasis. ChIP-seq showed TRIM28 binding to proteasome gene promoters (e.g., PSMB1, PSMD2, PSMD4), with its knockdown reducing proteasome subunit expression. This implies the role of TRIM28 in transcriptionally activating multiple proteasome genes. IP-MS and Co-IP assay demonstrated that TRIM28 interacts with 14-3-3ζ, a well-known negative regulator of autophagy. We observed a significant decrease in the polyubiquitination level of 14-3-3ζ in TRIM28 KD cells. TRIM28, acting as an E3 ligase, promoted ubiquitin-dependent degradation of 14-3-3ζ, thus enhancing autophagy in MM. The role of TRIM28 on MM cell sensitivity to proteasome inhibitors (PIs) was investigated due to its role in protein homeostasis. The results revealed that TRIM28 OE led to a notable reduction in the sensitivity of MM cells to bortezomib both in vitro and in vivo. In addition to protein homeostasis regulation,

TRIM28 could regulate cell proliferation, apoptosis and cell cycle in MM, indicating that TRIM28 plays a multifaceted role in MM. **Conclusions:** Our study provided novel important insights into the key role of TRIM28 in maintain protein homeostasis in MM. TRIM28 triggers activation of proteasome and autophagy pathway, which represents a promising therapeutic target in MM.

OA-32

p300 Catalytic Inhibition Selectively Disrupts IRF4 Oncogenic Programs Impacting Multiple Myeloma Cell Growth and Survival

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Introduction: Multiple myeloma (MM) is characterized by a non-oncogene addiction to the plasma cell lineage factor IRF4, making it a high-value therapeutic target. Using a transcription regulatory network (TRN)-based approach, we here defined the key regulatory activity of IRF4 and its druggable co-factors. This analysis identified lysine acetyl transferase (KAT) function of p300 as the nearest selective neighbor for therapeutic intervention whose deletion mirrors IRF4 deletion. Protein interactome analysis in MM cells revealed direct interaction between IRF4, p300 and key MM transcription factors; and a significant overlap between IRF4 interactome and p300 acetylation substrates. Furthermore, IRF4 and p300 colocalized significantly across the genome at important MM regulatory elements. These data confirmed the existence of an IRF4-p300 convergent functional network in MM cells, that can be perturbed for therapeutic purposes. **Methods:** Since TRN analysis suggested a more potent and potentially selective effect of p300/CBP KAT inhibition than historically observed with p300/CBP bromodomain inhibitors, we developed KB528, a highly selective KAT domain inhibitor of p300 and its close homolog CBP. We investigated its activity in vitro in MM cell lines and ex vivo in bone marrow mononuclear cells (BMMNCs) obtained from bone marrow aspirates of MM patients using luminescence- and flow cytometry-based assays; and in vivo in xenograft MM mouse models. Transcriptomic and epigenomic changes after treatment were evaluated by RNA-seq and ChIP-seq analysis respectively. **Results:** Treatment of MM cells with KB528 downregulated IRF4 mRNA and protein levels; and caused a reduction in chromatin acetylation at highly specific sites in the genome co-localized with IRF4, in contrast to broader agents like BET bromodomain inhibitors, as well as a disruption of the IRF4 transcriptomic signature. Furthermore, KB528 had a strong antiproliferative effect in MM cell lines, regardless of their cytogenetics or drug sensitivity profile, by downregulating the IRF4 TRN and inducing apoptosis more effectively than p300/CBP bromodomain inhibitors. Ex vivo treatment of BMMNCs of MM patients with stable (n=6) or relapsed-refractory (n=6) disease confirmed induction of apoptotic cell death on CD138+ primary MM cells, while sparing CD138-negative cells, supporting a therapeutic index. Since most successful regimens in MM therapy are combinatorial, we evaluated the activity of KB528 in combination with existing SOC agents and observed synergistic activity in combination with IMiDs and dexamethasone. Finally, KB528 demonstrated activity in vivo, with robust tumor growth inhibition at tolerated doses, together with reduced p300-dependent substrate acetylation and loss of IRF4. **Conclusions:** IRF4 dependency is a hallmark of MM that has been challenging to target with existing therapies and this study lays the groundwork for developing p300 KAT inhibitors for MM therapy.

OA-33

LILRB4 Is a Promising Dual Target for Tumor Cells and Immunosuppressive Myeloid Cells in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is still an incurable disease. Some high-risk patients experience rapid disease progression with short survival even in the context of active treatment. Our study aimed to identify novel treatment targets to improve the survival for these high-risk patients. **Methods:** We previously utilized single-cell transcriptomic sequencing to dissect the bone marrow niche of patients with survival less than two years. Bioinformatic analysis and biological experiments were performed to investigate the applicability of targeting LILRB4 in MM. **Results:** An enrichment of CD38+CD138lowLILRB4+ pre-matured plasma-cell cluster was observed in the patients with short survival compared with patients with durable remission. This pre-matured aggressive plasma-cell cluster displayed high expression of proliferating and drug-resistance related genes, complex chromosomal aberrancies and mutation burden. Importantly, MM patients with a higher proportion of this plasma-cell cluster often had inferior outcomes. LILRB4 was the most specifically highly expressed gene within this cluster. High expression of LILRB4 was correlated with short survival of MM patients (GSE2658; P< 0.0001). We found that the expression of LILRB4 was increased in the post-treatment residual MM cells. Consistently, LILRB4 expression was further increased in MM cells from relapse and refractory patients compared with newly-diagnosed patients. Additionally, we underscored the mechanisms underlying

the high expression of LILRB4 in MM cells. ATAC-seq analysis showed that MM cells with high level of LILRB4 retained higher chromosomal accessibility in LILRB4 promoter region. Gain-of-function studies in MM cell lines demonstrated that overexpression of LILRB4 could promote the tumor growth, clonogenicity, drug-resistance to proteosome inhibitor, and invasion ability of MM cells; the opposite effect occurred in LILRB4-deleted MM cell lines. The tumor-promoting effects could also be observed in xenograft NOD/SCID mice model by injecting LILRB4-overexpressed MM cell lines subcutaneously. Deletion of LILRB4 significantly suppressed the tumor growth in vivo as well. Additionally, MDSCs in MM patients expressed high level of LILRB4. Hence, we generated LILRB4-targeted synthetic T cell receptor and antigen receptor (STAR)-T cells. LILRB4 STAR-T cells showed strong cytotoxicity against MM cell lines in vitro and in vivo. Furthermore, LILRB4 STAR-T cells exhibited high cytotoxic activity against CD38+CD138lowLILRB4+ tumor cells and CD11b+LILRB4+ M-MDSCs. **Conclusions:** We demonstrated that LILRB4 played critical roles in promoting tumor growth and inducing the generation of immunosuppressive MDSCs. LILRB4 STAR-T cells performed good cytotoxicity towards both tumor cells and immunosuppressive myeloid cells. LILRB4-targeted immunotherapy might offer alternative promising options for these high-risk MM patients.

OA-34

HBI0101, an Anti-BCMA Chimeric Antigen Receptor T-Cell (CART) for Relapsed/Refractory Multiple Myeloma

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Introduction: Although anti-B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CART) therapy proved unprecedented efficacy in patients with relapsed/refractory (R/R) multiple myeloma (MM), its availability remains limited. HBI0101 is a novel second generation optimized anti-BCMA CART, that was developed in an academic setting. The phase I study evaluating HBI0101 (NCT04720313) demonstrated manageable safety and high efficacy. Here we present the updated results for the patients who received the recommended phase II target dose (RP2D) of 800x10^6 CART cells. **Methods:** The patients enrolled had R/R MM with at least 3 prior lines of therapy, including a PI, IMiD and anti CD38 antibody. Inclusion criteria were relatively permissive as compared with other CART clinical trials, including thresholds of 30x109/ml platelets, creatinine clearance of 20ml/min and performance status of < 2 by ECOG scale. **Results:** 84 patients with a median of 4 prior lines (range 3-13) were infused with the RP2D, most (73/84, 87%) were triple refractory, 32/84 (38%) were penta-refractory and 14/84 (17%) had received prior anti-BCMA therapy. 22/84 (26%) had extra-medullary disease, 33 of 81 (41%) had high-risk cytogenetics (t(4:14)/t(14:16)/del17), and 61/81 (75%) including 1Q gain. Of note: 48% would not have met the inclusion criteria for the registrational trials of approved anti-BCMA CART therapy. The overall response rate and complete response (CR)/stringent CR rates were 77/84 (92%) and 46/84 (55%), respectively, with 62/84 (74%) achieving minimal residual disease negativity at day +30. With a median follow-up of 12 months (range 4-30), the median progression-free survival was 11.6 months (95% CI: 8.6-14.6) and the median overall survival was not reached (NR) (95% CI: 19.6-NR). Safety was manageable with grade 3-4 hematological toxicities common (anemia -62%, thrombocytopenia- 42%, neutropenia-99%). Cytokine release syndrome (CRS) occurred in 80/84 (95%), including 16 patients with grade 3 CRS (19%), but no cases of grade 4/5. Neurological toxicity was rare and mild (3 cases, all of grade 1-2). No irreversible organ toxicities or treatment related deaths occurred. **Conclusions:** HBI0101 BCMA CART results demonstrate the high efficacy and manageable safety in a frailer and higher risk population as compared with the registrational studies of commercial products. This data not only support further utilization of HBI0101 CART therapy, but also supports CART production at an academic setting in general, ensuring a sufficient CART supply in the light of the increasing demand.

OA-35

Discovery of a Novel Class MMSET Inhibitor With Specificity for t(4; 14)-Positive Multiple Myeloma

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Introduction: The prognosis for multiple myeloma (MM) has continued to improve with the development of a series of novel molecular targeted drugs over time. However, the prognosis remains poor for cases with high-risk chromosomal abnormalities. Of such abnormalities, t(4;14) is the second most common, occurring in 15%

of patients with MM. MM cells carrying t(4;14) strongly express histone methyltransferase with a SET domain, called MMSET, making them resistant to key drugs against MM. Thus, MMSET is an effective therapeutic target for MM carrying t(4;14). However, most reports on MMSET inhibitors described the biochemical inhibitory effects and only a few were evaluated at the cellular level. **Methods:** In this study, we performed high-throughput screening for MMSET inhibitors against 56,291 compounds using small molecule compound libraries derived from RIKEN NPDepo, DMP, FBDD, Todai Core, and commercially available compounds predicted using an in silico model. Then, we identified RK-0080552 (RK-552) as a novel class and specific MMSET inhibitor. **Results:** RK-552 was significantly cytotoxic to t(4;14)-positive MM cells compared to t(4;14)-negative MM cells in vitro via MMSET inhibition at clinically relevant concentrations. RK-552 reduced the expression of major MM growth and survival factors, such as ATM, CCND2, HIF1A, IRF4, and STAT3. Of these, RT-PCR analyses revealed a significant down-regulation of IRF4 expression in the four MM cell lines carrying t(4;14). A global ChIP-seq analysis revealed that RK-552 decreased H3K36 methylation at the whole-genome level. Furthermore, methylation of H3K36 decreased through the entire range of the IRF4 gene and mainly acted in the intron region, suggesting that hypomethylation of H3K36 mediated IRF4 down-regulation via inhibition of transcriptional elongation. The forced expression of IRF4 significantly mitigated the cytotoxicity of RK-552. These results suggest that IRF4 is a bona fide target of RK-552 in MM cells carrying t(4;14) via MMSET inhibition. Next, we conducted an investigation into therapeutic effects in vivo using a xenograft murine model. Then, RK-552 inhibited the tumor growth of MM cells carrying t(4;14) in vivo via the down-regulation of IRF4 caused by the hypomethylation of H3K36. Moreover, RK-552 acted additively with pomalidomide in vitro and prolonged the survival of recipient mice without side effects. **Conclusions:** These results suggest that RK-552 is a novel class and clinically relevant MMSET inhibitor with safety and specific cytotoxicity to MM cells carrying t(4;14). Our study also provides a molecular basis and rationale for the inclusion of RK-552 in treatment strategies for MM with t(4;14). The clinical application of RK-552 may significantly improve the treatment outcome of MM with t(4;14).

OA-36

METTL14 Enhances Multiple Myeloma Progression via m6A RNA Methylation-Mediated Regulation of TRAF6 Translation

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Introduction: N6-methyladenosine (m6A) modification is critical in the pathogenesis and progression of multiple myeloma (MM). METTL14, a key component of the m6A methyltransferase complex, has not previously been explored in MM. This study aims to uncover the biological function and molecular mechanism of METTL14 in MM. **Methods:** We analyzed METTL14 expression in MM patients through bioinformatics, qRT-PCR, Western blot, and immunohistochemistry. To investigate METTL14's biological functions in MM, we developed lentiviral stable cell lines with METTL14 knockdown or overexpression. We assessed MM cell phenotypic changes using CCK-8, Transwell and angiogenesis assays. Initial bioinformatics analyses revealed a significant enrichment of H3K27ac at the METTL14 promoter and a robust correlation between the expressions of the acetyltransferase P300 and METTL14 in MM. Consequently, we created lentiviral stable cell lines with P300 knockdown to investigate P300's regulatory effects on METTL14 using ChIP-qPCR, qRT-PCR, and Western blot. Advanced molecular techniques, including MeRIP-seq, RIP-qPCR, RNA pulldown, and polysome profiling, were employed to identify downstream target genes and elucidate the molecular mechanisms regulated by METTL14. A subcutaneous tumor model in NOD/SCID mice was utilized to validate METTL14's role in MM pathogenesis and progression. **Results:** METTL14 was significantly overexpressed in MM. Survival analyses revealed that patients with elevated METTL14 expression had markedly shorter PFS and OS. Further analysis demonstrated a positive correlation between METTL14 expression levels and both the ISS and R-ISS staging. These findings indicate a strong association between METTL14 expression and both disease progression and adverse prognosis in MM. Functional assays showed that silencing METTL14 significantly inhibited MM cell proliferation, migration, invasion, and angiogenesis, while overexpression had the opposite effects. Mechanistic studies revealed that P300 enhances METTL14 transcription by acetylating H3K27 at the METTL14 promoter, thereby increasing its expression. The E3 ubiquitin ligase TRAF6, identified as a downstream target of METTL14, showed reduced m6A modification and protein expression levels following METTL14 knockdown, despite unchanged TRAF6 mRNA levels. Further studies identified that the m6A reader protein YTHDF1 specifically recognizes and binds to m6A sites on TRAF6 mRNA, facilitating its translation. In vivo experiments confirmed that METTL14 knockdown inhibited the growth of MM subcutaneous tumors in NOD/SCID mice, while TRAF6 overexpression reversed this effect. **Conclusions:** Our study demonstrates significant overexpression of METTL14 in MM and underscores its clinical relevance. We confirm that the P300-METTL14-m6A axis facilitates MM progression by modulating TRAF6 translation. These findings provide novel insights into the role of m6A modification in MM pathogenesis and identify promising targets for therapeutic intervention in this malignancy.

OA-37

Targeting LILRB1 to Sensitize Human Myeloma to Ferroptosis by Disrupting Cholesterol Homeostasis

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled clonal proliferation of

plasma cells in the bone marrow (BM). Despite the demonstrated benefits of novel therapies, relapses are frequent, and acquired resistance to MM treatment eventually emerges in most, if not all, patients. MM patients who suffer more aggressive progression usually result in poorer survival. The genes driving such unfavored outcomes in MM have not been fully understood. Therefore, there is an urgent need to identify the genes and mechanisms that contribute to the aggressive behaviors of MM to develop improved therapeutic strategies for the disease. **Methods:** To discover new potential therapeutic targets for MM patients, we analyzed gene-profiling data of MM patients and identified leukocyte immunoglobulin-like receptor B1 (LILRB1), a transmembrane receptor conducting negative immune response, as one of the top-ranked genes associated with poor prognosis. Therefore, we conducted mechanistic studies to explore the function of LILRB1 in tumor biology and evaluated whether LILRB1 may be a novel target for MM therapy. A series of in vitro and in vivo experiments with human MM cell lines and murine MM models were performed. **Results:** Our analysis of the patient data demonstrated that MM patients with high expression of LILRB1 are closely related to higher MM recurrence rates, advanced stages, and lower survival rates, indicating that LILRB1 is an important player in MM pathogenesis and thus a promising target for MM therapy. Interestingly, RNA-seq data of human MM cells from the BM of MM-bearing mice showed that knockdown (KD) of LILRB1 activated cholesterol metabolism- and ferroptosis-related pathways in murine BM. Moreover, KD of LILRB1 significantly impaired tumor progression in murine models. Consistently, in vitro experiments demonstrated that LILRB1 protected MM cells from ferroptosis inducer-mediated lipid ROS and ferroptotic cell death, indicating that LILRB1 promotes the progression of MM cells by protecting them from ferroptosis. Further studies were then conducted to elucidate the underlying mechanism. LC-MS/MS analysis followed by co-IP demonstrated that LDLRAP1, an adaptor protein that interacts with LDLR, bound with LILRB1, and formed a complex together with LDLR. KD of LILRB1 inhibited LDL uptake by disrupting the interaction between LDLR and LDLRAP1 and triggering the compensatory cholesterol synthesis by upregulating the expression of SQLE that converted squalene to (S)-2,3-epoxysqualene. With less squalene to protect MM cells from lipid peroxidation, MM cells were more susceptible to the induction of ferroptosis. **Conclusions:** This study uncovers a novel function of LILRB1 in regulating cholesterol metabolism and protecting MM cells from ferroptosis during MM progression and implicates LILRB1 as a promising therapeutic target for MM patients.

OA-38

Targeting SWI/SNF Extinguishes IRF4 Expression in Multiple Myeloma

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Introduction: Multiple myeloma (MM) co-opts transcriptional networks that underpin normal plasma cell biology to drive malignant growth and survival. The transcription factor IRF4 serves as the principal architect of gene expression programs supporting normal and malignant plasma cell biology. IRF4 is an important molecular target for treating MM, but current treatments fail to directly target IRF4, highlighting the need for new therapies that exploit this critical dependency. Therefore, we sought to discover novel IRF4 vulnerabilities by utilizing a multi-omics approach. **Methods:** To uncover mechanisms that govern IRF4 expression in MM, we employed a multi-omics approach combining functional genomics screening, spatial proteomics, and global chromatin focused on IRF4 biology. **Results:** Genome-wide CRISPR screens in 22 human MM cell lines identified IRF4 as the key MM-specific dependency. To understand how IRF4 expression is regulated in MM, we tagged endogenous IRF4 with GFP. This allowed us to perform additional CRISPR screens and identify factors that control IRF4 expression. We complemented these CRISPR screens with spatial proteomics to identify proteins located near IRF4. By integrating the results from these unbiased multi-omics screens, we discovered that ARID1A and the SWI/SNF complex regulated IRF4 expression. SWI/SNF is a family of chromatin remodeling complexes that control chromatin accessibility and gene expression. Global chromatin mapping by CUT&RUN determined that nearly all chromatin-bound IRF4 was functionally associated with ARID1A, and knockdown of ARID1A and other SWI/SNF members led to a loss of IRF4 expression. This phenotype extended beyond malignant cells, since Arid1a loss in murine germinal center B cells led to a substantial reduction of plasma cells. Inhibiting SWI/SNF activity using drugs that target SMARCA2/4 caused a rapid loss of IRF4 and its dependent transcriptional network. This resulted in significant toxicity to MM cells, both in vitro and in xenograft models. We found that a gene expression signature associated with SWI/SNF activity was linked to high-risk MM. Finally, we explored potential treatment strategies using a clinically relevant SMARCA2/4 inhibitor, FHD-286. We found that FHD-286 effectively reduced IRF4 levels in models of MM that had become resistant to IMiDs. In addition, large-scale drug screening identified a synthetic lethal interaction between FHD-286 and MEK inhibitors in MM cells driven by RAS mutations. **Conclusions:** This study identifies ARID1A and SWI/SNF as a novel plasma cell vulnerability. ARID1A is required for IRF4-dependent transcription in both normal and malignant plasma cells. Inhibition of SWI/SNF with SMARCA2/4 inhibitors effectively quenched oncogenic transcription and showed exceptionally toxicity to MM, even in models resistant to current therapies.

OA-39

Genomic Landscape of IgM MGUS and Stable Versus Progressive Asymptomatic Waldenström Macroglobulinemia Patients

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Introduction: The transition from the "pre-malignant" IgM monoclonal gammopathy of undetermined significance (IgM-MGUS) and asymptomatic Waldenström's macroglobulinemia (aWM) to symptomatic WM (sWM) is driven by a multi-step process involving both clonal and microenvironmental changes. The genetic composition of each clone is likely to determine the risk of disease progression, however, novel genetic prognostic markers are yet to be discovered. Although there is data on the genomic aberrations in sWM a detailed genetic landscape of "pre-malignant" lesions is missing. The aim of this study is to describe the genomic alterations that are present in IgM-MGUS and aWM patients and provide reliable genomic features able to identify the patients that will experience progression in WM from the one that will remain stable. **Methods:** We performed whole exome sequencing (WES) analysis on 166 samples from 88 patients with IgM monoclonal gammopathies including 10 serial samples. This cohort included 45 patients with IgM-MGUS, 21 with stable aWM (aWMst), 10 patients with progressive aWM (aWMpr) and 12 with symptomatic WM (sWM). In all patients with aWM that progressed to sWM (n=10), samples were collected at both the aymptomatic and symptomatic stage of the disease. All patients included in the analysis had matched tumor-normal samples. **Results:** We observed an increasing tumor mutation burden (total number of mutations per patient) through the stages of disease evolution: the median number of coding single nucleotide variants (SNVs) in IgM-MGUS patients was 28 (range 10-78), in aWMst was 51 (range (12-168), in aWMpr was 66 (range 52-129) and in sWM was 62 (range 10-137) (asWMst vs asWMpr p< 0.05). Genes such as KDM6A, ARID1B, CXCR4, TNFAIP3 and CD79B were more often mutated in the aWMpr group compared to the aWMst group (36% vs 28%). The genomic landscape of the entire cohort of patients showed alterations in the nuclear factor-kB pathway (58% with MYD88 and 8% with TNFAIP3 mutations), 20% with alterations in the mitogen-activated protein kinase (MAPK) pathway (MAP3K9, MAP3K10, NFKB1), 16% in DNA repair pathway (BCL2 and ATM) and 7% in ERK pathway (MAPK1 and EGFR). MYD88 was mutated in around 30% of IgM-MGUS, in 80% of aWMst and 100% in aWMpr and sWM patients. We next analyzed serial samples from 10 patients sampled at the aWM and sWM stage. We observed evidence of clonal heterogeneity with linear evolution in most patients, with a branching evolution in 2 out 10 patients and an increase in the CNV profile in 3 out of 10 patients. **Conclusions:** In conclusion, this is first study which focuses on the genomic profiling of IgM-MGUS and aWM patients and suggests that increasing mutation burden and specifically mutations in genes related to WM biology, could represent a potential biomarker for the identification of patients at high risk of progression.

OA-40

SWIFT-Seq: Single-Cell RNA Sequencing of Circulating Tumor Cells as a Comprehensive Clinically Applicable Liquid Biopsy Test for Patients With Multiple Myeloma and Its Precursor Conditions

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Introduction: Invasive bone marrow (BM) biopsies are required for staging and cytogenetic profiling of patients with multiple myeloma (MM) and its precursors monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). However, many precursor patients do not undergo BM biopsies or have too few tumor cells to yield conclusive results with current clinical assays. Profiling of circulating tumor cells (CTCs) may enable routine comprehensive disease assessment. **Methods:** We performed single-cell RNA sequencing (scRNA-seq) and single-cell B cell receptor sequencing (scBCR-seq) on 201 samples including paired CD138+ BM tumor cell and CTC samples from 73 patients (14 MGUS; 41 SMM; 18 NDMM), and 28 healthy donors. We obtained 1,292,479 CD138+ plasma cells (PCs) for subsequent analyses. **Results:** We introduce a scRNA-seq workflow to interrogate few tumor cells, SWIFT-seq, that unlocks using CTCs to obtain holistic clinically applicable information. We first evaluated the ability of droplet-based scRNA-seq to capture CTCs and leveraged clonotypic data to quantify CTCs. CTCs were detected in 90% of patients and the proportion of malignant PCs out of all PCs significantly increased with stage (Wilcoxon, MGUS vs SMM: q=0.04; SMM vs NDMM: q=0.04; MGUS vs NDMM: q=0.007). Thus, we established a sequencing-based enumeration strategy to quantify true clonal cells and capture prognostically relevant differences in tumor burden. Next, we developed a classifier to test using few CTCs to infer primary cytogenetic abnormalities. The classifier detected the presence of abnormalities with 98-100% accuracy compared to FISH or WGS, could reliably infer abnormalities using 10 CTCs, and reduced the frequency of unclassified patients from 48% to < 10%. CTC-based classification enables non-invasive routine testing and could improve prognostication. Next, since PC proliferative index holds prognostic value, we examined if scRNA-seq could identify proliferative CTCs. Indeed, with single-cell resolution we could detect cycling CTCs and the CTC proliferative index positively correlated with the BM (Pearson's, r=0.53, p=0.0006), suggesting CTCs can be used as a surrogate measure of BM tumor cell proliferative capacity. Additionally, the BM-derived high-risk gene signature GEP70 retained its prognostic value in CTCs, thus, CTCs may be a resource

for measuring validated expression signatures. Lastly, we systematically compared the frequency of clones between the BM and blood and observed a strong positive correlation (Pearson's, r=0.9, p=2.7e-44), providing evidence that clonal dynamics observed in BM tumor cells can be captured in CTCs. **Conclusions:** We proved the validity of scRNA-seq of CTCs to provide layered clinical information that would otherwise require four separate assays not widely performed across institutions and/or necessitate BM input. SWIFT-seq may be pivotal for advancing blood-based tumor profiling for precursor/active myeloma diagnostics, surveillance, and prognostication.

OA-41

Evaluation of the IMWG 2/20/20 IMWG SMM Risk Stratification Model in a Cohort of Patients Evaluated With Modern Imaging

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) and asymptomatic (smoldering) multiple myeloma (sMM) precede symptomatic myeloma (MM) but are characterized by significant heterogeneity in terms of biological characteristics and clinical course. Different risk stratification models have been suggested to identify patients' risk to progress to symptomatic disease. The IMWG proposed the 2/20/20 model based on data from a large cohort of patients. However, more sensitive imaging to identify bone lesions have been incorporated in clinical practice and serum FLCs measurement is preformed routinely. Thus, patients' with SMM diagnosed in the more recent era may have different characteristics and outcomes. **Methods:** We analyzed data of patients with asymptomatic non-IgM monoclonal gammopathies diagnosed after in the time period after 2014. All patients underwent bone marrow biopsy, and patients with ≥10% clonal plasma cells had further evaluation with at least low-dose CT scan (WBCT) and spine or wbMRI. A subgroup of patients were evaluated with consecutive ldWBCTs yearly. Blood tests were performed every 3 months for the first 2 years, and twice per year thereafter. **Results:** Overall 352 patients with SMM and 546 with non-IgM MGUS and complete baseline data were included. The median age of the SMM cohort was 65 years (range IQR 55-74), 44% were males, 72% were IgG and 24% of IgA isotype, 1% biclonal and 1% light chain only. The median M-protein was 1.3 gr/dl (IQR: 0.8-2) with 25% having ≥2 gr mg/dl; median BM infiltration by clonal plasma cells was 15% (IQR: 12-25%) with 42% having ≥20% plasma cells and 18% a FCL ratio ≥20. Cytogenetics were available for a minority (N=81) of patients and any FISH abnormality was present in 28%. According to 20/2/20 staging, 47% were low, 28% risk and 25% high risk. The median follow-up for the SMM cohort was 50 months (IQR 27-100) and 80 patients progressed to symptomatic MM; median time to progression among progressors was 28 months (range 6-120). The 2- and 5-year progression rate was 13% and 25% respectively. The 2-year progression rate among low risk SMM patients was 0.5% (95%CI 0-3%) and the 5 year risk was 2% (0.7-7%). Among intermediate risk patients the 2- and 5-year risk was 6.7% (95%CI 3.2-13.7%) and 17.3% (95%CI 10.7-27%). Finally, in the high risk subgroup, the 2-year risk for progression was 32.3% (95%CI 23.5-43.25%) and the 5-year progression rate was 60.1% (48.8-71.8%). Comparing the outcomes of patients within the low-risk group to MGUS (N=341), progression rates were similar at 2 years (1.2% vs 0.5% for low risk SMM) and at 5 years (1.9% vs 2% for low risk SMM). **Conclusions:** Our results suggest that if completely assessed patients rated as "high risk SMM", have a progression rate lower than expected, probably due to the identification of patients with symptomatic disease. In addition, patients rated as "low risk SMM" have similar outcome to non-IgM MGUS patients, with a very low risk of symptomatic progression.

OA-42

Single-Cell RNA-Sequencing of 6 Million Tumor and Immune Cells in Patients With Plasma Cell Premalignancy Unveils Co-Regulation of Disease Progression by Tumor Biology and Immune Dysregulation

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Introduction: Recent studies have revealed extensive immune dysregulation in patients with plasma cell premalignancy, such as Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). Nevertheless, our understanding of how immune dysregulation evolves with disease progression to overt Multiple Myeloma (MM) is limited. **Methods:** Here, we performed single-cell RNA-seq coupled with single-cell B cell receptor (BCR) and T cell receptor (TCR) sequencing (10X Genomics) on approximately 6 million tumor and immune cells from 533 bone marrow (BM) and peripheral blood (PB) samples of 365 patients with plasma cell dyscrasias and healthy donors (HD). For 241 individuals, both the CD138pos and the CD138neg fractions of the BM were sequenced to enable integrative analyses of tumor biology and immune dysregulation. **Results:** To identify immune cell populations that change significantly in abundance with disease progression, we compared BM immune cell proportions between patients with MGUS and patients with MM using Wilcoxon's rank-sum test. We observed a significant decrease in the abundance

of IL1B-expressing myeloid cells and a significant increase in the abundance of granzyme B-expressing (GZMB+) CD8+ effector memory T cells (TEMs) (q < 0.1). We previously demonstrated that increased exposure to IFN leads to the downregulation of the IL1B+ phenotype in myeloid cells. Indeed, across immune cell populations, a significant increase in IFN signaling was observed at the MM stage, suggesting that the observed change in the abundance of IL1B+ myeloid cells may be a reflection of increased IFN signaling. Additionally, we observed that GZMB+ CD8+ TEMs are more clonally expanded at the MM stage, compared to MGUS, and express higher levels of genes associated with terminal effector differentiation and T cell exhaustion and lower levels of genes associated with T cell proliferative capacity, suggesting progressive establishment of T cell dysfunction with disease progression. To understand whether these changes in the BM immune microenvironment may help shape tumor growth, we relied on BCR sequencing to identify tumor cells in the same patients and quantified their tumor's proliferative index as a metric of tumor cell growth and aggressiveness. Within the subgroup of patients with SMM, patients with highly proliferative tumors had significantly more GZMB+ CD8+ TEMs and fewer IL1B+ myeloid cells, suggesting that the observed changes in the BM immune microenvironment correlate with disease aggressiveness. **Conclusions:** We demonstrated that immune dysregulation evolves with disease progression from MGUS to MM and, importantly, correlates with aggressive tumor biology. This observation has implications for the risk stratification and prognostication of patients with MGUS/SMM and provides a rationale for testing the efficacy of early immunotherapy in patients with premalignancy and better preserved immune function.

OA-43

Interim Results of a Phase 2 Trial of Isatuximab-Lenalidomide for Patients with High-Risk Smoldering Multiple Myeloma

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Introduction: High-Risk Smoldering Multiple Myeloma (HRSMM) patients (pts) have a median time to progression to symptomatic multiple myeloma of < 2 years. Phase 3 randomized trials of lenalidomide (LEN) and LEN-dexamethasone have shown a progression-free survival benefit in such patients. We here report the results of a planned interim analysis from a phase II trial evaluating the combination of isatuximab (ISA) and LEN (ISA-LEN) in pts with HRSMM (NCT04270409). **Methods:** HRSMM was defined as per PETHEMA risk stratification (immunoparesis and ≥95% aberrant bone marrow plasma cells as measured by multiparametric flow cytometry). Patients were treated with ISA 20 mg/kg IV on days 1, 8, 15, and 22 of cycle 1, days 1 and 15 of cycles 2-6, and day 1 of cycles 7-30, with LEN 25 mg PO on days 1-21 every 28 days of cycles 1-6. The primary endpoint was overall response rate (ORR) after 6 months of ISA-LEN (Manasanch et al. ASCO 2023). Secondary endpoints were progression-free survival (PFS), defined as time from enrollment to development of symptomatic multiple myeloma (SLiM CRAB criteria), ORR at 18 and 30 cycles, and overall survival (OS). We here report efficacy and safety outcomes after 18 treatment cycles. **Results:** Between September 2020 and October 2022, 36 pts were accrued, of whom 33 were response evaluable after 18 cycles. ORR was 94% [stringent complete response 2 (6%), complete response 1 (3%), very good partial response 11 (33%), partial response 17 (52%)], and response depth improved in 12 patients (36.4%) between cycles 6 and 18. At data cut-off (March 2024), 2-year PFS was 97.1% (CI: 91.8%-100%). Median PFS has not been reached, and no patients have died. The most frequent (≥20%) hematologic grade ≤2 treatment-related adverse events (TRAEs) were leukocytopenia (69%), lymphopenia (58%), anemia (44%), thrombocytopenia (39%), and neutropenia (36%), while common non-hematologic TRAEs were fatigue (58%), diarrhea (53%), constipation (39%), nausea (28%), and peripheral sensory neuropathy (22%). The most frequent (≥5%) hematologic Grade 3 TRAEs were: neutropenia (42%), leukocytopenia (14%), lymphopenia (14%), and thrombocytopenia (6%); grade 3 non-hematologic AEs included fatigue and rash (6% each). Only 1 patient had a grade 4 TRAE (neutropenia). No grade 5 TRAEs occurred on study, and no patients discontinued therapy due to AEs **Conclusions:** ISA-LEN is a well-tolerated therapy for smoldering myeloma, with an ORR of 94% after 18 treatment cycles. Compared with the natural history of PETHEMA HRSMM patients (Perez-Persona et al. Blood 2007), treatment with ISA-LEN delayed progression to symptomatic myeloma. The results of this study support the ongoing phase 3 ITHACA trial evaluating ISA +/- LEN-DEX which has the potential to change the standard of care in HRSMM.

OA-44

Frontline Systemic Treatment Outcomes in POEMS Syndrome – Analysis from the UCLH POEMS Centre Registry Spanning 25 Years

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Introduction: Treatment for POEMS syndrome with >2 plasmacytomas or systemic disease is typically with high-dose melphalan and autologous stem cell transplantation (ASCT), with or without prior induction therapy, in those fit enough. We

describe outcomes of patients receiving systemic frontline treatment for POEMS syndrome at our specialist centre. **Methods:** We retrospectively reviewed sequentially treated patients in the UCLH POEMS Registry from 1998-2024. **Results:** POEMS syndrome was present in 156 patients; 142 had prerequisite data recorded. Systemic frontline chemoimmunotherapy was utilised in 100/142. Median age was 55 years (range 26-84), 71/100 were male. Bone marrow involvement (n=73) and/or Castleman's disease (n=18) was present in 87 patients, whereas 13 had multifocal plasmacytomas. A median of one line of treatment was delivered (range 1-4). Melphalan-conditioned ASCT was delivered in 59 patients frontline: 54 at 200 mg/m2 and 5 at 140mg/m2. A further five patients are planned for ASCT at data cut-off. Pre-ASCT induction was given in 30/59; 19 with lenalidomide (R)-dexamethasone (d), 4 cyclophosphamide(C)-d, 4 C-thalidomide-d, 2 CRd, 1 carfilzomib(K)Rd, and 1 bortezomib(V)d. The remaining 29/59 patients proceeded directly to ASCT. Median follow up durations was 66 months (range 3-309). Response was assessable in 56/59 following ASCT, with best VEGF complete response (CRv) in 47 (84%); partial response (PRV); 3 (5%) and no response (NRV) 6 (11%). Haematological CR (CRH) was seen in 18 (32%), PRH in 26 (44%), and NRH in 9 (16%). 5-year overall (OS) 96% (95%CI 91-100) and progression-free survival (PFS) 66% (54-81%). There was no significant OS or PFS (HR 0.99, 95%CI 0.38-2.54, p 0.98) difference between those who received pre-ASCT induction and those who did not, on univariable analysis, despite identical median age. No significant increase in CRV (80 vs 88%, p 0.21) or CRH (33 v 31%, p 0.67) was seen with pre-ASCT induction. Frontline therapy without ASCT was given in 36 patients; 27 were treated with Rd, 5 Cd, 3 VCd, 2 daratumumab-VD (DVd), 2 melphalan, and 2 steroids only. Response was assessable in 29, CRV in 17 (58%), PRV in 4 (14%), NRV in 8 (28%); CRH in 5 (17%), PRH in 10 (35%), and NRH in 14 (48%). 5-year OS 68.4% (54.5-85.8%) and PFS 45.7% (30.6-68.1%). Fourteen patients were refractory to frontline therapy and 30 relapsed. Only 3/18 (16%) who attained CRH relapsed, at a median of 106 months. Attainment of CRV (p< 0.001) and/or CRH (p=0.01) following frontline therapy were associated with a lower risk of relapse on univariable analysis. **Conclusions:** Frontline ASCT for POEMS syndrome is an effective therapy, with 5-year OS of 96.3% and PFS 66.1%. However, a third of patients were not fit for melphalan ASCT, with inferior depth of response and overall survival. Attainment of CRH and CRV is associated with a significantly lower relapse rate, but late relapses are still seen. Pre-ASCT induction therapy did not appear to result in OS or PFS benefit in this retrospective analysis.

OA-45

Subcutaneous Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Therapy in Newly Diagnosed Multiple Myeloma After Transplant: Primary Results from the Phase 3 AURIGA Study

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Introduction: Induction/consolidation (ind/con) with autologous stem cell transplant (ASCT) and lenalidomide (R) maintenance (maint) is standard of care (SoC) for transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM). Daratumumab (DARA) is a human anti-CD38 monoclonal antibody approved for ind/con treatment of TE NDMM. To date, no randomized trials have directly compared DARA-based therapy to SoC R maint therapy. Here we present the primary results of the phase 3 AURIGA study (NCT03901963) evaluating the addition of DARA to R maint in TE NDMM pts who were anti-CD38 naïve and positive (pos) for minimal residual disease (MRD) following ASCT after SoC ind/con. **Methods:** Eligible pts with NDMM were aged 18-79 yrs, in ≥VGPR and MRD pos (10–5; NGS) following ASCT, anti-CD38 naïve, received ≥4 ind cycles, and enrolled within 12 mos of start of ind therapy and 6 mos of ASCT. Pts were stratified by cytogenetic risk and randomized 1:1 to receive 28-day cycles of R maint (10mg PO D1-28 [after C3, 15mg PO, if tolerated]) ± subcutaneous DARA (DARA SC; 1,800mg QW C1-2, Q2W C3-6, Q4W C7+) for ≤36 cycles or until disease progression, unacceptable toxicity, or withdrawal. The primary endpoint was MRD-negative (neg) conversion rate (10–5) by 12 mos from start of maint therapy. **Results:** 200 pts were randomized (D-R, n=99; R, n=101). Demographic characteristics were well balanced between arms: median age (yrs) was 63 for D-R and 62 for R, and 25.3% and 23.5% of pts had ISS stage III disease. At diagnosis, 23.9% of D-R and 16.9% of R pts had high cytogenetic risk (del17p/t[4;14]/t[14;16]). Pts received a median of 5 (range, 4-8) ind cycles in both groups prior to study entry. The MRD-neg (10–5) conversion rate by 12 mos (primary endpoint) was 50.5% for D-R and 18.8% for R (odds ratio [OR], 4.51; 95% CI, 2.37-8.57; P< 0.0001) with a consistent benefit favoring D-R across all relevant subgroups. At median follow-up (32.3 mos), overall MRD-neg (10–5) rate was 60.6% for D-R and 27.7% for R. Complete response or better rate favored D-R (75.8% vs 61.4%; OR, 2.00; 95% CI, 1.08-3.69; P=0.0255). PFS favored D-R (HR, 0.53; 95% CI, 0.29-0.97); estimated 30-mo PFS rate was 82.7% for D-R and 66.4% for R. D-R and R pts

received a median of 33 and 21.5 maint cycles, respectively; 88.5% and 78.6% completed 12 cycles. Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 74.0% of D-R and 67.3% of R pts; infections (18.8% and 13.3%) and neutropenia (46.9% and 41.8%) were most common. Serious TEAEs occurred in 30.2% of D-R and 22.4% of R pts, and fatal TEAEs in 2.1% and 1.0%. **Conclusions:** The addition of DARA to R maint in TE NDMM pts who were MRD pos and anti-CD38 naïve post-ASCT resulted in a significantly higher conversion rate to MRD neg by 12 mos of maint treatment than with R alone. PFS data are immature but favor D-R. No new safety signals were observed. These results demonstrate the benefit of adding DARA to R maint therapy.

OA-46

Phase II Clinical Trial of Minimal Residual Disease Response-Adapted Deferral of Transplantation in Dysproteinemia (MILESTONE)

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Introduction: Minimal residual disease (MRD) is the most important dynamic prognostic marker of progression free (PFS) and overall survival (OS) in newly diagnosed multiple myeloma (NDMM). While autologous stem cell transplantation (ASCT) increases the proportion of patients (pts) reaching MRD negativity (< 10-5), it has short- and long-term toxicities. Quadruplets lead to high rates of MRD negativity creating the opportunity of MRD-adapted transplantation deferral. In the MILESTONE trial, we prospectively study the feasibility of using post induction MRD to defer ASCT in pts with NDMM. **Methods:** MILESTONE (NCT04991103) is a phase II clinical trial for ASCT eligible NDMM and AL amyloid pts. In cohort A (NDMM), treatment consists of daratumumab 1800 mg SC (typical schedule), weekly bortezomib 1.3 mg/m2 SC, lenalidomide 25 mg PO days 1-21 and weekly dexamethasone 40 mg PO/IV (DaraVRd) every 28 days for 6 cycles followed by assessment of MRD by next-generation sequencing (clonoSEQ). Pts with MRD< 10-5 defer ASCT and continue with consolidation DaraVRd x3 cycles, pts with MRD ≥10-5 proceed with ASCT. After consolidation, all pts continue with maintenance (daratumumab on D1 and lenalidomide 10 mg D1-21 every 28 days; DaraR). Pts achieving sustained MRD< 10-5 (2 consecutive assessments 1 year apart) discontinue maintenance and proceed with MRD surveillance (MRD-SURE). The primary endpoint is the rate of ASCT deferral. Secondary endpoints included MRD conversion with ASCT, complete response (CR) by IMWG criteria at end of induction and consolidation, PFS and OS. **Results:** We accrued 20 pts between 11/2021 and 5/2023. The median age is 69 years (37-78), 50% male, 45% racial and ethnic minorities, 40% with ISS stage III disease, 15% with high risk FISH abnormalities [t(4;14), t(14;16) and del17p]. All pts successfully collected sufficient stem cells for ASCT (>2 × 106 CD34+ cells/kg), 5/20 (25%) achieved MRD < 10-5 post induction leading to ASCT deferral and one additional pt deferred ASCT by choice. One pt withdrew from participation before the end of induction. Thirteen pts completed ASCT and 6 (46%) converted to MRD < 10-5. With a median follow up of 18.4 months, there are no progressions or deaths, 4 pts have transitioned to MRD-SURE and 15 remain on maintenance and cumulative MRD negative rate 60% (12/20). The overall response rate 100%, best response ≥CR 80% (16/20). **Conclusions:** Quadruplet induction results in deep responses allowing an opportunity to defer ASCT based on individual treatment response in NDMM. This study provides the initial feasibility of utilization of post induction MRD in guiding next steps in treatment. This approach is being further explored in the larger ongoing, randomized phase II MASTER-2 clinical trial to see if comparable clinical outcomes are possible without ASCT in those achieving deep response to induction therapy. Additionally, cohort B is accruing for pts with AL amyloidosis to defer transplantation based on MRD status.

OA-47

Daratumumab (DARA) + Bortezomib/ Thalidomide/Dexamethasone (D-VTd) and DARA Maintenance in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): CASSIOPEIA Minimal Residual Disease (MRD) Update

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Introduction: Previous results from CASSIOPEIA demonstrated superior MRD-negativity (neg) rates with D-VTd vs VTd induction/ consolidation (ind/conso) and increased MRD-neg rates with DARA maintenance (maint) vs observation (OBS) in patients (pts) with transplant-eligible (TE) NDMM. Here we report long-term MRD

outcomes. **Methods:** In Part 1 of the phase 3 CASSIOPEIA trial (NCT02541383), pts were randomized 1:1 to 4 cycles of pre-ASCT ind and 2 cycles of post-ASCT conso with D-VTd or VTd. In Part 2, pts in partial response or better after conso were re-randomized 1:1 to DARA maint Q8W or OBS for £2 y. MRD was assessed for all pts regardless of response at the end of both ind and conso; in pts with very good partial response or better at 6, 12, and 24 mo during maint; and at 1, 2, and 3 y follow-up in pts who had not progressed and were MRD neg at last assessment. MRD data presented for ind/conso are by MFC only (10–5). MRD data for maint and follow-up at 10–5 used combined NGS/MFC results (MFC used only when NGS not available). MRD data presented for maint at 10–6 is by NGS only, due to limitations of MFC at this threshold. **Results:** D-VTd improved overall MRD-neg rates (10–5) vs VTd at post ind (35% vs 23%; P< 0.0001) and post conso (64% vs 44%; P< 0.0001). During maint, overall MRD-neg rates were higher for pts who received DARA (D-VTd/DARA vs D-VTd/OBS: 10–5, 77% vs 71% [P=0.0417]; 10–6, 61% vs 52% [P=0.0365]; VTd/DARA vs VTd/OBS: 10–5, 71% vs 51% [P=0.0001]; 10–6, 48% vs 31% [P< 0.0001]). MRD-neg pts post ind had superior PFS outcomes; yet post-ind PFS was significantly improved in pts who received D-VTd vs VTd, whether they were MRD neg (HR 0.399; 95% CI, 0.271-0.586; P< 0.0001) or not (HR 0.741; 95% CI, 0.613-0.894; P=0.0018). Pts who achieved MRD neg post conso also had superior PFS; however, DARA maint offered benefit regardless of post-conso MRD status: DARA MRD neg vs OBS MRD neg (HR 0.544; 95% CI, 0.382-0.775; P=0.0007) and DARA MRD positive (pos) vs OBS MRD pos (HR 0.484; 95% CI, 0.387-0.604; P< 0.0001). An overlap in PFS was observed for MRD-pos pts who received DARA maint and MRD-neg pts in the OBS group. For overall MRD-neg rates and sustained MRD-neg rates (10–5 and 10–6), the highest rates were consistently observed at all measured timepoints in pts who received D-VTd/DARA, and rates were greater in pts who received DARA maint vs OBS within each respective ind/conso treatment group. **Conclusions:** Data from this MRD analysis demonstrate that receiving D-VTd in both ind/conso and DARA maint resulted in the deepest and most durable MRD neg outcomes in TE pts with NDMM. Furthermore, receiving DARA maint offers PFS benefit regardless of MRD status. These data support the use of D-VTd ind/conso as a standard of care in TE NDMM pts and demonstrate the additional benefit of DARA monotherapy use during maint for up to 2 y.

OA-48

Daratumumab (DARA)/Bortezomib/Lenalidomide/Dexamethasone (D-VRd) With D-R Maintenance (Maint) in Transplant-eligible (TE) Newly Diagnosed Myeloma (NDMM): PERSEUS Cytogenetic Risk Analysis

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Introduction: In PERSEUS, DARA + VRd induction/consolidation (ind/consol) and D-R maint improved progression-free survival (PFS) and increased rates of minimal residual disease (MRD) negativity and sustained MRD negativity vs VRd ind/consol and R maint in TE NDMM, regardless of cytogenetic risk status. We report an expanded analysis of PERSEUS (PFS, overall MRD negativity, and sustained MRD negativity) based on the presence of high-risk cytogenetic abnormalities (HRCAs), including gain(1q21) and amp(1q21). **Methods:** TE patients (pts) with NDMM were randomly assigned 1:1 to D-VRd or VRd. Pts in both arms received up to six 28-day cycles (4 pre-ASCT ind, 2 post-ASCT consol) of VRd and R maint (until progressive disease [PD]). In the D-VRd arm, pts also received subcutaneous DARA QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W during maint until PD. Cytogenetic risk was assessed by FISH. High risk was defined per protocol as the presence of ≥1 of the following HRCAs: del(17p), t(4;14), t(14;16). Revised high risk was defined as the presence of ≥1 of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21). Cytogenetic risk subgroups included standard risk (0 HRCAs; protocol definition); high risk (protocol definition); revised standard risk (0 HRCAs; revised definition); revised high risk; gain(1q21) and amp(1q21) (3 copies and ≥4 copies, respectively, of chromosome 1q21 ± other HRCAs); and (only) 1 HRCA and ≥2 HRCAs (revised definition). MRD-negativity rate was defined as the percentage of pts in ITT population who achieved both complete response or better and MRD negativity. **Results:** 709 pts were randomized (D-VRd,

n=355; VRd, n=354). At a median follow-up of 47.5 months, PFS favored D-VRd vs VRd across all cytogenetic risk subgroups. Overall MRD-negativity rates (10–5) were higher with D-VRd vs VRd across subgroups: standard risk (77.3% vs 48.1%; P< 0.0001), high risk (68.4% vs 47.4%; P=0.0086), revised standard risk (75.3% vs 47.3%; P< 0.0001), revised high risk (73.1% vs 49.3%; P< 0.0001), gain(1q21) (69.5% vs 46.5%; P=0.0086), amp(1q21) (85.7% vs 55.6%; P=0.0104), 1 HRCA (75.3% vs 50.0%; P=0.0002), and ≥2 HRCAs (66.7% vs 47.4%; P=0.1044). Rates of sustained MRD negativity (10–5) for ≥12 months were higher with D-VRd vs VRd across subgroups: standard risk (69.3% vs 31.2%; P< 0.0001), high risk (48.7% vs 25.6%; P=0.0032), revised standard risk (66.1% vs 31.7%; P< 0.0001), revised high risk (59.2% vs 27.7%; P< 0.0001), gain(1q21) (62.7% vs 29.6%; P=0.0002), amp(1q21) (71.4% vs 27.8%; P=0.0006), 1 HRCA (61.9% vs 28.2%; P< 0.0001), and ≥2 HRCAs (51.5% vs 26.3%; P=0.0303). Results for additional cytogenetic risk subgroups will be presented. **Conclusions:** DARA plus VRd ind/consol and R maint improved PFS and induced higher rates of deep and sustained responses vs VRd ind/consol and R maint across all cytogenetic risk subgroups. These data support D-VRd ind/consol and D-R maint as a new standard of care for TE NDMM, regardless of cytogenetic risk status.

OA-49

Phase 3 Study Results of Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) Versus VRd for Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma (IMROZ)

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Introduction: First line of treatment (tx) is important for patients (pts) with newly diagnosed multiple myeloma (NDMM) as pts may not have a chance for subsequent therapy. VRd is currently a standard of care (SOC) in NDMM. Isa is an approved CD38 monoclonal antibody inducing myeloma cell death through multiple mechanisms. In the Phase 3 IMROZ study (NCT03319667), we investigate efficacy and safety of Isa-VRd vs VRd in transplant-ineligible NDMM pts. **Methods:** IMROZ is a global, prospective, randomized, open-label study done at 102 study sites in 21 countries. Included pts were aged ≤80 and had active, measurable NDMM not considered for transplant due to elderly age or comorbidities. Pts were randomized 3:2 and stratified by age, R-ISS stage, and China vs non-China, to receive Isa-VRd induction followed by continuous Isa-Rd or VRd induction followed by continuous Rd. Isa-VRd pts received Isa (10 mg/kg IV); both arms received V (1.3 mg/m2 SC), R (25 mg PO), and d (20 mg IV/PO). Primary endpoint was progression-free survival (PFS). Key secondary endpoints were complete response (CR), minimal residual disease negativity (MRD-) (10-5 by NGS) in pts with CR, very good partial response or better, and overall survival. Adverse events (AEs) were graded with NCI CTCAE v4.03. **Results:** 446 pts (265 Isa-VRd, 181 VRd) were randomized; pt characteristics were well balanced. At data cutoff (26 Sep 2023), 125 (47.2%) Isa-VRd and 44 (24.3%) VRd pts were still on tx. Median (mdn) tx duration was 53.2 (Isa-VRd) vs 31.3 (VRd) mo; addition of Isa did not significantly affect relative VRd dose intensity. At mdn follow-up of 59.7 mo, mdn PFS was not reached (Isa-VRd) vs 54.3 mo (VRd); HR 0.596 (98.5% CI 0.406–0.876; p=0.0005). Estimated 60-mo PFS was 63.2% (Isa-VRd) vs 45.2% (VRd). PFS benefit with Isa-VRd was consistent across prespecified subgroups. In the intention-to-treat population, Isa-VRd led to deep and sustained responses over VRd in MRD- CR (55.5% vs 40.9%; Stratified Odds Ratio 1.803 [95% CI: 1.229–2.646]; p=0.003), sustained MRD- for ≥12 mo (46.8% vs 24.3%; 2.729 [1.799–4.141]; p< 0.0001), and CR rate (74.7% vs 64.1%; 1.656 [1.097–2.500]; p=0.01). PFS benefit was maintained through subsequent line of therapy (PFS2: HR 0.697; 95% CI: 0.51–0.952). Grade ≥3 treatment-emergent AE (TEAE) incidence was 91.6% (Isa-VRd) and 84.0% (VRd). Definitive tx discontinuations from TEAE occurred in 22.8% Isa-VRd and 26.0% VRd pts. **Conclusions:** IMROZ is the first Phase 3 study of an anti-CD38 with SOC VRd in transplant-ineligible NDMM to show significantly reduced risk of progression or death by 40.4% vs VRd and provide deep and sustained responses. Safety was consistent with addition of Isa to VRd. These results support Isa-VRd as a potential new SOC in pts not intended for transplant.
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OA-50

Phase II Study of Iberdomide Maintenance Therapy Post-Autologous Stem Cell Transplant in Multiple Myeloma: Results of a Planned Interim Analysis

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Introduction: Lenalidomide maintenance therapy following autologous stem cell transplant (ASCT) is a standard of care for patients (pts) with multiple myeloma (MM). However, nearly all pts will experience disease relapse. Historically, lenalidomide's toxicity profile has led to treatment discontinuation in ~30% of pts by one year (yr). Thus, more effective and better tolerated maintenance therapies are needed. Iberdomide (IBR) is a novel potent cereblon E3 ligase modulator. We report the results of a planned interim analysis of a Phase II trial assessing IBR maintenance therapy after upfront ASCT in MM. **Methods:** Pts > 19 yrs of age with active MM, within 1-yr of initiation of induction therapy and in a continued > partial response at day 80-110 post-ASCT were accrued. Disease assessment included bone marrow minimal residual disease (MRD) via flow cytometry (10-5) performed at a central lab. IBR was administered 1.0 mg orally on days 1-21 of a 28-day cycle. Up to 2 dose reductions (0.75 mg/day then 0.6 mg/day) were allowed. The trial design is a one-stage phase II study with a futility stopping rule to assess whether the proportion of pts who complete at least 1-yr of IBR is at least 80%. The primary objective is to estimate the proportion of pts who complete at least 1 yr of IBR. A planned interim analysis with a futility stopping rule was conducted once the first 11 pts had either been on treatment for 1-yr or had discontinued treatment for any reason prior to 1-yr. If < 6/11 pts completed at least 1 yr of IBR, then study enrollment would cease. **Results:** Seven males and 4 females (age range 46-64 yrs, median 58) composed the interim analysis cohort. R-ISS stage at diagnosis was I (n=2), II (n=5), III (n=2) and unknown (n=2) with 4 pts having high-risk disease (del(17p): n=2 ; t(4;14): n=2). The day 80-110 post-ASCT assessment revealed 100% > very good partial response rate, with 73% > complete response (CR) and 82% MRD-negative (neg). The median number of treatment cycles completed thus far is 18 (range: 12 – 24). Four pts required a dose reduction due to grade (gr) 3 decreased neutrophil count (n=2), gr 3 pneumonia (n=1) or gr 3 maculo-papular rash (n=1). Gr 2/3 treatment-related adverse events included decreased neutrophil count (n=1 (gr 2), n=5 (gr 3)), febrile neutropenia (n=1 (gr 3)), rash (n=1 (gr 3)), anemia (n=1 (gr 2)), COVID-19 (n=1 (gr 2)), diarrhea (n=1 (gr 2)), gastrointestinal infection (n=1 (gr 2)), pneumonia (n=1 (gr 2)), thromboembolic event (n=1 (gr 2)). No pts have discontinued protocol treatment; the stringent CR rate is 100% with MRD-neg rate of 91% after 1 yr of IBR. Thus, the trial will continue. **Conclusions:** This interim analysis demonstrates the feasibility, safety and promising activity of IBR maintenance following upfront ASCT and enables continuation of the trial. Enrollment is ongoing and longer follow-up is required to determine rates of sustained MRD-negativity, treatment duration and progression-free survival.

OA-51

Efficacy of Dara-RVD Induction Therapy in Newly Diagnosed Myeloma (NDMM) Patients ≥65 Years of Age

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Introduction: Quadruplet induction with DRVd demonstrated reduced risk of progression or death compared to RVd among newly diagnosed multiple myeloma (NDMM) patients 18-70 years old in the phase 3 PERSEUS trial (Sonneveld et al, NEJM 2023). However, the impact in patients ≥ 65 years (25.5% of patients) was less pronounced with HR for progression free survival (PFS) of 0.97 (CI 95%, 0.52-1.81) versus HR 0.30 (95% CI, 0.20-0.46) in patient < 65 years. We have previously presented institutional data of 326 patients induced with DRVd compared to 1000 historic controls induced with RVd showing comparable PFS to PERSEUS trial (Joseph et al, ASH 2023). Here, we present a comparative analysis specifically in transplant-eligible patients < 65 years versus patients ≥65 years of age to address the benefit of DRVd among older NDMM patients. **Methods:** 1000 consecutive NDMM patients treated with RVd between January 2007- August 2016, and 326 NDMM patients treated with DRVd induction therapy from April 2018 - August 2022 were included in this analysis. Patient were treated with 4-6 cycles of induction therapy, followed by autologous stem cell transplant (ASCT) and risk-adapted maintenance therapy until disease progression. Demographic and outcomes data were obtained from our institutional review board-approved myeloma database and with manual abstraction. Responses and progression were evaluated per IMWG Response Criteria. **Results:** Though these are sequential cohorts, the arms are well balanced with similar median age (DRVd vs RVd: 62.1 vs 61.2 years, respectively). 55.5% and 54.6% are male; 41.7% vs 36.3% are black; and the most common Isotype is IgG in 65.2% and 61.6% of patients in the DRVd and RVd cohorts, respectively. In the RVd cohort, 314 (31.4%) patients are ≥ 65 years, and in DRVd, 106 patients (32.5%) are ≥ 65 years, p=0.385. For the patients ≥ 65 years specifically, high risk disease was present in 13.7% and 16.2% (p=0.572), ISS stage 3 in 21.0% vs 21.3% (p=0.304) and R-ISS stage 3 in 5.1% and 8.7% (p=0.588) of patients in the DRVd and RVd cohorts, respectively. ≥VGPR rates 88.7% versus 66.4% in DRVd and RVd ≥65 years cohorts. The 4-year PFS for patients ≥65 in DRVd vs RVd cohorts was 95% vs 59%, and the 4-year PFS for patients < 65 in the DRVd vs RVd cohorts was 82% vs 61%. **Conclusions:** DRVd is a highly effective induction regimen demonstrating efficacy in the phase 3 setting, and that we have shown improves upon outcomes in a historical NDMM population treated with RVd in terms of depth of response and PFS benefit. Though benefit was not seen for patients 65-70 years of age in the phase 3 study, our data reflecting real-world clinical practice suggests that these patients can and do benefit from the addition of daratumumab upfront.

OA-52

Isatuximab Plus Lenalidomide and Dexamethasone With Bortezomib Versus Isatuximab Plus Lenalidomide and Dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma: The Benefit Study

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Introduction: CD38 targeting immunotherapy is approved in combination with lenalidomide and dexamethasone (DRd) in NDMM TI and considered the best standard of care. To improve current standard of care, we evaluated the added value of lite weekly bortezomib (V) to Isatuximab plus lenalidomide and dexamethasone (IsaRd versus Isa-VRd). **Methods:** This IFM phase 3 study randomized newly diagnosed multiple myeloma patients, 65-79 years old, nonfrail, transplant ineligible, to IsaRd versus Isa-VRd arm. The primary endpoint was minimal residual disease negative rate at 10-5 by next generation sequencing at 18 months from randomization. **Results:** At a median follow-up of 23.5 months, the 18-month MRD negative rates at 10-5 were reported in 35 patients (26%, CI95% 19-34) in IsaRd versus 71 (53%, 95%CI 44-61) in Isa-VRd [OR 3.16 (95%CI 1.89-5.28, p< 0.0001)]. The MRD benefit was consistent across subgroups at 10-5 and 10-6 , and was observed from month 12 months. The proportion of patients with ≥CR at 18 months was significantly higher with Isa-VRd than IsaRd (58% vs. 33%; p< 0.0001), as was the proportion of patients with MRDand ≥CR (37% vs. 17%; p=0.0003). There was no difference yet observed for survival times. The addition of lite bortezomib did not significantly affect relative dose intensity of IsaRd. **Conclusions:** Isa-VRd significantly increased MRD end points, including the 18-month negative rate at 10-5 , the primary end point, compared to IsaRd. This study proposes Isa-VRd as a new standard of care for NDMM TI non-frail patients.

OA-53

Isa-KRd in High-Risk Newly Diagnosed Multiple Myeloma – 4-Year-Follow-Up from the GMMG-CONCEPT trial

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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. Interim analysis showed high rates of minimal residual disease (MRD) negativity (neg), with the trial meeting its primary endpoint of MRD neg at the end of consolidation (67.7% [TE] and 54.2% [TNE]), and 2-year (Y)-progression-free-survival (PFS) rates of 78.3% (TE) and 62.6% (TNE). Here, we report longer-term outcomes of the first cohort with a ≥4-Y-follow-up for survival and MRD neg. **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 (amp1q21). Isa-KRd induction (6 cycles), high-dose therapy (for TE pts) or 2 cycles of 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. Data cutoff was 11.04.2024. **Results:** The first cohort included in total 153 pts (127 TE, 26 TNE) with a median age of 59 (TE) and 74 years (TNE); del17p and t(4;14) were the most common HR cytogenetic aberrations. With a median follow-up (mFU) of 54 months for TE pts, PFS-rates at 4, 5, and 6 years (Y) were 59.4% (51.2-68.9), 52.8% (43.6-64.1), and 52.8% (43.6-64.1), respectively. Four-year-overall-survival (OS)-rate was 72.3% (64.8-80.7); 5-Y- and 6-Y-OS-rates were 67.8% and 61.6%, respectively. In TNE patients (mFU of 51 months), 4-Y- and 5-Y-PFS-rates were both 54.3% (37.6-78.3) with 4-Y- and 5-Y-OS-rates of 65.9% each (49.1-88.4). Achievement of MRD neg conferred significant benefit in PFS for TE pts (hazard ratio [hr] 0.34 [0.13;0.88]; multivariable time-dependent Cox regression) which became even more pronounced for pts remaining in MRD-neg state (hr 0.11 [0.05;0.28]).Of 106 TE pts achieving MRD neg on study (83.5%), 85 pts had ≥1-Y-sustained MRD neg (80.2%). First MRDneg assessments of pts with ≥1-Y-sustained MRD neg occurred early on, during induction in 53 pts (62.4%), intensification in 12 pts (14.1%), consolidation in 18 pts (21.2%), and during maintenance in 2 pts (2.4%). For 18 TNE pts with MRD-negative results (69.2%), ≥1-Y-sustained MRD negativity was reported in 13 pts (72.2%) with their first MRD-negative assessment during induction in 7 (53.8%) or during consolidation in 6 (46.2%) pts. **Conclusions:** These data from our CONCEPT trial underline the high potency of Isa-KRd to not only induce but also maintain MRD neg remissions in HR NDMM pts irrespective of transplant status. Six years after treatment initiation, more than half of these HR pts are still alive and progression-free. **Funding and IMP:** Sanofi, Amgen, and BMS/Celgene.

OA-54

Efficacy and Safety of Isa-KRd Induction Before Response-Adapted Consolidation in Transplant Eligible Newly Diagnosed Multiple Myeloma: an Interim Analysis of the IFM2020-02 MIDAS Study

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Introduction: In patients (pts) with transplant eligible newly diagnosed multiple myeloma, induction therapy with a quadruplet regimen before autologous stem cell transplant (ASCT) is standard. The phase 3 IFM2020-02 MIDAS (Minimal Residual Disease [MRD] Adapted Strategy) study (NCT04934475) assessed an MRD-driven consolidation and maintenance strategy after isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) induction. Here, we report efficacy and safety data of this induction regimen. **Methods:** Eligible pts (< 66 years old) received 6 cycles of 28 days of Isa-KRd: isatuximab (10 mg/kg; weekly for 4 weeks then biweekly), carfilzomib (20 mg/m2 on day [D]1 cycle [C]1 then 56 mg/m2 D1, 8 and 15), lenalidomide 25 mg/day from D1-D21), dexamethasone (40 mg/week). Cytogenetics risk was assessed at diagnosis (by next generation sequencing [NGS]): Linear predictor (LP) score (using del(17p), t(4;14), del(1p32), gain 1q, trisomy 21 and trisomy 5) defined high risk (HR) if >1. Peripheral stem cells (PSCs) were collected after 3 cycles, G-CSF and plerixafor mobilization. Response was evaluated according to IMWG criteria. MRD was measured by NGS. **Results:** Between December 2021 and July 2023, 791 pts were enrolled in 72 centers. The median age was 59 years [range 25-66]. Sixty-one pts (8%) had SLiM criteria only. MM was classified as ISS III in 120 pts (15%), R-ISS III in 76 (10%). Cytogenetics was evaluated in 757 pts: 8% were HR with a LP score >1 (17% and 32% were HR with the new IMS and the R2-ISS scores, respectively); t(11;14) was present in 26%. Only 5 pts had extramedullary disease at diagnosis, 700 being evaluated by PET-CT; 53 (7%) had circulating plasma cells. All 791 enrolled pts initiated Isa-KRd induction, 766 (97%) had ≥1 PSC mobilization course and 761 had ≥1 apheresis: the median number of CD34+ cells collected was 7.106/Kg. The PSCs collected permitted potential tandem transplant in 719 pts. 757 pts completed 6 cycles of Isa-KRD. The ORR rate was 95%. In the intent-to-treat (ITT) population, 91% of the pts achieved a VGPR or better after induction (95%

in the per-protocol [PP] population). 751 pts had post-induction MRD: in the ITT population, the MRD negativity rate was 63% at 10-5 and 47% at 10-6 (66% and 50%, respectively, in the PP population). MRD negativity rates differed significantly with respect to ISS stage, and cytogenetic subgroups: data will be presented at the meeting. During induction, 7 pts had disease progression and 5 died: 1 from disease progression, 2 from cardiac adverts events (AEs), and 2 from other AEs. The most frequently reported grade 3-4 AEs were neutropenia (25%), thrombocytopenia (5%), and infections (7%). Peripheral neuropathy was reported for 6% of pts: mostly grade 1-2. **Conclusions:** Isa-KRd induction resulted in deep responses and high MRD negativity rates; and permitted PSCs to be collected for ASCT(s). No new safety signals were observed. The ongoing MIDAS study needs further follow-up for final analysis.

OA-55

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

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Introduction: Lenalidomide (LEN), combined with daratumumab (DARA) and dexamethasone (DEX), is a standard of care for patients (pts) with TNE NDMM. The novel CELMoD™ agent iberdomide (IBER) is more potent than LEN in inducing conformational changes in cereblon, enabling more rapid degradation of Ikaros/Aiolos, thus enhancing myeloma cell death and immune stimulation. IBER has synergistic activity with DEX and DARA in preclinical models; IberDd has shown notable efficacy and tolerability in relapsed/refractory MM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030). Here we report the first results from the CC-220-MM-001 dose-expansion cohort of IberDd in TNE NDMM. **Methods:** Eligible pts had untreated NDMM and no planned or recommended autologous stem cell transplant due to age/comorbidities. Oral IBER was given 1:1:1 at 3 doses (1.0, 1.3, and 1.6 mg) on days (D) 1–21 of each 28-day cycle (C) with subcutaneous 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 oral DEX (40 mg; 20 mg if > 75 years of age). IBER doses were not modified based on renal impairment. Endpoints included preliminary efficacy, safety, and minimal residual disease (MRD) assessment. **Results:** As of February 28, 2024, 75 pts received IberDd. Median age was 75 (range, 44–90) years, 42 (56.0%) pts were male, and 35 (46.7%) had creatinine clearance of 30 to < 60 mL/min. Extramedullary plasmacytomas were present in 6 (8.0%) pts and 31 (41.3%) pts had high-risk cytogenetics. Median follow-up was 11.14 (0.4–16.8) months. Median treatment duration was 10.7 (0.3–17.1) months, median number of cycles received was 12 (1–19), and 63 (84.0%) pts continued treatment; adverse events (AEs) were the most common cause of discontinuation (5.3%). Grade (Gr) 3/4 treatment-emergent AEs (TEAEs) occurred in 70 (93.3%) pts; most were hematologic. Most common was neutropenia (74.7%); 9 (12.0%) pts had Gr 3 febrile neutropenia. Gr 3/4 infections occurred in 24 (32.0%) pts, including pneumonia (14 [18.7%] pts) and COVID-19 (4 [5.3%] pts). Most common non-hematologic Gr 3/4 TEAE was hyperglycemia (10.7%); other Gr 3/4 TEAEs were infrequent. IBER dose interruptions and reductions due to TEAEs occurred in 55 (73.3%) and 23 (30.7%) pts, respectively. In the efficacy evaluable population (N = 73), overall response rate was 97.3% with 11 stringent complete responses, 22 complete responses (CRs), 29 very good partial responses (VGPRs), and 9 partial responses; 33 (45.2%) pts achieved ≥ CR and 62 (84.9%) pts ≥ VGPR. Median time to response was 1.0 (0.9–11.3) months; 76.1% of pts responded in < 6 weeks. MRD negativity at 10-5 was achieved in 28/62 (45.2%) pts at a response of ≥ VGPR. **Conclusions:** In pts with TNE NDMM, preliminary data with IberDd showed high efficacy and a manageable safety profile with no new safety signals. Similar results were observed across dose levels. IberDd is being evaluated in an ongoing phase 3 trial in RRMM, and these data further support the evaluation of IBER in NDMM.

OA-56

Single Cell Analyses of Bone Marrow Immune Microenvironment in RRMM Subjects Treated with MEK1/2 Inhibitors Reveal IRF1-Mediated IFN/PDL1 Signaling Axes

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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 high-risk relapsed/refractory myeloma subjects (RRMM). Myeloma subjects with activating mutations in NRAS, KRAS or BRAF ("MAPK Pathway") were treated with cobimetinib, a MEK1/2 inhibitor approved for the treatment of melanoma. The goal of our study is to evaluate the effects

of cobimetinib on the immune repertoire and cell-cell dynamics of myeloma subjects over the treatment course at single-cell resolution. **Methods:** Targeted sequencing of BM samples from subjects enrolled in MyDRUG trial was used to identify those with RAS or BRAF mutations. These subjects were treated with cobimetinib and dexamethasone (cobi-dex) for two 28-day cycles, then in combination with an ixazomib, pomalidomide and dexamethasone (IPd) backbone therapy until disease progression. BM samples were collected from subjects prior to therapy (baseline/BL), after 2 cycles of cobi-dex therapy (EOC2), after 2 cycles of cobi-dex + IPd (EOC4), and at the end of treatment or at disease progression (EOT). BM samples were processed into CD138+ myeloma cell and CD138- "immune cell" fractions and the CD138- immune cell fraction profiled by single-cell RNA-sequencing (3'-scRNAseq) at up to four time points. Additionally, the residual plasma cells in these CD138- immune cell fractions were also profiled. **Results:** Transcriptome profiles were generated from 50,121 cells across 22 samples from 9 subjects with tumor MAPK Pathway mutations at entry: BRAF (p.K483Q, p.V600E, n=2); KRAS (p.Q61H, p.G12V, p.G12R, n=3); NRAS (p.Q61H, p.Q61R, p.Q61K, n=4). Immune cell types identified include NK and T cells, CD14+, CD16+, CD14+CD16+ Monocytes, Granulocyte Monocyte Progenitors (GMP), B-cells, Plasma and Dendritic cells. Notably, in the monocyte/macrophage compartment, IRF1 is upregulated after cobi-dex treatment (EOC2) relative to baseline samples. IRF1 is a transcription factor involved in upregulating genes involved in the interferon response. Ingenuity pathway analysis suggests IFNg pathway activation in monocytes driven by STAT1 and IRF1 signaling after cobi-dex treatment. Furthermore, CD8 T cells post MEK1/2 inhibition exhibit increased expression of CD274 (PD-L1), CD69 and interferon response signaling genes (IFIT2, IFIT3, OASL, IFIT1), revealing cell-cell mediated interactions in the tumor microenvironment that are being modulated by MEK inhibition. **Conclusions:** These data indicate that targeted kinase inhibition with cobi-dex activates IRF1-mediated IRF1/IFNg and PD-L1 signaling axes in the tumor microenvironment of RRMM subjects. These results support further explorations of rational combinations of targeted and immune therapies for greater efficacy in this disease.

OA-57

Results of a Phase 1 Clinical Trial of Belantamab Mafadotin (BelMaf) Combined With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) for Multiple Myeloma (MM) After One Prior Line of Therapy (LOT)

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Introduction: BelMaf, a novel antibody-drug conjugate targeting BCMA, showed an overall response rate (ORR) of 32% and median duration of response (DOR) of 11 months in patients (pts) with relapsed or refractory MM (RRMM). However, a BelMaf dose of 2.5 mg/kg once every 3 weeks resulted in 27% grade 3 keratopathy. We hypothesized that BelMaf at lower doses given every 8 weeks in combination with KRd for pts with RRMM would be effective with acceptable safety. **Methods:** Phase 1 included a 3+3 dose escalation design followed by an expansion cohort to better inform the recommended phase II dose (RP2D). The primary objective for phase 1 was to establish the maximum tolerated dose (MTD) of BelMaf- KRd as determined by dose-limiting toxicities (DLTs) in cycle 1. Secondary objectives included ORR, response depth, DOR, progression-free survival, overall survival, and safety. Two doses of BelMaf were tested: 1.4 mg/kg and 1.9 mg/kg IV over 30 – 60 min every 8 weeks + KRd (K 20/56 mg/m2 IV days 1,8,15; R 25 mg po days1-21; and d 20/40 mg po weekly) in 28-day cycles. In the absence of progression or toxicity, pts were treated for 18 cycles followed by R maintenance. **Results:** With a data cutoff of April 4, 2024, 26 pts consented to phase 1, and 19 were enrolled; 6 pts at 1.4 mg/kg and 13 at 1.9 mg/kg. The median age was 63. 63% were male, while 42% were black, and 53% had high-risk cytogenetics (HRCGs). 50% of pts with available staging data had stage III MM and 42%, 11%, 26%, and 26% were refractory to lenalidomide, bortezomib, double refractory, and daratumumab, respectively. The median LOT was 1 (range 1-3). Out of 19 pts, 18 were DLT evaluable. At the 1.4 mg/kg dose level, one DLT of grade 4 thrombocytopenia was reported out of 6 pts. No DLTs were reported among the 12 DLT evaluable pts enrolled at 1.9 mg/kg dose (6 pts in dose escalation and 6 for dose expansion). Most common adverse events were non-specified eye disorders (total; ≥G3) (89.5%; 26.3%), blurred vision (73.7%; 26.3), hypokalemia (52.6%, 10.5%), fatigue (52%,0%), diarrhea (42.1%, 0%), pain (47.4%, 0%), and constipation (26.3%, 0%). 15 pts experienced ≥G2 corneal events per KVA (26 total ≥G2 events), and 15 pts experienced a decline of 2+ lines on Snellen Visual Acuity scale (25 events). Median follow-up (IQR) was 11.8 months (6.5; 19.2). The ORR was 100%. VGPR(+), CR(+), MRD negativity 10^-5 and 10^-6 by flow cytometry rates were 89.5%, 63.2%, 52.6% and 42%, respectively. Responses are expected to further deepen with treatment. **Conclusions:** The MTD and RP2D of BelMaf with KRd was 1.9 mg/kg every 8 weeks. KRd-BelMaf demonstrated deep responses in pts with high-risk features, including HRCGs and R refractory disease. Keratopathy was frequent but manageable with dose delays and reductions. Pts with high-risk newly diagnosed MM will be enrolled in the phase 2 portion of this trial.

OA-58

Sonrotoclax Plus Dexamethasone Was Tolerable and Demonstrated Antimyeloma Activity in Patients With Relapsed/Refractory Multiple Myeloma Harboring t(11; 14)

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Introduction: Although BCL2 inhibitors have shown clinical activity in patients with multiple myeloma (MM), no BCL2-targeted therapies are currently approved for MM. Sonrotoclax (BGB-11417) is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax in biochemical assays. BGB-11417-105 (NCT04973605), an ongoing phase 1b/2 trial, evaluated sonrotoclax as monotherapy or combination therapy in patients with relapsed/refractory (R/R) MM harboring t(11;14). Updated data for sonrotoclax 640 mg plus dexamethasone are presented. **Methods:** Eligible patients had R/R MM, centrally confirmed t(11;14), and ≥3 (dose finding) or ≥1 (dose expansion) prior therapy. Patients received sonrotoclax 640 mg orally once daily and dexamethasone 40 mg weekly. Adverse events (AEs) were graded per CTCAE v5.0 and disease responses were assessed per International Myeloma Working Group response criteria. **Results:** As of January 8, 2024, 20 patients (median prior therapies, 4; range, 1-12) were enrolled (640-mg dose escalation, n=10; dose expansion, n=10). Median follow-up was 6.2 months (range, 0.3-16.6); 70% and 80% of patients were refractory to anti-CD38 and immunomodulatory drugs, respectively. Thirteen patients (65%) remained on treatment (discontinuations: disease progression, n=3; AE, n=2 [hematuria, pancreatic cancer]; patient withdrawal, n=1; physician decision, n=1). The most common treatment-emergent AEs (TEAEs) were insomnia (30%) and diarrhea, fatigue, and nausea (each 25%). Three patients had hematologic TEAEs (thrombocytopenia, n=2 [grades 1 and 3]; neutropenia, n=1 [grade 1]). Three patients (15%) had serious TEAEs and 4 (20%) had grade ≥3 AEs; none were sonrotoclax related. No dose-limiting toxicities occurred. Two patients died on study (TEAE, n=1 [metastatic pancreatic cancer]; non-TEAE, n=1 [hepatocellular carcinoma–associated liver failure]; neither was considered treatment related). Infections in >1 patient were COVID-19 and upper respiratory tract infection (n=2 each [10%]). In efficacy-evaluable patients, objective response rate was 80% (12/15; 95% CI, 51.9%-95.7%); very good partial response or better rate was 40% (6/15). Median time to response was 0.7 months. Median duration of response (DOR) was 8.3 months (95% CI, 4.4-NR) and maximum DOR was 15.4 months (ongoing). **Conclusions:** With longer follow-up, sonrotoclax plus dexamethasone demonstrated a manageable safety profile, with low hematologic toxicity and infection rates. The combination provided deep and durable responses in this R/R population.

OA-59

Proteasome Inhibitor-Augmented Salvage Autologous Stem Cell Transplantation for First Relapse Management in Relapsed Multiple Myeloma

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Introduction: Salvage autologous transplantation (sASCT) in multiple myeloma (MM) improves PFS vs non-transplant consolidation (Cook et al., Lancet Oncol 2014). Attempts to augment high dose melphalan (HDM) at first line have not improved depth of response (DoR) and may increase toxicity (Roussel et al., Blood 2022; Lahuerta et al., Haematologica 2010). However, those relapsing after first ASCT have more refractory MM, so the UK-MRA Myeloma XII (ACCoRd) trial explored augmenting HDM with an oral PI, ixazomib, in the setting of sASCT. **Methods:** MM patients requiring treatment >12m after ASCT1 received ixazomib, thalidomide and dexamethasone (ITD) induction then randomization to sASCT with HDM or ixazomib-HDM (iMel). Primary endpoint was DoR post-sASCT. DoR to ITD induction, β2M, ASCT1 TTP and cytogenetic risk were stratification variables. A second randomization of observation vs post-sASCT consolidation is reported separately. **Results:** ACCoRd recruited 496 patients, and randomized 287 to HDM (n=144) vs iMel (n=143). Median age was 62.5y (34-78); 9% were >70. Median ASCT1 TTP was 32m (2-212); < 18m, 18-24m and >24m were 13%, 15% and 72%, respectively. 62.3% received prior IMiD, 63.1% prior PI. Cytogenetic risk (IMWG criteria) was SR 47%, HR 8.9%, unknown 44.2%. ≥VGPR after ITD was 24.6%; 32.4% in those proceeding to ASCT randomization. Median cell dose was 3.1x106 CD34+/kg. Time to neutrophil and platelet engraftment and hospital discharge was 1 day shorter for iMel (11 v 12, 11 v 12, 14 vs 15; respectively). sASCT SAEs occurred in 11.9%; mean SAEs per patient were 1.4 (iMel) and 1.1 (HDM). 56.4% were attributed to iMel, 38.7% to HDM. Infection (32.7% iMel, 38.7% HDM), GI (5.5% and 6.5%) and neuro (3.6% and 9.7%) SAEs were common. There were 7 non-relapse deaths by D100: 6 after iMel (1 cardiac and 5 infective) and 1 (cardiac) after HDM. 54.4% iMel and 46.5% HDM patients achieved ≥VGPR at 100d (OR 1.46, 95% CI (0.86-2.47), p=0.161).

36.8% evaluable iMel and 29.6% HMD patients achieved MRD-ve. Rate of PD was 1.4% and 7.6% respectively. By multivariate analysis only DoR post-ITD predicted DoR at D100 (OR 7.93, 95% CI (4.39-14.31), p=< 0.001). ASCT1 TTP and genetic risk predicted PFS in adjusted Cox regression. 5y estimated OS was 62.1% (52.4-70.4%); HDM vs iMel, β2M concentration, ASCT1 TTP and ASCT1 maintenance predicted OS. ASCT1 maintenance also reduced OS (HR 2.1, 95% CI (1.05-4.22), p=0.037). **Conclusions:** Even in PI- and ImiD-exposed patients, an oral and highly deliverable PI+IMiD combination followed by sASCT is effective; OS and PFS2 by sASCT modality will be further characterised as follow-up accrues. MRD-ve rates, in those evaluable, rise from 8.7% post-ITD to 25.3% at D100. Augmented HDM showed a trend towards improved DoR and reduced PD, but this must be balanced against the increased toxicity of this approach, meaning PIs in the sASCT setting may be best reserved for re-induction and post-sASCT consolidation/maintenance therapy (Cook et al, Blood 2023).

OA-60

The Anti-BCMA Antibody-Drug Conjugate HDP-101 with a Novel Amanitin Payload Shows Promising Initial First in Human Results in Relapsed Multiple Myeloma

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Introduction: Background: HDP-101 is a new antibody-drug conjugate targeting B-cell maturation antigen (BCMA) with a synthetic amanitin payload that inhibits RNA polymerase II, effectively stopping transcription and inducing apoptosis in tumor cells, regardless of their proliferation status. It's shown cytotoxicity in vitro against BCMA-positive myeloma cell lines and non-proliferating primary CD138+ cells from refractory myeloma patients, even with low BCMA density. **Methods:** Clinical Study: HDP-101-01 is a first-in-human, open-label, non-randomized, multicenter, phase 1/2a trial in patients with progressive or refractory multiple myeloma, aiming to determine the Maximum Tolerated Dose and/or the Recommended Phase 2 Dose in Phase 1. Dose escalation is guided by an adaptive Bayesian logistic regression model (BLRM) with overdose control. The primary objective in phase 2 is to assess anti-tumor activity. **Study Progress:** As of November 2023, 18 patients (7 females, 11 males) were enrolled in 5 consecutive dose cohorts of 20, 30, 60, 80, and 100 µg/kg. Patients had a median age of 70 years (48-82), were heavily pre-treated and multidrug-resistant, and had a median of 6.5 prior treatments (2-15). **Results:** Study Results: Preliminary data shows pharmacokinetics of HDP-101 aligns with expectations, and exposure is dose-proportional. Free payload was not detected in serum at a limit of detection of 30 ng/mL, and no anti-drug antibodies or immunogenic reactions were noted. 17 of 18 patients were evaluable for dose-limiting toxicities (DLT). Initial cohorts were well tolerated, without DLTs, including no hepatic and renal toxicities, infusion reactions, or ocular disorders. Mild ALT and AST elevations were detected in Cohort 5 at Cycle 1, which returned to baseline spontaneously and were not detected in later cycles. All patients in Cohort 5 had transient thrombocytopenia, with platelet reductions starting on Cycle 1/Day 2 (C1D2), a nadir on C1D5, and full recovery by C1D15 without clinical sequelae or interventions. Subsequent dosing did not produce similarly deep episodes of thrombocytopenia, suggesting it's not due to a direct cytotoxic effect against megakaryocytes. DLTs were observed in 3 patients in Cohort 5. Based on SRC recommendations, DLT rules were modified for thrombocytopenia and dose optimization strategies were developed with resetting the BLRM statistics. **Conclusions:** Efficacy: In cohort 3 (60µg/kg), one patient had 17 cycles with stable disease (SD). In Cohort 5 (100µg/kg), 3 patients achieved partial response (PR), 2 patients showed progressive disease, one with dose reduced after C1, one patient had stable disease as best response. One patient is ongoing in partial remission after 9 cycles with a decreasing trend in M-protein levels. These encouraging results support continuation of dose optimization. Updated data will be presented at the IMS 2024 meeting.

OA-61

All Oral Triplet Iberdomide Ixazomib and Dexamethasone in Elderly Patients With Multiple Myeloma Patients at First Relapse: Results of the IFM Phase 2 Study I2D

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Introduction: The triplet combination daratumumab, lenalidomide and dexamethasone (DRd) and bortezomib, lenalidomide and dexamethasone (VRd) are to date the standard of care for patients with transplant ineligible (TI) newly diagnosed multiple myeloma (MM). Most TI patients therefore present with MM refractory to lenalidomide and/or daratumumab at first relapse and represent a difficult-to-treat population. Iberdomide is a novel oral cereblon E3 ligase modulator (CELMoD) that demonstrated promising activity in MM patients refractory to lenalidomide/pomalidomide. Here we report efficacy and safety of the all-oral triplet iberdomide, ixazomib and dexamethasone in elderly patients with MM at first relapse. **Methods:** The Intergroupe Francophone du Myélome (IFM) multicenter, open-label, phase 2 study I2D enrolled MM patients aged over 70 years at first relapse (NCT04998786). Patients received iberdomide (oral, 1.6 mg on day 1 to 21), ixazomib (oral, 3 mg on day 1,8,15) and dexamethasone (oral, 20 mg on day 1,8,15,22 on cycle 1-2 and 10 mg on day 1,8,15,22 on cycle 3-6) (28-day cycle) until disease progression or unacceptable toxicity. The primary endpoint was very good partial response (VGPR) rate. **Results:** Seventy patients were included from December 2021 to May 2023 in 19 IFM centers. Median age was 76 (range 70-87) years. The International Myeloma Working Group (IMWG) frailty score was >2 in 35 (50%) patients. In evaluable patients (54/70), fluorescence in situ hybridization (FISH) analysis revealed the presence of del(17p) in 10 patients (18.5%) or t(4;14) in 8 (15%) patients. Based on inclusion criteria, all patients had received 1 prior line of treatment, including bortezomib in 31%, lenalidomide in 87% (refractory, 74%) and daratumumab in 40% (refractory, 37%) of patients. At data cut-off, 36 (51%) patients discontinued the study due to disease progression (n=30), adverse event (n=4) or death (n=2). After a median follow-up of 14 months, the overall response rate was 65%, including 36% VGPR. The 12-months progression-free survival (PFS) and duration of response were 52% and 76%, respectively. Patients with MM refractory to both lenalidomide and daratumumab (n=26) had similar PFS compared to the overall population. The 12-month overall survival was 85%. Overall, iberdomide, ixazomib and dexamethasone combination was well tolerated. Most common non-hematologic adverse events were gastro-intestinal disorders (36% of patients), infection (30%), peripheral neuropathy (22%), and were mostly grade 1 or 2. Most common grade 3-4 treatment related adverse events (>5% of patients) were neutropenia (46%), thrombocytopenia (9%) and infection (8%). Four patients discontinued treatment due to a severe adverse event (cytopenia (n=3), skin rash (n=1). **Conclusions:** Overall, the oral triplet iberdomide, ixazomib and dexamethasone demonstrated a favorable efficacy / safety profile in elderly MM patients at first relapse, including patients with lenalidomide and daratumumab refractory disease.

OA-62

Results From the Randomized Phase 3 DREAMM-8 Study of Belantamab Mafodotin, Pomalidomide, Dexamethasone vs Pomalidomide Plus Bortezomib, Dexamethasone (PVd) in Relapsed/Refractory Multiple Myeloma

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Introduction: Use of triplet/quadruplet therapies as 1L treatment for multiple myeloma (MM) raises the need for novel combinations at first relapse. In DREAMM-7, belamaf plus bortezomib and dexamethasone (BVd) led to a significant improvement in progression-free survival (PFS) and a strong trend in improved overall survival (OS) vs daratumumab-Vd in patients (pts) with ≥1 prior line of therapy (LOT). We report results from DREAMM-8 (NCT04484623), which met its primary endpoint of independent review committee–assessed PFS at a prespecified interim analysis. **Methods:** DREAMM-8 is a phase 3, open-label, randomized, multicenter trial evaluating BPd vs PVd in pts with RRMM who received ≥1 prior LOT including lenalidomide. Pts were randomized 1:1 to BPd (28-day [D] cycles)—belamaf 2.5 mg/kg IV (D 1, cycle [C] 1), then 1.9 mg/kg (D1, C2+) + pomalidomide 4 mg (D 1-21, all C) + dexamethasone 40 mg (D1, QW, all C) vs PVd (21-D C)—pomalidomide 4 mg (D 1-14, all C) + bortezomib 1.3 mg/m2 SC (D 1, 4, 8, and 11 [Cs 1-8]; days 1 and 8 [C 9+]) + dexamethasone

20 mg (D of and 1 D after bortezomib dose). **Results:** At data cutoff (29 Jan 2024), 155 pts were randomized to BPd (median [range] LOT, 1 [1-6]) and 147 to PVd (median [range] LOT, 1 [1-9]); 25% and 29% of pts had prior anti-CD38 antibody, respectively. With a median (range) follow-up of 21.78 mo (0.03-39.23), median PFS (95% CI) was NR (20.6-NR) with BPd vs 12.7 mo (9.1-18.5) with PVd (HR, 0.52; 95% CI, 0.37-0.73; P< 0.001); 12-mo PFS rate (95% CI) was 71% (63-78) with BPd vs 51% (42-60) with PVd. ORR (95% CI) was 77% (70.0-83.7) with BPd vs 72% (64.1-79.2) with PVd; rate of CR or better (95% CI) was 40% (32.2-48.2) with BPd vs 16% (10.7-23.3) with PVd. Median duration of response (95% CI) was NR (24.9-NR) with BPd vs 17.5 mo (12.1-26.4) with PVd. A positive trend favoring BPd was seen for OS (HR, 0.77; 95% CI, 0.53-1.14); follow-up is ongoing. In the safety analysis set, adverse events (AEs) were observed in the BPd (n=150; [any grade, >99%; grade 3/4, 91%]) and PVd arms (n=145; [96%; 73%]). In the BPd arm, 89% of pts had ocular AEs (CTCAE) (grade 3/4, 43%) vs 30% (grade 3/4, 2%) in the PVd arm; serious AEs (SAEs) were reported in 63% and 45% of pts, respectively; fatal SAEs were reported in 11% of pts in both arms. 15% and 12% of pts discontinued treatment due to AEs in the BPd and PVd arms, respectively. AEs were generally manageable and broadly consistent with the known safety profile of the individual agents. Additional analyses will be presented. **Conclusions:** DREAMM-8 demonstrated a statistically significant and clinically meaningful PFS benefit with BPd vs PVd in RRMM with ≥1 prior LOT. BPd led to deeper and more durable responses, showed a favorable OS trend, and had a manageable safety profile.

POSTER PRESENTATIONS

P-001

Impact of Age and Frailty on Outcomes of Patients with Multiple Myeloma Receiving CAR T-Cell Therapies – A Single Center Experience

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Introduction: Despite higher incidence of multiple myeloma (MM) in older patients (pts), they are underrepresented in CAR T-cell trials. However, older pts vary in fitness level. Frailty predicts adverse outcomes with systemic therapy in MM, but impact on CAR T outcomes is not established. We conducted a retrospective study to evaluate CAR T-cell outcomes in our institution based on age and frailty. **Methods:** We included adult pts with MM who received CAR T from August 2016-December 2023 as standard of care or trial. We compared outcomes of older (≥70 years [y]) vs younger pts including: best response, progression-free (PFS) and overall (OS) survival, early mortality within 90 days, and toxicity in 6 months including: cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), healthcare utilization (ED/unplanned hospitalizations), and infections. We also assessed outcomes based on frailty in pts ≥ 60y using the simplified frailty index (Facon et. al) which includes age, ECOG performance status and Charleston Comorbidity Index (CCI). A score ≥2 = frail. Unless stated, P values are insignificant. **Results:** We included 257 pts. Median age was 65y (33-83y); 30% were ≥70y; 42% were female. Median follow-up was 1.8y (95%CI: 1.6-2.0). There was no significant difference in PFS (median: 1y), early mortality (4% vs 3%), or OS (median: 3.8 vs 2.4y, 1y OS: 83% vs 78%) in pts < vs ≥70y, respectively. There was no difference in CRS incidence (79% vs 86%), Grade >2 (2% vs 5%), or recurrence (5%). Patients ≥70y had earlier onset (median: 1 vs 2 days, P=0.03), and longer CRS duration (3 vs 2 days, P=0.03). For ICANS, pts < and ≥70y had similar incidence (13% vs 21%), Grade≥2 (3% vs 8%), time to onset (3 days), and duration (2 days). There was no significant difference in healthcare utilization (58% vs 64%) between the groups. Pts ≥70y had higher infection rate (29% vs 18%, P=0.047). Among pts >60y (N=248), 33% were frail. There was no difference in ≥VGPR (78%) or PFS (1y) in frail vs non frail pts. There was no significant difference in CRS incidence (86% vs 82%), Grade >2 (3% vs 4%), time to onset (1 vs 2 days), duration (3 days), or recurrence (5% vs 6%). There was no difference in incidence (23% vs 18%) or Grade >1 (9% vs 4%) ICANS, but duration was longer in frail vs non frail pts (3 vs 1 day, P=0.03). Frail pts had higher healthcare utilization (74% vs 56%, P=0.02), but similar infection (31% vs 20%) and early mortality (5% vs 4%) rates. OS was shorter in frail vs non frail pts (2.4y vs not reached, P=0.02; 1y OS: 79% vs 82%). On univariate analysis, ECOG >1 was associated with decreased OS, but age and CCI > 1 were not. **Conclusions:** Older pts have higher infection rates post CAR T. Otherwise, efficacy and toxicity are similar in older vs younger pts. Frail pts have similar response and toxicity, but higher healthcare utilization compared to non frail pts. Frailty, defined by the simplified index, is associated with decreased OS but age and CCI criteria alone are not.

P-002

Ide-Cel Real-World (RW) and Clinical Trial Long-Term Safety Experience: A Special Focus on Movement and Neurocognitive Treatment Adverse Events (MNT AEs) and Second Primary Malignancies (SPMs)

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Introduction: Emerging reports of MNT AEs and SPMs after treatment (tx) with BCMA-directed CAR T cell therapies are of high interest to healthcare providers. Here, we provide a report

of ide-cel safety, including AEs of special interest (AESIs) from clinical trial and RW settings, as reported to BMS Clinical Trial and Pharmacovigilance Databases. This analysis also reports Guillan–Barré syndrome (GBS), parkinsonism/Parkinson's disease, and cranial nerve palsies with ide-cel, which are MNT AEs of high interest for making tx decisions with CAR T cell therapies in relapsed and refractory multiple myeloma (RRMM). **Methods:** A retrospective review of the BMS Clinical Trial and Pharmacovigilance Databases since inception of the clinical program (Oct 30, 2015 – Mar 25, 2024) was conducted. This analysis included patients (pts) with RRMM who were treated with conforming or non-conforming ide-cel in the clinical trial and RW (post-marketing) settings. All reported events were included regardless of seriousness or causality, and were assessed at pt level. Events reported from non-conforming ide-cel delivered via expanded access program were included as clinical experience; tx with non-conforming ide-cel after sIND/EU approval of ide-cel was considered RW experience. Events reported voluntarily and spontaneously in long-term follow-up registries were excluded as these were not entered systematically into the BMS Database. Additional AESIs (cytokine release syndrome, neurotoxicity, macrophage activation syndrome/hemophagocytic lymphohistiocytosis, infections) will be reported at the time of presentation. **Results:** Among 3996 pts (total exposed: clinical, n=829; RW, n=3167) included in this analysis who were treated with ide-cel in either the clinical trial or RW settings, there were no reports of GBS. Two (0.24%) cases of parkinsonism (1 grade [gr] 2, 1 gr 3) occurred in the clinical setting with time to onset of 22d and 151d, respectively; gr 3 case resolved at the time of this reporting. Six (0.19%) cases of parkinsonism/Parkinson's disease occurred in the RW setting. Four (0.48%) cases of cranial nerve palsies (2 [0.24%] total VI nerve paralysis [1 gr 1, 1 gr 2], 1 Bell's palsy [gr 2], 1 cranial nerve disorder [gr 1]) occurred in the clinical setting; all were unrelated to ide-cel and resolved (time to onset, 44–278d; time to resolution, 3–52d). No cranial nerve palsies were reported in the RW setting. In the clinical trial setting, there were 43/647 (6.64%) pts with SPMs, including 9 (1.40%) pts with acute myeloid leukemia/myelodysplastic syndrome (time to onset, 284–919d); 1 case was of T-cell origin, with no insertional oncogenesis detected. **Conclusions:** Within the reporting period, the AESI incidence rates were consistent between the clinical trial and RW experiences, and similar to previous reports in FAERS and CIBMTR databases. This review indicates that tx with ide-cel is associated with low incidence of MNT AEs, including GBS, parkinsonism/Parkinson's disease, cranial nerve palsies, and SPMs.

P-003

Determinants of Response to Anti-CD38 and Bispecific Combination Therapy in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: The TRiMM2 study is an ongoing phase 1b study which combines anti-CD38 therapy with Bispecific antibody (BiAb) therapy. BiAb therapy has yielded response rates of over 70% in relapsed/refractory multiple myeloma (RRMM) patients, however a subset of patients do not maintain a durable response. Identifying predictive markers and the immune dynamics associated with treatment response and durability is an unmet need. Here, we investigated the immune profiles of MM patients receiving BiAb in combination with anti-CD38 therapy and analyzed their correlation with treatment outcomes. **Methods:** We identified 27 RRMM patients enrolled in the TRiMM2 clinical trial that received BiAb in combination with anti-CD38 therapy. One third of patients (n=9) were on doublet therapy of BiAb and anti-CD38 therapy only while 67% patients (n=18) had the addition of Pomalidomide to theBiAb and anti-CD38 backbone. Of the 27 patients, 5 received Anti-BCMA BiAb and 22 received Anti-GPRC5D BiAb therapy. Prior to BiAb therapy, 52% of patients had progressed on previous T cell directed therapy (BiAb n= 6, or anti-BCMA CAR-T n=8) and 48% had progressed on other salvage therapies (n=13). Immune profiling was performed by high-dimensional spectral flow, focusing on T cell exhaustion, activation, and senescence markers. Patients were categorized based on their progression-free survival (PFS) duration with patients divided into < 6 months PFS and >6 months PFS groups. **Results:** We profiled T cells in peripheral blood mononuclear cells (PBMCs), prior to initiation and during BiAb therapy. Patients with shorter PFS had higher presence of checkpoint inhibitors prior to the start of therapy. Specifically, these patients had a higher presence of PD1+CD8+ T cells (p=0.02) and TIGIT+ CD8+ T cells (p=0.04). Shorter PFS patients had more senescent CD4+ T cells co-expressing CD57+ and TIGIT compared to those with more durable responses (p=0.04). During BiAb therapy, patients with shorter PFS had a significant decrease in their white blood cell and lymphocyte counts not seen in responders (p< 0.01). Patients with greater PFS had a significant shift to an effector memory phenotype in both CD4+ and CD8+ T cells (p< 0.001) during therapy. In addition, these patients also showed a significant increase of activation markers on CD8+ and CD4+ T cells (p< 0.01) that was not present in patients with shorter PFS (p=0.23). Frequency of Tregs were significantly lowered during therapy in patients that had a durable response (p=0.017) that was not seen in patients that progressed within 6 months. **Conclusions:** Our findings show that the state of T cells at baseline impacts the outcomes of BiAb therapy in RRMM patients. Patients with PFS of less than 6 months had an increase of checkpoint inhibitors on CD8+ T cells prior to treatment. During treatment, patients with a durable response had a decrease in Treg population and increased CD8+ and CD4+ T cell activation.

P-004

Association Between Risk Factors and Outcomes Following Fully Human Anti-BCMA CAR-T Progression in Patients with Relapsed/Refractory Multiple Myeloma

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Introduction: Anti-B-cell maturation antigen-directed chimeric antigen receptor T-cell (BCMA CAR-T) therapy has revolutionized the treatment of relapsed/refractory multiple myeloma (RRMM). However, a subset of patient experiences disease progression following anti-BCMA CAR-T therapy. Understanding the characteristics of these patients is crucial for patient selection, establishing survival outcomes after anti-BCMA CAR-T progression, and developing novel strategies to improve outcomes. **Methods:** A retrospective, single-institution study on a cohort from China, comprising a total 54 patients with RRMM who received the same fully human anti-BCMA CAR-T therapy (CT103A). Among these, 23 patients experienced progression (progression > 3 months after CAR-T infusion). Associations between baseline characteristics and outcomes were analyzed, and risk factors, survival rates and salvage approaches were established. **Results:** Patients experiencing disease progression exhibit poor survival outcomes (median survival:30.2 months) and achieve lower best response rates. Additionally, patients with a history of previous haematopoietic stem cell transplantation (HSCT), triple exposure, high marrow burden, or a best response ≥ complete response (CR) have an increased risk of progression when compared to patients maintaining durable remissions. The presence of two or more of these factors was significantly associated with a negative impact on progression-free survival (PFS) ($p < 0.001$). Among the 23 patients experiencing progression, the overall survival (OS) rate was 45.4% (95% CI, 20 to 68) at 12 months following the time of progression. Furthermore, in an analysis of BCMA status of patients who progression, no significant difference was observed in the cumulative rate of recurrence between BCMA+ and BCMA- disease phenotypes. Disease progression in patients with BCMA- is associated with poor OS ($P = 0.0035$). **Conclusions:** We identified specific factors (a history of previous SCT, triple exposure, high marrow burden, or a best response ≥ CR) as independent predictors of progression. An increase in the number of risk factors correlates with a progression in patient. In addition, in the post-anti BCMA CAR-T progression setting, BCMA– progression is distinctly associated with decreased survival outcomes. Corresponding author: Chunrui Li

P-005

Effectiveness of Bridging Therapy Corresponds to Improved Outcomes After Receiving CAR-T Therapy: Phase 3 CARTITUDE-4 Study of Patients With Relapsed, Lenalidomide-Refractory Multiple Myeloma

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Introduction: In the phase 3 CARTITUDE-4 trial, ciltacabtagene autoleucel (cilta-cel) vs standard care significantly improved progression-free survival (PFS; hazard ratio [HR] 0.26, P< 0.0001) and rates of overall response (85% vs 67%) and complete response or better (73% vs 22%) in patients with relapsed, lenalidomide-refractory MM after 1–3 prior lines of therapy. Patients who received cilta-cel as study treatment (ie, did not have disease progression before cilta-cel infusion) had high rates of overall response (99.4%), complete response or better (86.4%), and 12-month PFS (89.7% from randomization). Bridging therapy controls disease while CAR-T cell therapy is being manufactured and potentially reduces the risk of toxicities by debulking. The impact of disease control prior to CAR-T infusion on postinfusion clinical outcomes is not well established. We present post hoc analyses describing cilta-cel efficacy by response to bridging therapy in patients who received cilta-cel as study treatment in CARTITUDE-4. **Methods:** Patients in the cilta-cel arm underwent apheresis, received bridging therapy with either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd), and then a single cilta-cel infusion 5–7 days after the start of lymphodepletion. PFS (measured from randomization) was analyzed in patients who had a ≥25% reduction in paraprotein from baseline (prior to apheresis) to the start of lymphodepletion vs others (paraprotein either increased, no change, or <25% reduction). CAR+ T cells in peripheral blood were assessed by flow cytometry. A ligand-

binding assay was used to quantify serum soluble BCMA (sBCMA). In vivo effector-to-target (E:T) ratio was derived by peak CAR-T cell expansion normalized to pre-infusion sBCMA levels. **Results:** Among 176 patients who received cilta-cel as study treatment (DPd, n=158; PVd, n=18), 148 had a ≥25% reduction in paraprotein during the bridging period. At 15.9-month median follow-up, median PFS was not reached (95% CI, not estimable [NE]-NE) in patients with ≥25% reduction vs 19.2 months (95% CI, 15.8-NE) in the others (HR, 0.32; 95% CI, 0.16-0.66). Estimated 12-month PFS rates were 91.8% and 78.1%, respectively. In patients with available biomarker data (n=171), a significantly higher in vivo E:T ratio was observed in those with a ≥25% reduction in paraprotein vs the others (median [IQR], 62.6 [139.2] vs 5.4 [62.3]). **Conclusions:** Greater response to bridging therapy (≥25% paraprotein reduction) correlated with longer PFS. This may be explained mechanistically by a higher in vivo E:T ratio, previously shown to be associated with longer PFS (Montes de la Oca, ASH 2023). These data emphasize the importance of optimized bridging therapy for disease control prior to receiving cilta-cel.

P-006

Differential Neutrophil Trajectory in Duffy-Null Multiple Myeloma Patients Mimics Delayed Neutrophil Recovery Following BCMA-directed CART

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Introduction: BCMA-directed CART therapy has shown remarkable efficacy in RRMM, but a proportion of patients develop prolonged cytopenias as a significant source of morbidity. It has been previously shown that self-reported Black patients had significantly longer recovery from grade 3/4 myeloid cytopenias compared to other ethnicities (Thibaud et al., ASH 2023, abstract #2002). Approximately two-thirds of individuals of African ancestry carry the duffy-null genotype, which is associated with lower baseline absolute neutrophil count (ANC). We hypothesized that delayed post-CART hematologic recovery in Black patients is due to prolonged neutropenia driven by high prevalence of the duffy-null genotype in this population. **Methods:** We reviewed medical records for MM patients at our institution who received a BCMA-directed CART between 2017 and 2024. Patients were censored at progression or at 120 days, and any missing ANC values were linearly interpolated from surrounding data. Recovery date was defined as the first of 30 continuous days with ANC≥1500 cells/uL. Baseline ANC was defined as the minimum within 7 days prior to lymphodepletion, with medians compared by Mann-Whitney U test. Time-to-recovery from CART infusion was estimated by Kaplan-Meier survival analysis, and a Cox proportional hazard model was used for multivariable analysis. **Results:** A total of 190 CART patients were identified, and 152 patients (80%) with available duffy panel testing and at least 1 month of follow up prior to relapse were included. Self-reported race was White in 80 patients (58%) and Black in 33 patients (23%). 28 patients (18%) were duffy null, including 25/33 Black patients (76%). Duffy-null patients had a similar median age at CART (60 vs 62 years) and number of prior lines of therapy (median 5 vs 5) with a lower rate of prior ASCT (64% vs 79%) compared to non-duffy-null patients. Despite no significant difference in median baseline ANC (2.05 vs 2.5, p=.16), duffy-null patients had significantly longer median time to ANC recovery (68 vs 40 days, p=.04). Duffy-null patients had lower median ANC at day 30 (0.73 vs 1.1, p=.015), but this difference was no longer evident by day 90 (1.55 vs 1.9, p=.14). After multivariable adjustment, Duffy-null status (HR 0.44, 95% CI 0.25-0.78, p=.005) and ≥3 prior lines of therapy (HR 0.41, 95% CI 0.25-0.65, p< .001) were significant risk factors for delayed recovery. Notably, Black patients who were not duffy-null (n=8) also had a longer time to neutrophil recovery than the corresponding non-Black patients (n=105). **Conclusions:** Duffy-null genotype was independently associated with delayed neutrophil recovery after CART therapy in a large single-center analysis, suggesting a possible genomic driver for disparities in CART hematotoxicity. These data underscore the need for updated ANC reference ranges in duffy-null MM patients. Additionally, non-duffy-null Black patients with delayed ANC recovery require further exploration to identify additional risk factors for hematotoxicity.

P-007

Absolute Lymphocyte Count at Day 30 (Not Earlier) and Early CRS Predict Delayed Responses to Teclistamab: Results From the US Myeloma Immunotherapy Consortium

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Introduction: In MajesTEC-1 and several real-world analyses of teclistamab (tec) in multiple myeloma, median time to first response (≥PR) was approximately 30 days. Predictors of delayed responses to tec, i.e. Day (D) 30 non-responders who may still benefit from continued therapy, are uncertain. We aimed to identify predictors of D90 response among patients (pts) without a response at D30 following tec initiation. **Methods:** We analyzed data from 14 centers within the US Myeloma Immunotherapy Consortium, focusing on D90 outcomes in pts with ≥90 days of follow-up (or death between D31-D90) after tec initiation between 10/2022-10/2023. Pts with missing D30/D90 assessments were excluded, as were pts who had responded or died at/before D30. We analyzed D90 response predictors including isotype; cytogenetics; radiographic progression of EMD (if present) leading up to the first tec step-up dose (SUD); prior BCMA therapy; presence/timing of CRS relative to the first SUD (early-onset if at/below the median time to CRS onset, otherwise late-onset vs absent); use of tocilizumab or steroids; baseline absolute neutrophil count [ANC, in thousands of cells per microliter (K/uL)]; and absolute lymphocyte count (ALC, in K/uL) at baseline, D7, and D30. **Results:** Among D30 non-responders (n=140), 23.6% (n=33) later achieved a D90 response. No association was found between D90 responses and cytogenetics, progressive EMD, prior BCMA therapy, or CRS management. CRS distributions were significantly different (p=0.03): 48.5% early-onset (CRS onset D3 or earlier) / 21.2% late-onset (D4 or later) / 30.3% absent in responders, vs 23.4% / 29.0% / 47.7% in non-responders. Baseline ANC was comparable (median 4.22 vs 3.57), but median ALC values were higher in responders: baseline ALC 1.00 vs 0.59 (p< 0.01), D7 ALC 0.40 vs 0.21 (p=0.02), and D30 ALC 1.0 vs 0.42 (p< 0.01). In multivariable logistic regression, early CRS and D30 ALC (but not baseline or D7 ALC) were independent predictors of D90 responses. D90 responses occurred in 43.1% of pts with D30 ALC ≥0.50 vs 10.9% of pts with D30 ALC < 0.50 (p< 0.001). D90 responses occurred in 39.0% of pts with early-onset CRS vs 18.4% late-onset vs 16.4% absent (p=0.03). Treating (1) D30 ALC ≥0.50 and (2) early-onset CRS as independent predictive factors in D30 non-responders, 48.2% of pts with both factors achieved a D90 response vs 23.6% with one vs 7.3% with neither (p< 0.01). **Conclusions:** This is the largest study of early versus delayed responses to teclistamab to date. While limited by its retrospective nature and missing data (such as CD4/CD8 subsets or the exact timing of subsequent SUD), we found that D30 ALC and early-onset CRS were significant predictors of subsequent responses in early non-responders. For pts who have not achieved a response after 1 full cycle of tec, treatment continuation may be most beneficial in those with higher ALC values (e.g., ALC ≥0.50 K/uL) and/or in whom CRS onset occurred ≤ D3 relative to the first SUD.

P-008

A Rare and Unexplored Entity of Colitis Post-BCMA Directed CAR T-Cell Therapy; Insights From a Multicenter Case Series

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Introduction: B-cell maturation antigen (BCMA) CAR T cells have emerged as a cornerstone in the treatment of relapsed refractory multiple myeloma (RRMM). However, the potential to induce immune-related adverse events resembling autoimmune diseases or graft versus host disease remains unclear. In this study, we describe a novel entity of severe diarrhea and colitis following BCMA CAR T cell therapy in a cohort of patients with RRMM. **Methods:** Five U.S. academic centers contributed data to this analysis. Patients (pts) developing diarrhea that was unexplained after CAR T-cell therapy were included. Other causes of diarrhea, particularly infectious etiologies were ruled out. Pt data was extracted via chart review. Baseline pt characteristics, diarrhea onset and duration, endoscopic results, treatment and clinical course were summarized using descriptive analyses. CTCAE v5.0 and ASTCT grading was used for diarrhea/colitis and CRS/ICANS respectively. IMWG response to CART, progression and survival data were obtained. **Results:** Twelve pts were identified, all received ciltacabtagene autoleucel under SOC. Median age at CAR-T infusion was 66 [39-77]; 6 female; 4 non-white; 3 pts had high-risk cytogenetics and 2 had EMD disease. Median lines of prior therapy was 4 [4-8], 7 pts had prior ASCT and 10 were triple-class refractory. Eleven pts had ≥CR and 1 had VGPR. CRS occurred in 9 pts at grade(gr) 1/2; 1 pt had gr 3 ICANS, 3 pts had CN palsy. Median time of diarrhea onset from CART infusion was 98 days [60-211]. Eleven pts had gr 3/4 diarrhea, 1 pt had gr 2. Seven pts had grade 3/4 colitis of which 3 had pneumatosis intestinalis on imaging. On endoscopic evaluation 10 pts had both upper and lower GI involvement and 10 pts had finding of cryptitis/crypt apoptosis. In 3 pts, diarrhea resolved with supportive care only. Seven pts received IV or high dose oral steroids, 6 of which did not have significant improvement. Of the 7 pts, 2 received selective immunosuppressive therapy with infliximab. Other treatments were budesonide (7 pts), octreotide (1pt). Of the 12 pts, 5 had resolution of diarrhea at a median of 46 days, 3 had improvement to gr 1 at a median of 127 days and 4 persisted. Eleven pts required at least 1 hospitalization and 7 pts received TPN. Four pts had 8 infectious complications including gram negative bacteremia, CMV reactivation without organ involvement, nocardia and disseminated zoster. Two pts died due to colitis complications, 1 pt died due to PD, > 8 months after colitis resolution. The other 9 pts were alive and in CR at time of data cut off 5/20/24. **Conclusions:** We present

a multicenter experience of post-BCMA CAR-T colitis. While the pathophysiology is not fully understood, an inflammatory colitis with a variable clinical course which may be severe and unremitting, is emerging as a possible complication post CART. Additionally, there is significant morbidity and optimal therapy is not known. Increased awareness and investigation into this entity is needed.

P-009

Digital Remote Patient Monitoring for Cytokine Release Syndrome in ABBV-383 Treatment: Methodology and Setup

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Introduction: Trial in progress. Patients with triple-class relapsed or refractory multiple myeloma (RRMM) have limited treatment options after progression. B-cell maturation antigen (BCMA) is a validated target for RRMM, and several BCMA-directed therapies (BDTs) are approved. With the use of some approved BDTs (ie, chimeric antigen receptor T-cell and T-cell engagers), cytokine release syndrome (CRS) is a common adverse event, occurring in 45–95% of treated patients. Novel T-cell based immunotherapies with improved safety and tolerability are needed. The BCMA×CD3 bispecific antibody ABBV-383 comprises 2 high-affinity BCMA-binding domains and a low-affinity CD3-binding domain designed to reduce cytokine release with potential for minimal T-cell exhaustion. In an ongoing phase 1 study, mainly low-grade CRS events were observed; all events resolved with a median resolution time of 2 days.. To better understand CRS and guide interventions, we aim to characterize CRS-related vital sign changes before, during, and after CRS and assess their association with baseline clinical, demographic, and bio-sampling data in clinical trial patients receiving ABBV-383. **Methods:** In selected countries, patients receiving ABBV-383 treatment in two clinical trials (NCT06158841 and NCT05650632) will be equipped with wearable digital health devices (Current Health Wearable and Vivalnk Fever Scout™), allowing continuous monitoring of vital signs. Vital signs that will be assessed include axillary temperature, cardiac and respiratory vital signs, and physical activity. The monitoring will commence before cycle 1 infusion and continue for a predefined period. The collected data will be used for exploratory characterization of the CRS profile. Granular characterization of CRS onset and resolution will be assessed retrospectively. Statistical and machine learning techniques will be used to identify patterns and establish predictive models for CRS and characterize vital sign dynamics upon CRS-mitigative intervention. **Results:** The remote patient monitoring data will be analyzed to identify any significant changes in vital signs preceding the onset of CRS. We will employ statistical and machine learning techniques to identify patterns and establish predictive models for CRS. We will also evaluate the efficacy of interventions (eg, reduced hospitalizations and CRS severity) by tracking the return of CRS-related vital sign changes to normal levels after appropriate interventions. **Conclusions:** Selected trials within the ABBV-383 clinical trial program will utilize digital remote patient monitoring to comprehensively evaluate CRS, with the aim to identify early warning signs of CRS and assess the effectiveness of interventions. The findings from this study will contribute to a better understanding of CRS, inform the needed resource utilization with respect to routine monitoring and required hospitalization, and guide personalized interventions in patients receiving ABBV-383.

P-010

Efficacy/Safety of Ciltacabtagene Autoleucel ± Lenalidomide Maintenance in Patients With Multiple Myeloma Who Had Suboptimal Response to Frontline Autologous Stem Cell Transplant: CARTITUDE-2 Cohort D

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Introduction: CARTITUDE-2 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 less than complete response (CR) after autologous stem cell transplant (ASCT) frontline therapy (tx). We report efficacy and safety for this cohort. **Methods:** Adults with newly diagnosed multiple myeloma 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 (target dose, 0.75×106 CAR+ viable T cells/kg) 5–7 d after the start of lymphodepletion. Per protocol, safety was assessed in the first 5 pts with cilta-cel only; subsequently, 12 pts initiated continuous len maintenance ≥21 d post cilta-cel for ≤2 yrs. Primary endpoint was minimal residual disease negativity (MRD neg) at 10–5 based on next-generation

sequencing or flow. **Results:** As of Sept 5, 2023 (median follow-up, 22 mo [range, 5–39]), 17 pts received cilta-cel (with len, n=12; without len, n=5). Median age was 54 yrs, 6% had high-risk cytogenetics, and 100% were International Staging System stage I at baseline. Of 15 MRD-evaluable pts, 12 (80%) achieved MRD neg at 10–5; median time to MRD neg was 1 mo (range, 1–6). Overall response rate was 94% (n=16/17; ≥CR, 94%). Median duration of response was not reached, and median time to first response was 1 mo. Progression-free survival and overall survival rates at 18 mo were 94% each. CAR+ T cells peaked in blood at a median of 12 d post infusion (mean, 2187 cells/μL; SD, 2102 cells/μL) and remained detectable for a median of 43 d (range, 26–209). All pts had grade (gr) 3/4 TEAEs. Hematologic TEAEs included neutropenia (94%), lymphopenia (65%), thrombocytopenia (47%), and leukopenia (41%). Infections occurred in 12 (71%) pts (gr 3/4, 29%). CRS occurred in 14 (82%) pts, and median time to onset was 8 d. All CRS events were gr 1/2 and recovered in a median of 3 d. ICANS occurred in 1 pt (gr 1); median time to onset was 7 d and recovery was 1 d. Other neurotoxicities occurred in 6 pts (gr 1, n=1; gr 2, n=4; gr 3, n=1); median time to onset was 21 d and recovery was 70 d (n=4). No MNTs/parkinsonism occurred. One pt had a secondary malignancy of gr 3 MDS with an onset on d 353 that was not treatment related per investigator assessment. **Conclusions:** In pts who had < CR after frontline ASCT, a single cilta-cel infusion ± len maintenance demonstrated deep responses that were durable. TEAEs were consistent with the known safety profile of cilta-cel. These data show promising efficacy and safety with cilta-cel ± len maintenance in pts who achieved < CR after ASCT frontline tx

P-011

Impact of Daratumumab Refractoriness on Clinical Outcomes Following CAR T-cell Therapy for Relapsed/Refractory Multiple Myeloma

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Introduction: Ciltacabtagene autoleucel (cilta-cel) and idecabtagene vicleucel (ide-cel) are two chimeric antigen receptor T-cell (CAR T) products recently approved for the treatment of relapsed/refractory multiple myeloma (RRMM) with 1-2 prior lines of therapy (LOT) based on the results of CARTITUDE-4 and KarMMa-3 trials. While daratumumab (dara) refractoriness is predictive of inferior outcomes with subsequent therapies, not all patients (pts) enrolled in these pivotal trials were dara refractory. We conducted a single-center retrospective analysis to compare the outcomes of RRMM pts who received BCMA-directed CAR T-cell therapy based on dara refractoriness status. **Methods:** Our analysis included all pts with RRMM who received ide-cel, cilta-cel, or orvacabtagene autoleucel (orva-cel) between April 2018 and November 2023. All pts were dara exposed and divided into two groups according to their dara refractoriness status: dara refractory (DR) and dara non-refractory (DN). Key outcomes of interest included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and incidence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Response categories were determined per IMWG consensus definitions. CRS/ICANS were graded based on ASTCT criteria. **Results:** Of 127 pts included (age range: 37-86 years) in the analysis, 28 (22%) were DN at the time of cell infusion. The analyzed groups (DR vs DN) had comparable rates of pts with ECOG performance status >0 (68.7% vs 60.7%) and high-risk cytogenetic abnormalities (70.7% vs 71.4%), including del(17p)/TP53 mutation, t(4;14), t(14;16), t(14;20), 1q gain/amp and/or del(1p). In contrast, the DR group had higher rates of extramedullary disease (EMD) (46.5% vs 28.6%), prior BCMA-directed therapy (24.2% vs 7.1%) and prior LOT (6 vs 4). With a median follow-up of 12 months (range: 1-72) for the entire population, best ORR was 77.7% (40% sCR/CR, 22% VGPR, 15% PR) in the DR group vs 85.7% (50% sCR/CR, 14% VGPR, 21% PR) in the DN group. The 12-month PFS was 38% (95% CI: 28-not reached [NR]) in the DR group vs 57% (95% CI: 37-NR) in the DN group (HR: 0.6, p=0.08). The 12-month OS was 74% (95% CI: 64-NR) in the DR group and 86% (95% CI: 68-NR) in the DN group (HR: 0.56, p=0.18). CRS and ICANS rates were similar between the two groups: 74.7% (4% grade ≥3) and 13.1% (2% grade ≥3), respectively, in the DR group, and 78.6% (4% grade ≥3) and 21.4% (0% grade ≥3), respectively, in the DN group. **Conclusions:** A majority of pts treated with BCMA-directed CAR T for RRMM in this single-center experience were dara refractory. Despite more prior LOT, higher rates of EMD, and higher rates of prior BCMA-directed therapy, the DR group showed similar efficacy outcomes to DN group. Longer follow up with more patients, as well as details of efficacy and safety outcomes with univariate and multivariate analysis will be presented at the meeting.

P-012

Real-World Safety and Early Efficacy of Talquetamab in Patients with Heavily-Pretreated Relapsed/Refractory Multiple Myeloma

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Introduction: Talquetamab (Talq), a G protein-coupled receptor, class C group 5 member D (GPRC5D)-directed bispecific T-cell antibody (BsAb), was approved in August 2023 for patients (pts) with relapsed/refractory multiple myeloma (RRMM) who have received ≥4 prior lines of therapy (LOTs), based on the results of MonumenTAL-1 trial. Here, we evaluated the real-world safety and early efficacy of Talq in a heavily pretreated pt population including those who would have been considered ineligible for the MonumenTAL-1 trial. **Methods:** This single center retrospective study included pts with RRMM who received standard of care Talq monotherapy between August 2023 and March 2024. Only pts who received ≥1 therapeutic doses were included, and all pts had at least one month of follow up available at data cut off. Responses were determined per IMWG response criteria. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Other adverse events (AEs) were graded based on CTCAE v5.0. Kaplan-Meier analysis was used for progression free survival (PFS) and overall survival (OS) assessments. **Results:** Among 28 pts analyzed (61% Female, 18% Black), median age was 65 years (range, 43-85) and median number of prior LOTs was 7 (range, 4-14). All pts were triple class exposed, 36% were penta refractory, 50% had high-risk cytogenetics, 50% had extramedullary disease, and 11% had ≥5% circulating plasma cells at baseline. ECOG performance status was 0-1 in 89% of pts. Notably, 16/28 (57%) pts would not have met eligibility criteria for MonumenTAL-1 trial, primarily due to prior T-cell-redirecting therapy (32%) and/or baseline grade (G) 3-4 cytopenias (36%). Non-hematologic AEs of interest included CRS in 57% (G1-2 only), ICANS in 14% (1 G3 event), skin/rash-related AEs in 79% (1 G3 event), nail-related AEs in 43% (G1-2 only), weight loss in 68% (1 G3 event), dysgeusia in 64% (G1-2 only), dry mouth in 54% (G1-2 only), and dysphagia in 29% (G1-2 only). Rates of G3-4 hematologic AEs were 11% for anemia, 25% for thrombocytopenia, 11% for neutropenia, and 43% for lymphopenia. No treatment-related mortality was observed, although 3/28 (11%) pts had died at data cut-off due to disease progression. For response-evaluable pts (n=26), overall response rate was 58% (CR 12%, VGPR 27%, PR 19%), with 81% (95% CI, 57-92%) showing an ongoing response at 6 months. With a median follow up of 3.6 months (range 1.0-7.7), estimated 6-month PFS and OS were 61% (95% CI, 40-76%) and 89% (95% CI, 70-96%), respectively. **Conclusions:** This study represents one of the first real-world experiences of Talq for RRMM. While there were considerable rates of dermatologic and oral toxicities, no major life-threatening AEs were observed. Despite aggressive disease biology and more than half of the pts being MonumenTAL-1 ineligible, early efficacy results are encouraging.

P-013

CERVINO: A Phase 3, Multicenter, Randomized, Open-Label Study of ABBV-383 Compared With Standard Available Therapies in Patients With Relapsed or Refractory Multiple Myeloma (RRMM)

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Introduction: Trial in progress. RRMM has a poor prognosis, and patients have limited treatment options after progression on available therapies including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 mAbs. B-cell maturation antigen (BCMA) has been validated as a target for RRMM, and several BCMA-directed therapies have been approved. However, more tolerable, efficacious, and convenient BCMA-targeted therapies are needed to improve outcomes. The distinctive BCMA × CD3 bispecific antibody ABBV-383 is composed of 2 high-affinity BCMA-binding domains, a low-affinity CD3-binding domain designed to reduce the risk for cytokine release syndrome (CRS), and a silenced Fc tail resulting in an extended half-life that supports Q4W dosing. Encouraging efficacy and a manageable safety profile were seen in the first-in-human phase 1 trial with ABBV-383 in heavily pretreated patients with RRMM (Rodriguez et al. J Clin Oncol. 42, 2024;suppl 16:7531). The primary objective of this trial is to evaluate the efficacy, safety, and tolerability of ABBV-383 monotherapy compared with standard available therapies (SATs) in patients with RRMM following ≥2 prior therapies. **Methods:** This global, phase 3, multicenter, randomized, open-label, parallel-group study (NCT06158841) enrolls patients (≥18 years) with RRMM and an ECOG performance status ≤2 who received ≥2 prior lines of therapy, including exposure to a PI, IMiD, and anti-CD38 mAb. Patients who received prior BCMA-targeted therapy are excluded. Patients are randomized 1:1 to receive IV ABBV-383 60 mg Q4W without step-up dosing or investigator's choice of SAT (carfilzomib + dexamethasone, elotuzumab + pomalidomide + dexamethasone, or selinexor + bortezomib + dexamethasone), and will continue treatment until confirmed progressive disease or other discontinuation criteria are met. ABBV-383 may be administered in an outpatient setting at sites with institutional guidelines. Otherwise, patients are admitted to hospital for ≥24 hrs on cycle 1 day 1 to monitor for CRS. In select countries, wearable digital health devices are used to collect vital sign data to characterize the CRS profile; these may include axillary temperature, cardiac and respiratory vital signs, and physical activity. The dual primary end points are progression-

free survival and overall response rate. Secondary end points include overall survival, complete response (CR), very good partial response or better, minimum residual disease negativity with ≥CR rates, and change in disease symptoms and physical functioning. Biospecimens are collected at different time points to assess PK and evaluate biomarkers. Approximately 140 sites total across Australia, Austria, Belgium, Canada, China, Czechia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, Poland, Portugal, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, UK, and USA will enroll ~380 total patients. **Results:** n/a. **Conclusions:** n/a.

P-014

Efficacy and Safety of ABBV-383, a BCMA Bispecific Antibody, in Black Patients With Relapsed/Refractory Multiple Myeloma: A Subgroup Analysis of a Phase 1 Trial

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Introduction: There is an unmet need for novel therapies with convenient dosing and improved safety to optimize patient (pt) adherence and outcomes in multiple myeloma (MM), particularly for disease refractory to current therapies. ABBV-383, a distinctive, next-generation B-cell maturation antigen × CD3 T-cell–engaging bispecific antibody, has demonstrated promising results in an ongoing first-in-human phase 1 trial in relapsed/refractory MM (RRMM) pts (Rodriguez et al. ASCO 2024. Abstract 7531; Weisel et al. EHA 2024. Abstract S211). Although MM incidence is higher in some historically underrepresented populations, there remains limited clinical outcomes data for these pt groups. Here we report the efficacy and safety of ABBV-383 at 40–60 mg in the Black/African American subgroup from this ongoing phase 1 trial (NCT03933735). **Methods:** This phase 1 open-label, dose-escalation/expansion trial enrolled pts with RRMM who received ≥3 prior lines including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. In the dose-expansion phase, ABBV-383 was evaluated at 40 or 60 mg Q3W and 60 mg Q4W. Demographics and efficacy, safety, and pharmacokinetics (PK) of ABBV-383 were analyzed in Black/African American pts in this trial. **Results:** In total, 37/220 (17%) pts were Black/African American with 17% (24/140) in 40- to 60-mg dose cohorts. Median age was 62 years, with 4 median lines of prior therapy (range 3–10). As of January 18, 2024, median duration of follow-up was 21.5 months. Objective response rate was 61% (14/23 pts), with 57% (13/23) of pts having ≥VGPR and 39% (9/23 pts) with ≥CR. Median progression-free survival was 11.8 months (4.7, NE). Treatment-emergent adverse events of any grade (G)/G3/4 occurred in all (100%)/18 (75%) pts, respectively. Incidence of G3/4 neutropenia was 33% (8 pts), anemia 25% (6 pts), and thrombocytopenia 13% (3 pts). G3/4 infections rate was 21% (5 pts); the most common infections were COVID-19 (2 pts; 8%) and pneumonia (2 pts; 8%). There was no reported ICANS in this subgroup and CRS occurred in 15 pts (63%); 12 pts (50%) had G1 and 3 pts (13%) had G3 CRS. The ABBV-383 population PK analysis using data from the phase 1 trial (Polepally et al. ASCPT 2024. Abstract PII-065) indicated that race (Black/African American vs White/Other) was a nonsignificant covariate. **Conclusions:** ABBV-383 demonstrated a tolerable safety profile and antitumor activity in Black/African American pts that was comparable with the total pt population (Rodriguez et al. ASCO 2024. Abstract 7531; Weisel et al. EHA 2024. Abstract S211). In addition, clinical outcomes between racial groups were similar when the equivalent treatment was administered. Furthermore, no difference in PK was found between Black/African American and White/Other pts. No new safety signals were reported. ABBV-383 at 60 mg Q4W will be investigated in the registrational phase 3 trial (NCT06158841) in RRMM.

P-015

Response of CD8+ T Lymphocytes Under Stimulation of Dendritic Cells Fused With Multiple Myeloma Plasma Cells

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Introduction: Despite the various treatments available, Multiple Myeloma (MM) remains an incurable disease. Immunotherapy research has been explored to prolong the lives of patients affected by this condition. Recently, it was confirmed that vaccination using dendritic cell (DC)/MM fusions can increase the presence of MM-reactive lymphocytes in the bloodstream and strengthen the clinical response after autologous stem cell transplantation. The effects of the interaction between DCs fused with tumor cells on the lymphocyte response are crucial in this therapy. Specifically, CD8+ T lymphocytes play an essential role in the defense against cancer. In this study, we propose an in vitro model to exclusively investigate the behavior of CD8+ T lymphocytes under the influence of DC fused with plasma cells. **Methods:** The source of plasma cells for fusion was the RPMI 8226 cell line. DCs were obtained through isolation and differentiation of monocytes from healthy donors' blood. Before fusion (plasma cells/DCs), the RPMI 8226 cell line was labeled with FAR RED and dendritic cells with CFSE. To promote fusion, the cells were treated with a 50% polyethylene

glycol solution. After fusion, the cells were irradiated with 25 Gy. The fused (DF) and non-fused(DNF) cells were concentrated by cell sorting through flow cytometry. These cells were co-cultured for five days with autologous CD8+ T lymphocytes (obtained from blood mononuclear cells and subsequent negative selection). On the fifth day of culture, IL-15(10ng/ml) was added to expand the lymphocytes for an additional 12 days. These lymphocytes were quantified, phenotyped, and subjected to a cytotoxicity assay against RPMI 8226 cell line cells at ratios of 1:1 – 20:1 (lymphocyte: tumor cell). **Results:** The fusion rate of DCs with the RPMI 8226 cell line was 4-19%, and the post-selection purity was 91%. The production of CD8+ T lymphocytes was higher in cultures stimulated by DF than by DNF - 4.77x104/well and 1.94x104/well, respectively (n=3, p< 0.0253). Lymphocytes stimulated by hybrid cells showed higher production of CD8+/CD314+(median:4.56x104/well) and CD8+/CD314+/CD56+(median:1.80x104/well) than DNF (medians of 1.90x104/well and 0.18 x104/well, respectively) in all experiments. Lymphocytes induced by DF showed major production of perforin, granzyme-β, and IFN-γ. In the cytotoxicity test, lymphocytes maintained with DF provided a mortality rate of up to 78.2% at the 20:1 (lymphocyte: tumor cell) ratio, while stimulation by DNF maintained the baseline mortality rate of the cell line at 33.0% at all evaluated ratios. **Conclusions:** Through phenotype analysis and functional assays, we demonstrated that CD8+ T lymphocytes stimulated by DF after co-culture expanded with IL-15 exhibit cytotoxic potential against MM. The mechanisms underlying the induction of this cytotoxicity against MM by these cells must be investigated, as well as strategies to further enhance this response.

P-016

Comparative Efficacy of CARVYKTI in CARTITUDE-4 versus Alternative Treatments from Daratumumab Clinical Trials for the Treatment of Patients with Lenalidomide-Refractory Multiple Myeloma

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Introduction: In CARTITUDE-4, a phase 3 open-label randomized controlled trial, CARVYKTI (ciltacabtagene autoleucel; cilta-cel), demonstrated superior progression-free survival (PFS) and response rates over daratumumab, pomalidomide and dexamethasone [DPd], or pomalidomide, bortezomib and dexamethasone [PVd], in patients with relapsed and refractory multiple myeloma (RRMM) who are refractory to lenalidomide and have received 1-3 prior line(s) of therapy (LOTs) including an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). The objective of this abstract is to evaluate the comparative efficacy of cilta-cel vs. a combined group of alternative treatments from daratumumab clinical trials. **Methods:** Data were available for patients from CARTITUDE-4 who received cilta-cel, and from nine daratumumab trials (CASTOR, CANDOR, APOLLO, ALCYONE, MAIA, GRIFFIN, CASSIOPEIA, POLLUX and EQUULEUS) who received active or subsequent treatments with or without daratumumab (mixed cohort of regimens where the most frequently used were carfilzomib and dexamethasone [Kd], daratumumab with Kd [DKd], pomalidomide and dexamethasone [Pd], and DPd, among others). Patients from the daratumumab clinical trials had either newly diagnosed MM (NDMM) or RRMM at study enrolment. Patients were included in the comparator cohort if they satisfied the key eligibility criteria of CARTITUDE-4 at enrollment or at a subsequent line of therapy. Inverse probability of treatment weighting was used to adjust for imbalances between cohorts on key patient characteristics. Overall response rate (ORR), very good partial response or better rate (≥VGPR), complete response or better rate (≥CR), PFS, real-world PFS (RW-PFS) and time to next treatment (TTNT) were assessed. Sensitivity analyses were conducted using different analytical methods and additional characteristics. **Results:** The cilta-cel cohort consisted of 208 patients in the CARTITUDE-4 trial and the combined comparator cohort included 800 patients from the daratumumab trials. After adjustment, baseline covariates were similar across the cohorts. Cilta-cel demonstrated improved ORR (odds ratio [OR]: 3.51; 95% confidence interval [CI]: 2.21-5.65), ≥VGPR (OR: 7.25; 95% CI: 4.66-11.49), and ≥CR (OR: 16.45; 95% CI: 9.99-28.00) vs. the comparator cohort. Cilta-cel was found to reduce the risk of progression or death by 63% (PFS hazard ratio [HR]: 0.37; 95% CI: 0.26-0.52) and 73% (RW-PFS HR: 0.27; 95% CI: 0.19-0.37), and reduce the risk of progression, death or next treatment by 72% (TTNT HR: 0.28; 95% CI: 0.20-0.39). All results were statistically significant (p< 0.0001) and consistent across sensitivity analyses. **Conclusions:** Cilta-cel showed superior efficacy compared to alternative treatments from the daratumumab clinical trials across all outcomes, highlighting the potential for cilta-cel to be considered a new standard of care option for lenalidomide-refractory RRMM patients, who have received 1-3 prior LOTs, including an IMiD and a PI.

P-017

Impact of Genetic Ancestry on Outcomes and Toxicity of Ide-cel in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: CAR-T therapy has revolutionized RRMM treatment, but racial and ethnic disparities persist. We examined the influence of genetic ancestry, which has been linked to various myeloma cytogenetic and clinical features, on CAR-T efficacy and safety. **Methods:** This retrospective single-center study included RRMM patients who underwent apheresis for idecabtagene vicleucel between 11/2018 and 02/2023 in clinical trials (KarMMa-2, KarMMa-3) or as standard of care (SOC). Data on demographics, disease features, treatment, and follow-up were extracted from medical records. Efficacy outcomes were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Safety outcomes were incidence and grade of CRS/ICANS, hematological toxicity, and infection. Number of medications and a revised HCT-CI score were used as measures of comorbidities. Genetic ancestry was estimated using ADMIXTURE from germline DNA genotyping. Patients were categorized by ancestral origin: African (AFR ≥75% or < 75%), European (EUR ≥50% or < 50%), and admixed (ADM ≥30% or < 30%). Comparisons used chi-squared tests and ANOVA. Associations with genetic ancestry were tested using logistic regression. **Results:** Our analysis included 49 patients (10 trial, 39 SOC), 26 of whom self-identified as White, 13 as Black, and 10 as Hispanic/Latino. Median age was 60.1y (51.5-66.6). Those with AFR ≥75% had a higher rate of organ involvement (i.e. visceral extramedullary disease including myeloma renal disease; 67% vs 29%, P=0.03) and high bone marrow (BM) plasma cell burden with ≥50% involvement (56% vs 13%, P< 0.01) than AFR < 75%. Patients with EUR ≥50% had lower rates of organ involvement (24% vs 56%, P=0.03) and high BM plasmacytosis (10% vs 37%, P=0.02) than EUR < 50%. ECOG scores significantly differed at CAR-T referral, with AFR ≥75% associated with ECOG score ≥2 (67% vs 25%, P=0.02). ADM ≥30% was associated with higher BMI (35.6 vs 27.8 kg/m2; P=0.04). AFR ancestry was linked to a higher number of medications and more exclusions from clinical trials due to organ dysfunction, but baseline eGFR did not differ. High AFR ancestry was associated with risk of infectious complications (OR 7.82; 95% CI: 1.33-45.91; P=0.02) and grade 3+ neutropenia (OR 7.74; 95% CI: 1.18-50.77; P=0.03). Patients with higher AFR ancestry tended to have higher levels of inflammatory markers (ferritin and CRP). Ancestry was not associated with HCT-CI score or with ORR, PFS, OS, or rates of CRS/ICANS. **Conclusions:** Our study highlights significant disparities in patient characteristics and treatment toxicity based on genetic ancestry. Patients with high AFR ancestry had more severe disease at baseline, higher ECOG scores, and greater rates of posttreatment severe neutropenia and infectious complications. Those with higher EUR ancestry had fewer baseline complications and severe adverse events. Our findings underscore the need to consider genetic ancestry in planning and prognosis for CAR-T therapy. Multivariate analysis is ongoing.

P-018

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

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Introduction: Talquetamab (tal) is the first approved GPRC5D-targeting bispecific antibody for treatment of patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) based on results from the MonumenTAL-1 study (NCT03399799/NCT04636552). LocoMMotion (NCT04035226) and MoMMent (NCT05160584) are two prospective, consecutive, observational studies evaluating real-world physician's choice treatment (RWPC) in pts with TCE RRMM. Both studies were designed to mirror ongoing, single-arm trials to enable their use as external control arms. We report updated adjusted comparisons to determine the relative efficacy of tal vs RWPC. **Methods:** Individual pt-level data (IPD) from MonumenTAL-1 were included for pts who received subcutaneous tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W) (data cut-off [DCO] Jan 2024; median follow-up of 29.8 and 23.4 months, respectively). An external control arm was created using IPD from LocoMMotion (final data; median follow-up of 26.4 months) and MoMMent (DCO Aug 2023; median follow-up of 13.9 months) that met MonumenTAL-1 eligibility criteria. Imbalances in baseline characteristics were adjusted for using

inverse probability of weighting with average treatment effect in the treated. Balance after adjustment was assessed using standardized mean differences (SMD). ORR, ≥VGPR, ≥CR, DOR, PFS, time to next treatment (TTNT), and OS outcomes were assessed. For binary outcomes, a weighted logistic regression was used to estimate odds ratios and response ratios with 95% CIs. For time-to-event outcomes, a weighted Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs. Sensitivity analyses evaluated the impact of alternative statistical methods and variable adjustment. **Results:** The RWPC cohort included 175 pts who met MonumenTAL-1 eligibility criteria, with 73 different treatment regimens. After weighting, the RWPC cohort was well balanced vs tal cohorts, with all SMD < 0.22. Pts who received tal QW (n=143) had superior outcomes vs RWPC: pts were 2.5, 4.5, and 95.8 times more likely to achieve a response (ORR), ≥VGPR, and ≥CR, respectively; had longer DOR (HR [95% CI], 0.72 [0.47–1.11]) and significantly longer TTNT (HR, 0.51 [0.39–0.67]; P< 0.0001); and had reduced risk for progression or death and death by 46% (P< 0.0001) and 62% (P< 0.0001), respectively. Similarly, pts who received tal Q2W (n=154) had superior outcomes vs RWPC: pts were 2.4, 4.8, and 124.0 times more likely to achieve a response (ORR), ≥VGPR, and ≥CR, respectively; had significantly longer DOR (HR, 0.49 [0.32–0.75]; P=0.001) and TTNT (HR, 0.44 [0.34–0.58]; P< 0.0001); and had reduced risk for progression or death and death by 54% (P< 0.0001) and 64% (P< 0.0001), respectively. Results were consistent across sensitivity analyses. **Conclusions:** Tal QW and Q2W showed superior efficacy outcomes compared with RWPC with longer follow-up, highlighting its clinical benefit in pts with TCE RRMM.

P-019

Cytotoxic CD4+ T cells are major drivers of side effects and response after chimeric antigen receptor T cells against BCMA

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Introduction: Variables that predict long-term response and side effects after chimeric antigen receptor (CAR) T cell therapy for relapsed/refractory multiple myeloma (RRMM) are currently unkown. We conducted a large longitudinal single-cell multi-omics study to identify factors that predict cytokine release syndrome (CRS) and clinical outcome to BCMA-directed CAR T cells. **Methods:** We analyzed 61 RRMM patients treated with Ide-cel (n=34) or Cilta-cel (n=28). Peripheral blood (PB) mononuclear cells (PBMCs) were isolated (n=113 samples) on the day of leukapheresis (LP), on day 30 and 100 after CAR T cell infusion. PBMCs were subjected to single cell RNA, TCR, BCR and ADT sequencing. Additionally, flow cytometry of PB was performed at the day of LP, after lymphodepletion (d0) and on days 7, 14, 30 and 100 following CAR therapy. **Results:** More than 400,000 single cells were sequenced and passed quality assessment. Cellular composition of PB between patients with or without CRS was distinct at LP and on days 30 and 100. Patients with CRS ≥2 harbored more CD4+ cells at LP and CD8+ cells on day 30 and 100 after therapy compared to patients without CRS. Fewer classical monocytes were observed at all time points in patients with CRS ≥2. We observed an association between the proportion of CD4 cells at the time of LP and increasing CRS severity after infusion (p=0.022). Increased CRS was associated with higher cytotoxic enrichment score among CD4 clones, but not CD8 clones on day 30. We also observed a significantly (p=0.038) higher proportion of polyfunctional T-cells on day 30 in patients with more severe CRS. PFS was significantly better for patients treated with Cilta-cel compared to Ide-cel (log-rank test, p=0.004). Flow cytometry showed a strong association of response with CAR-T expansion measured at day 14 and 30 after infusion. For patients treated with Cilta-cel, expansion was initially slower but reached significantly higher levels of CAR+ T cells on day 14 compared to Ide-cel. There was a significantly higher proportion of CD4+ CAR-T cells in Cilta-cel compared to Ide-cel patients (day 14: 35% vs 10%). TCR repertoires showed an increased clonality in non-progressive disease(PD) compared to PD at time of leukapheresis and day 30. TCR diversity analysis of CD4+ T cells revealed increased diversity (p< 0.05) on day 30 and day 100 and for CD8+ T cells onday 30 in patients with non-PD compared to PD. T cell subtypes revealed an increased diversity of cytotoxic CD4 cells in non-PD compared to PD across all time points. Longitudinal analysis indicated persistence of PB plasma cells with distinct BCR clones and copy number variations in patients with PD. **Conclusions:** Cytotoxic CD4+ T cells play a significant role in the response and side effects following BCMA-directed CAR T cell therapy. This effect is more pronounced in Cilta-cel compared to Ide-cel.

P-020

Treatment Positioning Model to Evaluate the Survival Benefit of Ciltacabtagene Autoleucel in Second-Line Compared With Later-Line Treatment of Lenalidomide-Refractory Multiple Myeloma

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Introduction: There are numerous potential benefits to early use of chimeric antigen receptor (CAR)-T cell therapies in patients (pts) with lenalidomide (len)-refractory multiple myeloma (MM). These

include improved treatment responses, fewer pts lost to attrition/rapid progression, and potentially improved long-term outcomes. Ciltacabtagene autoleucel (cilta-cel) was recently approved based on the CARTITUDE-4 trial (NCT04181827), which demonstrated superior efficacy of cilta-cel vs physician's choice of pomalidomide, bortezomib, and dexamethasone, or daratumumab, pomalidomide, and dexamethasone in pts with relapsed/refractory MM (RRMM) who received 1–3 prior lines of therapy (LOT) and were len refractory. We adapted a modeling approach to evaluate the survival benefit of using cilta-cel earlier in the treatment pathway in relapsed, len-refractory MM pts. **Methods:** A Markov model was used to compare the survival benefit of using cilta-cel in second line (2L) followed by standard of care (SOC) in third line or greater (3L+) vs using SOC in 2L followed by cilta-cel in 3L+. SOC was defined based on the treatment regimens received by pts with len-refractory MM previously treated with 2L and 3L+, respectively, in the Flatiron Health database, with different distributions of treatments between 2L and 3L+. Inclusion/exclusion criteria of the CARTITUDE-4 population were applied to the SOC population from the Flatiron cohort and weighted on key prognostic factors and treatment effect modifiers. Time spent in 2L and 3L+ was defined by time to next treatment and overall survival (OS) derived from CARTITUDE-4 and Flatiron 2L and 3L+ subgroup datasets, respectively. Standard parametric survival models were used to estimate the transition probabilities over time. Attrition rates were defined by the number of deaths divided by deaths plus the number of those who progressed from the Flatiron dataset and were assumed to be the same in both arms. **Results:** The cilta-cel arm of the CARTITUDE-4 intent-to-treat cohort consisted of 208 pts (data cut-off, November 2022; median follow-up, 16 months) and the adjusted Flatiron cohort consisted of 1977 observations (data from February 2016–December 2022; median follow-up, 34 months). According to this simulation model, using cilta-cel in 2L resulted in longer OS benefit compared with using cilta-cel in 3L+ after SOC (8.8 vs 5.5 years, respectively). When cilta-cel was used in 2L, predicted OS rates at 5, 10, and 15 years were 69.6%, 45.6%, and 31.9%, respectively, compared with 53.0%, 33.6%, and 24.0% when cilta-cel was used in 3L+. Results of scenario analyses consistently demonstrated the survival benefit of using cilta-cel in 2L vs 3L+. **Conclusions:** Our simulated model suggests that using a single infusion with cilta-cel earlier might result in better survival outcomes for len-refractory pts with RRMM. However, more investigation, including comparison of real-world data is needed to test the results seen with this model.

P-021

A German Multicenter Real-World Analysis of Talquetamab in 102 Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: Bispecific T-cell engagers (BTCE) are revolutionizing the treatment landscape of relapsed/refractory multiple myeloma (RRMM). Talquetamab is a CD3xGPRC5D bispecific antibody approved by FDA and EMA based on results from the pivotal MonumenTAL-1 trial. However, clinical trial patients must meet strict enrollment criteria and benefit from intensive clinical care, which has led to discrepancies between trial and standard treatment results in the past. We therefore aimed to explore the efficacy and safety of talquetamab in the real-world setting. **Methods:** This multicenter retrospective observational study included 102 patients with RRMM who had received at least one full

dose of standard-of-care talquetamab at one of 20 German myeloma centers. Treatment response was determined by investigators according to IMWG criteria. Near complete remission (nCR) was defined as serological CR without bone marrow status. Cytokine-release syndrome (CRS) and immune effector-cell associated neurotoxicity (ICANS) were graded according to ASTCT criteria, other adverse events according to CTCAE v5.0. **Results:** The median age was 64 years (range 24-84), and 31 patients were female (30%). Among evaluable patients, 36% (n=31/85) had ISS stage 3, 42% (n=39/93) had extramedullary disease and 51% had high risk cytogenetic abnormalities (n=43/85), defined as presence of del(17p), t(4;14) and/or t(14;16). Patients had received a median of 6 prior lines of therapy (range 3-15). Triple-class and penta-drug refractory disease were found in 85% (n=87/102) and 52% (n=52/100) of patients, respectively, and prior BCMA-directed CAR T-cell and/or BTCE therapy in 36% (n=37/102) and 22% (n=22/102), respectively. The majority of patients (57%; n=55/97) would not have been eligible for the MonumenTAL-1 trial. Seventy patients (69%) were affected by CRS, including 49 grade 1 (48%), 18 grade 2 (18%) and three grade 3 (3%) events. ICANS occurred in 6% of evaluable patients (n=6/98) and did not exceed grade 2. During cycle 1, CTC grade ≥ 3 neutropenia, anemia and thrombocytopenia were observed with a frequency of 33% (n=29/88), 39% (n=40/102) and 40% (n=41/102), respectively. With a median follow-up of 4.0 months (95% CI 3.0-4.7), CTC grade ≥ 3 infections were observed in 31 cases (30%). CTC grade 2 dysgeusia and grade ≥ 2 weight loss were observed in 54% (n=54/100) and 12% (n=11/90) of the patients, respectively. The overall response rate (≥ partial response) was 57% (n=58/102). Twenty patients achieved a nCR or better (20%). The median PFS was 5.7 months (95% CI 3.6-NA). **Conclusions:** Our real-world analysis confirms the safety and efficacy of talquetamab in RRMM. Response and survival rates appeared lower than in the trial population, albeit with a short follow-up period. However, our cohort included a higher proportion of patients with disease-associated risk factors, and the majority would not have been eligible for trial enrollment.

P-022

Discovery of Shared, MHC-Promiscuous Antigens in Multiple Myeloma Patients

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal expansion of malignant plasma cells in the bone marrow. Clonality suggests the presentation of a conserved tumor antigen landscape on surface major histocompatibility complex (MHC). Identification of shared tumor antigens across patients offers a promising avenue for developing broad-spectrum immunotherapies. Here, we investigate the presence of shared MHC class I-presented antigens in multiple myeloma patients to identify novel targets for immunotherapy. **Methods:** We performed HLA haplotyping on tumor and germline samples from 20 multiple myeloma patients. Using immunoprecipitation, we isolated MHC class I complexes from malignant CD138+ cells derived from patient bone marrow samples and healthy cells. The peptides were identified using liquid chromatography tandem mass spectrometry (LC-MS/MS) to generate complete, patient-individual class I HLA immunopeptidomes. Peptides were classified as either "healthy" (self-antigens) or "non-healthy" (tumor-associated antigens). We also reconstituted B cell receptor (BCR) sequences from RNA-sequencing for each patient's dominant myeloma clone and predicted high-affinity binding peptides for their tumoral HLA haplotypes. We verified the immunogenicity and HLA promiscuity of candidate peptides in MM patient bone marrow samples using several HLA supergroup-spanning MHC tetramers. **Results:** Analysis of the immunopeptidomes revealed that, as expected, most MHC class I-eluted peptides were 9-10 amino acids in length. Non-healthy peptides included both cancer-associated antigens (CAAs) and peptides from non-canonical translation products (nuORFs). Several antigens were common among multiple patients. Notably, a peptide from synaptonemal complex central element protein 1 (SYCE1) was found in 70% of patients. Additionally, we identified one BCR-derived neoantigen in the IGKV hypervariable region of one patient's dominant clone. T cells targeting such immunoglobulin-derived antigens were found in several patients. Further, a minimal epitope derived from cancer/testis antigen 2 (CTAG2) was identified as a recurrent antigen recognized by T cells across patients with different HLA haplotypes. Flow cytometry with MHC tetramers loaded with this novel peptide confirmed T cell reactivity against this antigen in four distinct HLA-A supergroups. **Conclusions:** Our findings suggest the frequent occurrence of private, MM immunoglobulin-derived antigens, presenting new potential targets for personal immunotherapy. Furthermore, shared, MHC-promiscuous antigens such as SYCE1 and CTAG2 can induce conserved bone marrow T cell responses in multiple myeloma patients. These shared antigens could be exploited for vaccination approaches or adoptive cell therapies, offering a new therapeutic strategy for MM patients with limited neoepitope loads. Future studies will focus on validating these targets in larger patient cohorts and exploring their potential in clinical applications.

P-023

Efficacy and Safety of CAR T-cell Therapy for Plasma Cell Leukemia

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Introduction: Plasma cell leukemia (PCL) is unique in the spectrum of malignant monoclonal gammopathies and characterized by a poor prognosis. Despite significant improvement over recent years, the use of immunomodulatory drugs, proteasome inhibitors and either autologous or allogeneic stem cell transplantation cannot overcome the poor prognosis in this disease. Chimeric antigen receptor (CAR) T-cell therapy represents a revolutionary treatment for multiple myeloma, but its role in PCL is unclear. **Methods:** This is the first comprehensive international study on current CAR T-cell therapy for patients with PCL. We aimed to describe patient characteristics and efficacy and safety of CAR T-cell therapy in this challenging patient population. Furthermore, detailed description of post-relapse treatments and outcomes will be reported. **Results:** Patient characteristics. The total cohort included 22 patients with PCL with a median age of 59 years at time of CAR T infusion (range, 28-76 years), of whom more patients (59%) were male. The majority was of white/caucasian background (86%), while 9% were black and 5% Hispanic. ECOG performance status was 0 (35%), 1 (47%), 2 (12%), and 3 (6%). Extramedullary disease (EMD) was present in 36%. High-risk cytogenetics (including del(17p), t(4;14), t(14;16), and gain/amp chromosome 1) was present in 73%, and 36% had two or more high-risk aberrations. Treatment characteristics. Refractory status before CAR T was triple-class refractory in 36% and penta-refractory in 14%, and 94% of patients had received autologous or allogeneic transplant before CAR T. Median number of prior lines of therapy was 5 (range, 1-11). In terms of CAR T product: 11 (50%) received ide-cel, 3 (14%) received cilta-cel, and 8 (36%) received academic CAR T. Median time to CAR T from diagnosis was 3 years. Safety. The incidence of CRS was 45% (n=10), occurring within a median of 1 day after infusion and lasting a median of 3 days (range, 1-8 days). Only 1 case of grade 3 CRS occurred. The incidence of ICANS was 5% (n=1), which was of grade 1, occurring 4 days after infusion and lasting 3 days. One patient developed severe HLH and eventually died. Efficacy. The median follow-up from CAR T infusion was 16 months, and 1 patient (5%) died between apheresis and infusion due to progressive disease. Overall response in 21 evaluable patients was 81%, with 29% complete response. The 1-year overall survival estimate in the intention-to-treat cohort of all 22 patients was 58% and the 1-year progression-free survival was 42%. Concurrent EMD was associated with worse progression-free survival (P=0.04). **Conclusions:** This first comprehensive report on CAR T-cell therapy for PCL with long follow-up indicates feasibility with promising survival outcomes in this challenging and heavily pretreated patients.

P-024

Phase Ib Study Investigating the Safety, Pharmacokinetics, and Efficacy of Subcutaneous Administration of ABBV-383 in Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) that progresses on available therapies have a poor prognosis. B-cell maturation antigen (BCMA) is an established target in MM, yet there is a need for highly effective therapies with improved safety/tolerability that also provide increased quality of life, administration convenience, and reduced treatment burden with simplified schedules. ABBV-383 is a distinctive BCMA x CD3 bispecific antibody T-cell engager composed of bivalent high-avidity BCMA-binding domains, a low-affinity CD3-binding domain designed to reduce cytokine release and with potential for minimal T-cell exhaustion, and a silenced Fc tail that retains FcRn binding designed for extended half-life with dosing every 4 weeks. ABBV-383 as intravenous (IV) administration has shown promising efficacy with a manageable safety profile in the first-in-human study in patients with RRMM who had received ≥3 prior lines of therapy (Rodriguez et al. ASCO 2024. Abstract 7531; Weisel et al. EHA 2024. Abstract S211). **Methods:** This open-label, global, multicenter phase 1b study (NCT06223516) will enroll patients (≥18 years) with RRMM with ECOG ≤2 who had received 3–5 prior lines of therapy and with prior triple-class exposure to a proteasome inhibitor, an anti-CD38 monoclonal antibody, and an immunomodulatory drug in 2 parts. The primary objectives are to characterize the safety, tolerability, and pharmacokinetics (PK) of ABBV-383 after single subcutaneous (SC) administration and IV administration thereafter (part 1) and after SC administration until the end of treatment (part 2), and to determine the dose of ABBV-383 that would yield exposures comparable to that of the IV administration. Secondary objectives are to assess the efficacy and immunogenicity. Each part will consist of screening, treatment, and follow-up periods. In part 1, patients will receive ABBV-383 at 1 of the 2 planned doses. The ABBV-383 dose for part 2 will be selected on the basis of ABBV-383 safety and PK data from part 1. Primary endpoints are CRS and ICANS, and PK parameters (Cmax, Tmax, Ctrough, and AUC).

Secondary endpoints include overall response rate, rates of stringent complete response, complete response, very good partial response, and partial response, duration of response, progression-free survival, time to response, and immunogenicity determined by antidrug antibodies and neutralizing antidrug antibodies. Approximately 25 sites across France, Germany, Israel, Japan, and the US will enroll ~55 total patients. Enrollment is planned to start on July 5, 2024. **Results:** n/a. **Conclusions:** n/a.

P-025

Real-world outcomes of teclistamab for the treatment of relapsed/refractory multiple myeloma at UC San Diego Health: A single-institution experience

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Introduction: Teclistamab, a bispecific antibody targeting B-cell maturation antigen (BCMA) expressed on plasma cells, received FDA approval for the treatment of relapsed/refractory (R/R) multiple myeloma (MM) in 2022. Here we describe the real-world experience of teclistamab at a single institution. **Methods:** We retrospectively reviewed patients with R/R MM who received teclistamab at University of California, San Diego and had at least 6 months of follow up. Baseline characteristics, efficacy outcomes, and safety outcomes were collected. Kaplan-Meier method was used to describe survival. **Results:** A total of 25 patients who received teclistamab between 01/01/2023 and 11/15/2023 were included in this analysis. The median age was 67 years old (range 46-86). Median prior lines of therapy was 5 (range 3-11). Twenty-four patients had triple-exposed disease; 23 had penta-exposed disease. Extramedullary plasmacytomas were present in 48% of patients at time of teclistamab initiation; 32% had received prior BCMA therapy (2 belantamab, 6 idecabtagene vicleucel) before teclistamab. Cytogenetics profiles were available for 20 patients; 17 (85%) had high risk cytogenetics (t(4;14), t(14;16), t(14;20), Del17p, Gain1q). 9 had a single high-risk mutation, 7 had two, and 1 had three. Cytokine release syndrome (CRS) occurred in 17 patients (68%), (3 (18%) grade 2, no grade 3-5); 8 (47%) received tocilizumab. Immune effector cell-associated neurotoxicity syndrome (ICANS) incidence occurred in 2 patients (8%), (1 (50%) grade 2, no grade 3-5). Pain crisis occurred in 6 patients (24%), of whom 2 (33%) discontinued treatment after crisis. Infection occurred in 60% of patients. Of 21 discrete infections, 10 (48%) were grade 1-2, 11 (52%) ≥ grade 3; 2 (13%) were grade 5. The overall response rate (ORR) by IMWG criteria was 57%. Median duration of response for the entire cohort was not reached. Median progression-free survival (PFS) was 5.8 months (95% CI 3.2 – not reached (NR)); median overall survival (OS) was NR (95% CI NR–NR). Univariate analyses showed no statistically significant relationship between response and prior BCMA therapy (p = 1), response and presence of extramedullary disease (p = .25), or response and high-risk cytogenetics (p = .06). Upon subgroup analysis of PFS, higher risk cytogenetics were associated with lower PFS (HR = 9.7, 95% CI 2.1 - 45.1; p< .001). PFS did not vary between subgroups with or without prior BCMA therapy (p = 0.79), or with or without extramedullary disease (p=0.38). **Conclusions:** Overall, the incidence and grades of CRS, ICANS, and infection in our cohort were similar to those observed in the phase I/II MajesTEC-1 trial. The ORR was also comparable. In contrast, the PFS in this study was lower compared to the MajesTEC-1 study. Considering the association between high risk cytogenetics and poor PFS described, this difference may be in part due to the higher proportion of patients with high-risk cytogenetics in our population vs the trial population.

P-026

Combined GPRC5D and BCMA-targeted T-cell Redirecting Therapy in the Treatment of RRMM

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Introduction: BCMA and GPRC5D are clinically validated independent immunotherapy targets in MM. Antigen down regulation and modification are mechanisms of treatment resistance, providing the rationale for multi-targeting strategies. BCMA-directed CAR T-cell therapies provide rapid and deep disease control, but responses are not indefinite. Disease progression between apheresis collection and CAR T-cell infusion accounts for substantial treatment attrition and contributes to post CAR T-cell toxicity. The availability of the GPRC5D-targeted bispecific T-cell engager talquetamab (TAL) provides the opportunity to improve disease control during BCMA CAR T-cell manufacturing and potentially improve outcomes by sequencing targeted therapies. **Methods:** We adopted TAL as standard bridging therapy for patients with triple-class refractory (TCR) RRMM proceeding with BCMA-directed CAR T-cell therapy. All patients were T cell redirection naïve. TAL step up was started promptly after apheresis collection and continued until completion of product manufacturing and at least 2 full TAL doses (0.8 mg/kg, 2 weeks apart) were administered. After at least 1 week from last dose of TAL, patients received standard fludarabine + cyclophosphamide lymphodepletion chemotherapy (LDC) followed by administration of the CAR T-cell product at least 3 days later. Patients underwent guideline-based safety monitoring and infection mitigation. **Results:** To date 8 patients with TCR RRMM underwent apheresis collection and initiated TAL bridging therapy. None of the patients had received prior BCMA or GPRC5D-directed therapy. Median age is 68 years (range 49-77), median prior lines of therapy is 4 (range 3-6), 3 had cytogenetically defined high risk disease and 4 extra medullary disease. Median follow up is 7.3 weeks (from apheresis). During TAL phase, 5/6 patients developed CRS, all grades 1-2. No patient developed infections or other complications during TAL precluding or delaying CAR T-cell treatment. Median

time between TAL first dose and CAR T-cell infusion was 6.0 weeks (N=6, range 5.1-6.9). In 5/6 patients who reached LDC and CAR T infusion, there was reduction of disease burden during TAL phase. Among the 5 patients who have reached CAR-T infusion (3 ide-cel, 2 cilta cel) and 2+ weeks of post-CAR T follow up, 3 developed grade 1 and 1 developed grade 2 CRS and none developed ICANS or post CAR T infection. All patients achieved objective response at 4 weeks post CAR T assessment. **Conclusions:** Combined GPRC5D and BCMA-targeted T-cell redirecting therapy with TAL bridging followed by anti-BCMA CAR T-cell therapy is feasible and highly effective strategy without any unexpected safety concerns or treatment delays. Expanded cohort with extended follow up, MRD results and immunoprofiling will be presented at the meeting

P-027

Real World Experience of Standard of Care Talquetamab in Patients with Relapsed and Refractory Multiple Myeloma

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Introduction: Talquetamab (Talq) is a GPRC5D bispecific antibody approved for triple class exposed patients (pts) with relapsed and refractory multiple myeloma (RRMM), after MonumenTAL-1 study demonstrated an ORR of 71.7% at a dose of 0.8mg/kg subcutaneous every 2 weeks (Q2W) after step-up doses. Here, we present data further supporting the safety and efficacy of Talq in RRMM pts. **Methods:** This retrospective study at Moffitt Cancer Center evaluated pts with RRMM that were treated with standard of care (SOC) Talq at a dose of 0.8mg/kg subcutaneous Q2W after step-up doses between September 2023 and May 15, 2024. CRS and ICANS were graded per ASTCT consensus criteria, while responses were graded based on the IMWG response criteria. **Results:** A total of 39 pts was treated with Talq in our institution; 30 pts with intent to treat until disease progression or intolerable adverse events, and 9 pts with intent to bridge to CAR-T with only 1 cycle of therapy. Median age was 65 years (range 39-89), 46.2% (n=18) were male, and 20.5% (n=8) had an ECOG PS ≥2. 69.2% (n=27) had high risk cytogenetics (defined as del17, t(4;14), t(14;16), and gain 1q). Pts were heavily pretreated with a median of 7 (4-11) prior lines of therapy. 92.3% (n = 36) were triple-class refractory, and 48.71% (n=19) were penta-class refractory. 71.8% (n=28) received prior B-cell maturation antigen targeted therapies (BCMA-TT). 51.3% (n=26) of pts did not meet inclusion criteria for the MonumenTAL-1 study, including 35.9% (n = 14) for cytopenia, 20.5% (n=8) for renal dysfunction, and 15.4% (n=6) for ECOG ≥2. With a median follow up of 5.7 (1-9) months, progression free survival (PFS) and overall survival (OS) has not been reached. Overall response rate was 76.9% (n=30) with 12 pts (30.77%) achieving a complete response or better (≥CR). Ten pts (25.6%) achieved minimal residual disease (MRD) negativity by next generation sequencing (NGS). ORR was 66.7% (n=20/30) among pts receiving Talq as primary treatment and 88.9% (n=8/8) among those receiving Talq as bridging. Toxicity was comparable to the MonumenTAL-1 trial. CRS occurred in 53.8% (n=21) of pts, (12 pts with grade 1, 8 pts with grade 2, and only 1 pt with grade 4), with 25.6% (n=10) requiring Tocilizumab. Median time to onset of CRS was 4.9 (1-10) days after the first dose. 15.4% (n=6) pts had ICANS, (3 pts with grade 1, 2 pts with grade 2, and 1 pt with grade 3). Infections were seen in 11 (28.2%) pts. Dysgeusia, weight loss, skin-related changes, and nail-related were seen in 79.5% (n=31), 43.6% (n=17), 64.1% (n=25), 43.6% (n=17) of pts respectively. Pts bridged with Talq had more skin-related changes, but less dysgeusia than those primary treated, but weight loss was comparable. **Conclusions:** This single center real world safety and efficacy analysis was comparable to that reported in the MonumenTAL-1 study. Longer follow up and larger numbers are needed to properly understand the role of Talq as bridging therapy for CART.

P-028

Characteristics of Bridging Therapy and Impact of Pre-lymphodepletion Tumor Burden on Clinical Outcomes of Idecabtagene Vicleucel

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Introduction: Idecabtagene vicleucel (ide-cel) is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapy approved to treat triple-class exposed (TCE) patients with relapsed/refractory multiple myeloma (RRMM) after ≥2 prior lines of therapy. In this initial analysis, we explore the use of bridging therapy (BT) and evaluate the impact of pre-lymphodepletion (pre-LD) tumor burden on ide-cel outcomes in a standard of care (SOC) setting. **Methods:** This retrospective study at Moffitt Cancer Center examined TCE RRMM patients with adequate labs to assess response, who received BT before SOC ide-cel between April 15, 2021 and February 20, 2024. Patient characteristics, including BT type and response based on adaptation of IMWG criteria, were analyzed using descriptive statistics. Efficacy and safety outcomes were evaluated, stratified by pre-LD tumor burden (< 50% vs. ≥50% plasma cells). **Results:** Of 146 patients who underwent apheresis, 95 (65%) TCE RRMM patients received BT followed by SOC ide-cel, with 23/77 (29.8%) achieving at least a partial response or better among those with measurable disease. The ide-cel overall response rate was higher in BT responders compared to non-responders, although not statistically significant (85% vs. 73%, p=0.4). Several unique BT regimens were used, of

which IMiD/CD 38 mAb combinations, alkylators, selinexor, and PI combinations were each observed in >10% of the cohort. Patients with < 6 vs ≥6 prior lines of therapy were more likely to receive an alkylator or IMiD +/- CD 38 mAb combinations (p=0.019). BT responders were less likely to have undergone prior autologous stem cell transplantation (43% vs. 72%, p=0.016). No differences in baseline characteristics by BT regimen time or responses were observed, likely due to limited sample size, heterogeneity in disease characteristics, and BT type. Similarly, safety outcomes did not differ based on BT type or response to bridging. Patients with low (< 50%, N=35) vs high (≥50%, N=21) pre-LD tumor burden (data available in 56 patients with measurable disease with ≥ 90 days of follow up) showed higher response rates to ide-cel (ORR: 94% vs. 62%, p=0.0046; ≥CR: 60% vs. 29%, p=0.023) and longer progression-free survival (median 13.9 months vs 4.4 months, p=0.0046). Low pre-LD tumor burden was also associated with a significantly lower rate of grade ≥3 CRS compared to high pre-LD tumor burden (0% vs. 13%, p=0.045), while no differences in neurotoxicity were observed. **Conclusions:** Heterogeneous BT use for ide-cel-treated patients was observed, without increased safety events. Patients with low pre-LD tumor burden who received BT had lower rates of severe CRS, higher response, and longer PFS. Further research with a larger patient cohort and longer follow-up is warranted to better evaluate the effectiveness of different BT regimens and their impact on ide-cel outcomes.

P-029

Pharmacokinetics (PK) and Immunogenicity of Linvoseltamab in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) in LINKER-MM1

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Introduction: Linvoseltamab, a BCMA×CD3 bispecific antibody, showed deep and durable responses and acceptable safety when administered intravenously (IV) to heavily pretreated RRMM pts in the Phase (Ph) 1/2 LINKER-MM1 study (NCT03761108; Jagannath et al. AACR 2024). Two of the main objectives of LINKER-MM1 were to characterize the PK and immunogenicity profiles of linvoseltamab, and use these data to further describe its safety and efficacy. Here, we report descriptive PK and immunogenicity of linvoseltamab in LINKER-MM1. **Methods:** Pts received step-up doses in Weeks (Wks) 1–2 and full doses from Wks 2–3 onward, depending on the cohort (COH). To assess the concentration (Conc)–time profile of total linvoseltamab, serum was taken at specified timepoints through the dosing period. Total linvoseltamab (both unbound and BCMA-bound) was measured with an enzyme-linked immunosorbent assay. Anti-linvoseltamab antibodies (ADA) were assessed with an electrochemiluminescence bridging immunoassay. **Results:** 281 pts were analyzed (Ph1: 73; Ph2 50 mg: 104; Ph2 200 mg: 104). In Ph1, step-up dosing (range 1–32 mg) led to an approximately dose-proportional increase in linvoseltamab Ctrough (Ctr), with Cmax at end of infusion. For full doses (range 3–800 mg), a greater than dose-proportional increase in linvoseltamab Ctr was seen during QW dosing to Wk 16, especially at ≥96 mg, and median accumulation ratio was 2.0–4.2 with multiple dosing. In Ph1 pts receiving 5/25 mg step-up doses, Conc–time profiles were similar among COHs in the first 2 wks. In Ph2, linvoseltamab showed time-dependent changes in Ctr, with greater than dose-proportional increases between 50 and 200 mg COHs. Mean Ctr and Cmax were ~3.5-fold higher in the 200 vs 50 mg COHs (consistent with 4-fold dose increase) at Wk 3. However, it increased over time, leading to Ctr ratio (200 vs 50 mg) of 8- and 10-fold at Wks 14 and 22, respectively. The greater than dose-proportional changes in Ctr are likely a result of Conc- and time-dependent changes in linvoseltamab clearance due to decreasing disease burden (thus decrease in BCMA) in response to treatment (leading to reduced target-mediated clearance), and changing IgG dynamics due to disease improvement (most notable in IgG MM pts). After switching from QW to Q2W dosing, Ctr gradually declined to Wk 24, at which point steady state was reached for Q2W dosing. In Ph2 200 mg pts with VGPR who switched to 200 mg Q4W, median Ctr declined (in a greater than dose-proportional manner consistent with nonlinear kinetics) vs pts who remained on 200 mg Q2W. However, median Ctr remained higher vs pts on 50 mg Q2W, with a maintained response. Overall incidence of treatment-emergent ADA was 1.0% (2/192 pts), and ADA status did not lead to meaningful differences in linvoseltamab Conc. **Conclusions:** In pts with RRMM, linvoseltamab was administered as IV infusion (≥30 min infusion duration) across a broad dose range (3–800 mg). The disposition of linvoseltamab was Conc- and time-dependent. Incidence of ADA was low (~1%).

P-030

Low Infection Rates in Patients (pts) With Relapsed/Refractory Myeloma (RRMM) Treated With Alnuctamab (ALNUC) in a Setting of Infection Reduction Strategies (IRS) and Less Frequent Dosing

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Introduction: Treatment with BCMA T-cell engagers (TCEs) increases infection risk. ALNUC is an IV or subcutaneously (SC) dosed TCE with bivalent BCMA binding and head-to-tail structure. SC ALNUC has shown a low rate of grade (G) ≥3 infections in a phase 1 study (NCT03486067) in pts with RRMM (Bar N et al. ASH. 2023). We hypothesized that less frequent dosing in later cycles and IRS implementation are associated with lower infection risk. **Methods:** Pts had ≥3 prior therapy lines and were triple-class exposed. IV ALNUC (0.15–10 mg doses; enrolled 2018–2021) and SC ALNUC (3–60 mg doses; enrolled 2021–2023) were given QW in cycle (C) 1–3 (after step-up doses, if used), Q2W in C4–6, and Q4W in C7+ (28-d cycles). IRS were implemented in IV cohorts after March 2020 in response to G≥3 infections and in SC cohorts for entire duration. IRS included exclusion of pts with respiratory viruses and prophylaxis against bacteria (eg, levofloxacin; C1–3 and during G≥3 neutropenia), Pneumocystis (eg, trimethoprim-sulfamethoxazole; all Cs), and HSV/VZV (eg, acyclovir; all Cs). ALNUC was held for infections until recovery (G≤1/baseline). Immunoglobulin (Ig) levels were measured every C; Ig replacement therapy (IRT) was recommended for IgG < 400 mg/dL. Peripheral blood immune parameters were measured by flow cytometry. Correlations between baseline features and infections were assessed using 2-sided Wilcoxon test. Data cutoff was 4-Sep-2023. **Results:** Of 70 pts who received IV ALNUC (median follow-up [MFU], 8 months), infections (any-G/G3–4/G5) occurred in 66%/36%/4%; 1 G5 event each of pneumonia, bacterial respiratory tract infection, and sepsis. Infection rates were reduced in the 39% of pts who enrolled after IRS implementation (56%/26%/0%) vs 61% of pts who enrolled prior (72%/42%/7%). There were no reported COVID-19 infections prior to IRS implementation; 5 pts (7%) had a COVID-19 event. Of 78 pts who received SC ALNUC (MFU, 12 months), infection rates (any-G/G3–4/G5) were 59%/17%/1%; 1 G5 influenza event occurred. Opportunistic infections (4%) included cytomegalovirus reactivation (3%; n=2, both G2 and no organ involvement) and fungal esophagitis (1%; n=1, G1). COVID-19 events occurred in 24% of pts. IgG < 400 mg/dL occurred in 56% of pts (≥1 events) and was more common in pts with than without G≥3 infections, particularly in later cycles (64% vs 35% at C4D1). IRT was used in 41% of pts. Rate of G≥3 infections decreased over time; 7.8% in C1–3, 7.5% in C4–6, 8.8% in C7–9, 6.5% in C10–12, 3.8% in C13–15, and 0% in C16+. Baseline pt factors (eg, disease burden, baseline labs, and immunophenotyping data) were not found to be associated with on-treatment G≥3 infections among pts who received SC ALNUC. **Conclusions:** These data suggest that aggressive IRS, IRT, and reduced dosing frequency of ALNUC in later cycles contributed to successful reduction of infection rates. Additional immunologic analyses are ongoing to determine the relationship between low infection rates and the unique bivalent format/schedule of ALNUC.

P-031

Phase I Study to Evaluate Cellular Immunotherapy Using CS-1 Targeting Autologous CAR T Cells in Patients with Relapsed and Refractory Multiple Myeloma (RRMM)

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Introduction: CAR T cell therapies targeting BCMA have resulted in durable responses, but not curative and options post relapse remain limited. CS-1 receptor belongs to the signaling lymphocytic activation molecule (SLAM) receptor family, promoting cell adhesion and growth. SLAMF7 (CS-1) targeting CAR T has been reported (CARAMBA trial). CS-1 is highly expressed on MM cells, with low expression in NK cells, small T-cell subsets, and no expression on other tissues. **Methods:** We developed autologous memory-derived T cells using a self-inactivating lentiviral vector to express a CS1-targeting, hinge-optimized, 41BB-costimulatory CAR [CS1(dCH2)BBζ], as well as a truncated human EGFR. RRMM patients (pts) with ≥ 3 prior lines of therapy containing a proteasome inhibitor, an IMiD, and an anti-CD38 therapy were eligible. Pts received bridging therapy if needed. A single dose of CS-1 CAR T cells with or without lymphodepletion chemotherapy (LDC) was infused. We used the toxicity equivalence range design of Blanchard and Longmate for escalation and de-escalation rules. The primary endpoints were toxicities and activity profile. **Results:** A total of 8 pts were enrolled. The median age was 60 (50-72), pts received 7 (5-12) median prior lines of therapy, 4 (50%) had high-risk cytogenetics, and 5 (62%) had extramedullary disease. Grade 3/4 treatment-emergent adverse events related to CS-1 CAR T cells were reported in 5/8 (62%) pts; of these, the most frequent were anemia (62%), Neutropenia (50%) and thrombocytopenia (25%). Cytokine release syndrome was reported in 2/8 (25%) pts, all grade 1/2. Immune effector cell associated Hemophagocytic lymphohistiocytosis-like syndrome (HLH) developed in 2 (25%) pts (grade 3 in pt #443 which was reversible and grade 5 in pt # 340, respectively). Significant CAR expansion was only seen in the pts (#340 and #443) who received Fludarabine (Flu) + Cyclophosphamide (CY) LDC (Table 1). **Conclusions:** The first 2 patients treated with full dose LDC had a massive expansion of CAR T cells, likely leading to HLH even though pts achieved PR. Hence the next cohorts were treated with escalation doses without LDC or Cy alone to establish safety. However, efficacy was limited and therefore, we plan to enroll in the next cohort with a reduced dose of LDC with a cell dose of 10

million to induce a lower expansion of CAR T cells. This study was financially supported by Mustang Bio., U.S.

Table 1 (abstract P-031) Overview of cell dose, best response, and DLT.

Pts	LDC	CAR T cell dose (million)	Best Response	DLT
340	Flu (30 mg/m²) + Cy (500 mg/m²)	100	PR	Grade 5 HLH
443	Flu (30mg/m²) + Cy (500 mg/m²)	10	PR	Grade 3 HLH
524	None	10	PD	
542	None	10	SD	
568	None	50	PD	
619	None	50	PD	
638	Cy (300 mg/m²)	10	PD	
674	Cy (300 mg/m²)	10	SD	
Next cohort	Reduced dose Flu (25 mg/m²) + Cy (300 mg/m²)	10		

PD - progressive disease

P-032

Real-World Analysis of Teclistamab Treatment for Relapsed Refractory Multiple Myeloma in Two Belgian University Hospitals

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Introduction: T-cell redirection therapies, either bispecific antibodies or CAR-T cells, are revolutionizing the treatment of multiple myeloma by achieving impressive and durable response rates in relapsed refractory disease (RRMM). Teclistamab (Tec) is the first BCMA x CD3 directed bispecific antibody to be approved for the treatment of patients (pts) with RRMM, based on the results of the pivotal phase 1/2 MajesTEC-1 trial. Recently available in Belgium, we report our real-world experience. **Methods:** We retrospectively evaluated the efficacy and tolerability of Tec in 16 patients treated in 2 Belgian academic hospitals to determine whether the outcome is comparable in the real-world setting. Tec was administered weekly at a dose of 1.5 mg/kg, after 2 step-up doses of 0.06 and 0.3 mg/kg, according to recommendations. High-risk (HR) cytogenetics was defined by the presence of t(4;14), t(14;16) and/or del(17p). Responses were defined according to the IMWG 2016 criteria. Survival analyses were performed using the Kaplan-Meier method. Adverse events (AEs) were graded according to CTCAE v5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT guidelines. **Results:** Between December 16, 2022 and April 22, 2024, 16 pts received at least 1 dose of Tec. Median age was 68 years, 56% were female, 33% had HR cytogenetics and 20% had stage III ISS. Pts had received a median of 5 lines of therapy (LOT), 81.2% and 6.2% had triple or penta-refractory disease, respectively, and most (87.5%) were refractory to the last LOT. None had received prior BCMA-directed therapy, only 1 pt had been exposed to talquetamab. With a median follow up of 6 months (range 0.8-16.2), the ORR was 93.7% with 81.2% of pts achieving at least VGPR. The median time to first/best response was 27/39 days, respectively. No mPFS, mDOR or mOS were achieved. All pts experienced at least 1 AE, grade (gr) ≥3 in 75%. CRS occurred in 50% of pts (no gr≥3), all during the step-up dose or cycle 1, 3 pts (18.7%) experienced ICANS (gr 3 in 1). Cytopenias were common (any gr/gr≥3): anemia (100%/25%), neutropenia (81.2%/56.2%), thrombocytopenia (75%/18.7%) and lymphopenia (75%/31.2%). 41 infectious episodes were reported in 14 pts with an incidence (any gr/gr ≥3) of 87.5%/43.7%. Respiratory infections were the most common (37%), followed by bacteremia (20%). COVID-19 infections occurred in 5 pts, influenza in 1, and esophageal candidiasis in 1. 87,5% of pts received immunoglobulin substitution. **Conclusions:** Tec showed a similar efficacy and safety profile in the real-world setting as in the pivotal trial and other real-world reports, with the exception of a higher ICANS rate, which is difficult to interpret due to several confounding factors. Of note, one patient with prior talquetamab exposure still had at least 12.6 months of VGPR at data cutoff.

P-033

External Control Analysis for KarMMa-3: Idecabtagene Vicleucel (ide-cel) vs Real-World Standard of Care (RW SoC; Connect MM) for Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: KarMMa-3 (NCT03651128) is a phase III randomized controlled trial that demonstrated ide-cel (a chimeric antigen receptor [CAR] T therapy) extended progression-free survival (PFS) versus So in patients with TCE RRMM (hazard ratio [HR] 0.49 [95% CI: 0.38, 0.65]). Evaluating overall survival (OS) in KarMMa-3 is challenging given that 62% of patients in the SoC arm crossed over to ide-cel upon disease progression (i.e., OS estimates for SoC were confounded by subsequent ide-cel use). An external control arm (ECA) based on RW SoC from the Connect MM disease registry provides OS estimates from the United States, which can supplement the comparative effectiveness of ide-cel versus SoC. The aim of this study was to evaluate the comparative effectiveness of ide-cel versus RW SoC in terms of OS and PFS in patients with TCE RRMM. **Methods:** Individual patient data for ide-cel from KarMMa-3 (April 2023 cutoff date; intention-to-treat population) and RW SoC from Connect MM (October 2022 cutoff date) were used. To align with KarMMa-3, Connect MM patients with TCE RRMM (November 2015 to December 2020) were restricted to those who 1) received a non-CAR T index therapy in the 3-5L setting, 2) had no prior CAR T therapy nor allogeneic stem cell transplantation (SCT), and 3) had an ECOG performance score of 0-1. Inverse probability of treatment weighting (IPTW) was used to balance pre-specified patient characteristics. Weights from propensity scores (average treatment effect on the treated) were applied to the RW SoC cohort (KarMMa-3 as the target population). Model covariates included were selected based on published rank-ordering of prognostic factors and data availability: triple-class refractory status, high-risk cytogenetics, disease stage, extramedullary disease, time to progression on last regimen, number of prior lines, time since diagnosis, age, hemoglobin, lactate dehydrogenase, prior autologous SCT, race, and sex. Multiple imputation was performed for covariates with ≤30% missing data. Relative treatment effects from Cox proportional hazards models were summarized as HRs with 95% CIs. A sensitivity analysis was performed using regression. **Results:** Model covariates were generally balanced between the KarMMa-3 ide-cel cohort (N=254 patients) and Connect MM RW SoC cohort (N=145 patients) following IPTW adjustment. Median OS was 41.4 months for ide-cel and 11.6 months for RW SoC, while median PFS was 13.8 months for ide-cel and 2.9 months for RW SoC. Ide-cel demonstrated improvements versus RW SoC in OS (adjusted HR 0.37 [95% CI: 0.26, 0.53]), which was more precise than KarMMa-3 crossover-adjusted HR. Ide-cel also extended PFS versus RW SoC (adjusted HR 0.45 [95% CI: 0.32, 0.64]), leading to consistent estimates with KarMMa-3. Sensitivity analyses suggested similar results for OS and PFS. **Conclusions:** Ide-cel was associated with improved OS and PFS compared to RW SoC, providing evidence regarding the clinical benefit of ide-cel in patients with TCE RRMM.

P-034

Real world Experience of Talquetamab in Relapsed Refractory Myeloma, First Report From the IMWG Consortium

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Introduction: Talquetamab (TAL) is a GPRC5D targeting bispecific antibody approved for the treatment of relapsed refractory multiple myeloma. Herein we report the results of real-world experience of TAL from seven international institutions. **Methods:** Patients were enrolled and consented in an IMWG retrospective protocol; patients treated with TAL outside of a clinical trial from Jan 2023 through March 2024 were eligible. **Results:** 101 patients were included in this analysis. The median age was 64, median LOT was 6, 92% (58/63) were triple drug refractory and 49% (38/77) were Penta refractory. The median number of immunotherapies before TAL was 2 (range 1,4) and 74% received prior anti-BCMA therapy, 49% (n=51) would not have been eligible for TAL clinical trial due to exclusion criteria, 21% (14/65) had an ECOG of 2 or greater, 76% (38/50) had high risk cytogenetics, one had plasma cell leukemia and seven had extra medullary disease. 84% (83/99) received TAL as an inpatient with a median hospitalization of 10 (0,37) days. CRS during Step up Dose (SUD) 1 was present in 33% (32/97) Gr 1 (56%), Gr2 (9%), Gr 3 (6%), CRS during SUD 2 was present in 35% (33/94), Gr 1 (66%), Gr 2 (9%), CRS during SUD 3 was present in 23% (15/65), Gr 1 (80%), Gr 2 (6%) and with first full dose was 14% (13/95), Gr 1 (69%). ICANS occurred in 7% (7/99), Gr 1 (14%), Gr 2 (28%), Gr 3 (14%). Non hematological toxicities included skin toxicity presented as rash, dryness, itching and peeling in 80% (57/71), Gr 1 (68%), Gr 2 (28%), Gr 3 (4%), with 8% (3/36) needing dose interruptions. Nail toxicity occurred in 43% (20/47), Gr 1 (75%), Gr 2 (25%) with 10% needing dose interruptions. Dysgeusia was present in 65% (51/78), Gr 1 (49%), Gr 2 (49%), Gr 3 (2%) with 17.6% (n=6/34) needing dose interruptions. Oral toxicity including stomatitis, glossitis, ulcerations, or dry mouth occurred in 69% (34/49), Gr1 (71%), Gr 2 (23%), Gr 3 (6%) with 16% (5/32) needing dose interruptions. Infections after starting TAL at any timepoint occurred in 49% (34/69) of patients, with CMV reactivation in 19% (10/53). Response rates will be reported at the time of presentation. **Conclusions:** The RWE of TAL in a heavily pretreated population including those with prior immunotherapy has a similar toxicity and safety profile to the clinical trial experience, with the exception of higher rates of dysgeusia and CMV reactivation. This may be in part due to a higher proportion receiving prior immunotherapy thereby accounting for higher rates of CMV subsequently. The high incidence of oral toxicity and

dysgeusia described here suggests that optimal management of these side effects is key in maintaining patients on TAL.

P-035

Can Bispecific T Cell Engagers for Multiple Myeloma be Safely Administered in The Community? A Single Center Experience

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Introduction: The majority of patients with multiple myeloma (MM) are treated in community settings. Teclistamab and talquetamab (T&T), highly effective bispecific T-cell engagers (BiTE), are approved for the treatment of relapsed and/or refractory MM, but have the potential lethal toxicity of cytokine release syndrome (CRS). Due to the risk of CRS, providers and pharmacies must be REMS-certified prior to prescribing or dispensing treatment. CRS most commonly occurs after the first 3-4 doses with a median onset of 1-2 days. Hospitals most comfortable administering and monitoring for BiTE toxicities are typically transplant/cellular therapy centers. It is recommended that patients are hospitalized for 48 hours following the administration of the first 3 doses of teclistamab or first 3 to 4 doses of talquetamab, depending on the dosing schema. Subsequent outpatient treatment typically continues at these centers, limiting patient access to highly effective treatment. Whether T&T can safely be given in community infusion centers (CIC) with a less vigorous monitoring schedule is unknown. We established a monitoring guide to expand MM BiTE accessibility to 17 CIC in our network. **Methods:** At Allegheny Health Network (AHN), a monitoring guide was devised for T&T based on safety data regarding the incidence and timing of CRS. Patients would be admitted for the first 3 to 4 doses and monitored for 48 hours after each dose. Starting with the fourth teclistamab or fifth talquetamab dose (following biweekly ramp-up schedule), MM BiTE administration at CIC with no additional monitoring was allowed if there were no CRS events with the immediately preceding dose. If the patient experienced a CRS event with the preceding dose, the patient would be monitored for 1 hour, at a site with rapid response (RR) capabilities, until a dose was tolerated with no subsequent CRS events. Nursing and pharmacist education was arranged for all CIC regarding CRS identification and management. All CIC pharmacies were prospectively enrolled in the T&T REMS program at the time education was deployed. Prescribing providers were REMS certified as well. **Results:** Between 1/2023 and 5/2024, a total of 20 patients (16 teclistamab and 4 talquetamab) were treated at 12 AHN infusion centers. Of the patients treated with talquetamab, 3 had received prior teclistamab. Of the 12 centers, 11 were CIC and 7 were non-RR CIC. Out of the 15 patients treated at CIC including 12 treated at non-RR centers, starting with the fourth teclistamab or fifth talquetamab dose, none experienced subsequent CRS events, and no patients were subsequently hospitalized for BiTE toxicities. **Conclusions:** BiTE for MM can be safely administered at CIC, including centers without RR capabilities, starting with the fourth teclistamab or fifth talquetamab dose after prior ramp-up administration. Post-injection monitoring may be reduced without increased incidence of CRS-related toxicities. Our monitoring guide may serve as a model for the safe administration of T&T in CIC.

P-036

BCMA after GPRC5D: Efficacy of BCMA-Directed Therapy on Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Progressing After GPRC5D-Directed Therapy

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Introduction: T-cell redirecting therapy (TCRT; chimeric antigen receptor T cells and bispecific antibodies) has revolutionized the treatment landscape of RRMM. However, the optimal sequencing of available TCRT is unclear. With the development of BCMA TCRT before GPRC5D TCRT, the safety, efficacy and feasibility of BCMA-directed, then subsequent GPRC5D TCRT is relatively well established. However, outcomes of patients who experience disease relapse on a GPRC5D TCRT and subsequently receive BCMA TCRT is unknown. **Methods:** We reviewed all patients who received TCRT at a single large high volume academic multiple myeloma program. We included patients who received a GPRC5D TCRT in an investigational or commercial setting and followed longitudinally. We identified patients who evolved with disease progression and received subsequent BCMA TCRT. **Results:** Between 1/2020 and 5/2024, we identified 77 patients who received a GPRC5D TCRT. Of those, 42 have not progressed, 5 died without progression and 30 had progression. Of the 30, 21 started subsequent treatment and 12 received subsequent BCMA TCRT in the immediate or subsequent next line of therapy (5 post GPRC5D TCE; 7 post CART) and had ≥6 months of follow up. The cohort consists of 75% male, 41% racial and ethnic minorities, 25% with ISS stage III disease, 41% with high risk FISH abnormalities [t(4;14), t(14;16), del17p and gain/amp 1q], 25% EMD. All patients had triple class refractory MM, 75% were penta-refractory and 92% received prior ASCT. At time of post-GPRC5D TCRT progression, 9 of the 12 received BCMA TCRT directly following GPRC5D (5 BCMA TCE, 4 BCMA CART) and 3 received BCMA targeted therapy in subsequent line of treatment (all BCMA TCE). Of the 12 patients, 5 were BCMA naïve. For the 7 BCMA exposed patients, the BCMA TCRT used prior to GPRC5D TCRT was CART in 6 patients and TCE in 1 and produced overall response rate (ORR) 86% with median PFS 12.8 months, justifying re-exploring BCMA after failure of GPRC5D TCRT. The ORR to subsequent BCMA TCRT was 50% (80% BCMA naïve, 29% BCMA exposed). With median follow up of 12.23 mos (95% CI 0-37.6), the median PFS of patients with subsequent BCMA TCRT was 7.06 months [8.2 mos BCMA naïve (95% CI 2.34-NR), 1.38 mos BCMA exposed (95% CI 0.36-NR)]. ORR according to type of BCMA TCRT is 75% for CART and 38% for TCE. The median PFS according to type of BCMA TCRT was 7.07 mos (95% CI 1.25-NR) for CART and

2.39 mos (95% CI 0.26-NR) for TCE. **Conclusions:** GPRC5D and BCMA are promising, independent immunotherapeutic targets for MM therapy. Our dataset is one of the first reports showing favorable outcomes of BCMA directed TCRT following initial GRPC5D TCRT. Although limited by small sample size, these findings suggest that target switching in either direction may be feasible with deep and durable responses. Therefore, optimal sequencing is best guided by patient and disease characteristics as well as treatment availability.

P-037

Longitudinal Single Cell Multiomic Analysis Allow the Identification of Mechanism of Persistence and Resistance to CAR-T Cells in MM

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Introduction: Despite high remission rates observed after BCMA CAR-T cells in R/R Multiple Myeloma (MM) patients, a significant number of patients still relapse, and the molecular mechanisms governing CAR-T cell (dys)function are largely unknown. To shed some light on specific transcriptomic programs activated after CAR-T cell administration and identify potential mechanisms of resistance and persistence we interrogated longitudinal samples of CAR-T cells collected from patients enrolled in CARTBCMA-HCB-01 (NCT04309981). **Methods:** We characterized >60.000 CAR-T cells from 17 samples collected from 3 patients, including infusion products and CAR-T cells isolated from paired bone marrow (BM) and peripheral blood (PB) samples at different times after infusion (month 1 to 18). Single-cell RNA and TCR sequencing was performed using Chromium Single-Cell Immune Profiling solution. Gene Regulatory Network (GRN) analysis was performed using SimiC, a novel machine learning method. **Results:** scRNA-seq revealed that CAR-T cells remaining after infusion were mainly non-proliferating CD8+ cells, with effector/effector-memory phenotypes. Interestingly, we found that CAR-T cells infiltrating BM presented increased expression of cytotoxic and exhaustion markers compared to their PB counterparts. GRN analysis showed that PRDM1 regulon, already associated with CAR-T cell exhaustion, presented increased activity in the BM. Additionally, transcriptomic profile of CAR-T cells differed among patients. Partial responders presented increased presence of terminally differentiated effector cells with an exhausted signature, while complete responders presented CAR-T cells in transition to central or effector memory phenotype. Importantly, combination of scTCR-seq and scRNA-seq allowed the identification of a hyperexpanded CAR-T clone in the BM of the patient with partial response. Deeper characterization showed that this clone had increased expression of IL10. Additional in vitro studies suggested that activation of endogenous TCR along with CAR-T activation led to IL10 production, and functional validations corroborated that IL10 alters CAR-T cell functionality. Then, to deepen in the mechanism of CAR-T cell persistence, we analyzed post-infusion CAR-T cells of one of the few patients with detectable CAR-T one year after infusion. The analysis showed a prevailing CD8+ population expressing key markers related to T-cell memory and survival. However, prior to relapse, cells with increased cytotoxic features expanded in the BM, indicating CAR-T cell reactivation. GRN analysis in this patient identified FOS and NR4A2 regulons as potential drivers of CAR-T reactivation in response to tumor recurrence. **Conclusions:** Overall, our analysis combining scRNA-seq/scTCR-seq with novel machine learning models allowed us to identify several molecular markers associated to CAR-T dysfunction, that represent potential targets to be modulated for the development of improved CAR-T therapies against MM.

P-038

Phase I Trial of MCARH109, a First-in-Class G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D)-Targeted CAR T-cell Therapy for Relapsed or Refractory Multiple Myeloma: Updated Analysis

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Introduction: B cell maturation antigen (BCMA) targeted CAR-T therapy induces robust responses in relapsed/refractory multiple myeloma (RRMM). G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) is an established target in RRMM, but has no FDA-approved CAR-T product. Here we report updated safety and efficacy of MCARH109, a first-in-class GPRC5D targeted CAR-T therapy, in patients with RRMM. **Methods:** We conducted a phase 1 dose-escalation trial of MCARH109 using a 3+3 design at four dose levels - 25×106, 50×106, 150×106, and 450×106 CAR T cells. Primary endpoint was safety, and secondary endpoints included response by IMWG criteria and bone marrow minimal residual disease (MRD) negativity by multicolor flow cytometry (sensitivity: 10-5). We also performed exploratory T-cell profiling via high-dimensional spectral cytometry on apheresis and manufactured CAR T products. **Results:** 17 RRMM patients received MCARH109 between 10/22/2020 and 11/10/2021, with no new serious adverse events in this updated analysis. 2 patients treated at the 450×106 CAR-T cell dose had g3 cerebellar disorders. As of 05/19/2024, at 31 and 38 months (M) follow-up respectively, both patients had persistent but stable cerebellar symptoms. No patients treated at smaller doses developed cerebellar disorders or other dose-limiting toxicities. Additional MCARH109-related toxicities included g1 nail changes in 11 patients (65%) that resolved in 9/11 patients and g1 dysgeusia in 3 patients (18%) that resolved in 2/3 patients. 12 patients (71%) achieved a partial response (PR) or better, including 7 (41%) stringent complete response (sCR), 3 (18%) very good partial response, and 2 (12%) PR. 8 patients were previously treated with BCMA CAR-T therapy, with 6 (75%) achieving PR or better and 3 (38%) achieving sCR. 2 (12%) patients had an ongoing sCR at the data cutoff at 29M and 39M, respectively. Of the 12 patients with a PR or better, 8 (67%) were MRD negative. The median duration of response (DOR) was 8.7M (1.9 - 37.7 M), including 5/12 (42%) with a DOR of >1 year. Apheresis products from MCARH109 responders had a 3.2-fold increase in CD8+CD45RO+CCR7-CD95+ effector memory T cells (P = 0.0024) with high relative expression of HLA-DR and 2B4. No significant lymphocyte subpopulation differences between responders and non-responders were identified in manufactured CAR T cells. **Conclusions:** In this updated analysis of MCARH109, persistent cerebellar disorders were seen in 2 patients treated at the highest dose of 450×106 CAR-T cells but not at lower doses. At the maximum tolerated dose of 150×106, no new toxicities were observed. Responses were noted across all dose levels and in BCMA-exposed patients. Responses were deep with an MRD negativity rate of 67% for responders and durable with 42% of patients in ongoing response of >1 year. Exploratory immune profiling showed that a pre-existing T cell landscape enriched with differentiated effectors associated with response.

P-039

CMV Reactivation During Treatment with Bispecific Antibodies for Relapsed/Refractory Multiple Myeloma

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Introduction: Infections are a serious concern among relapsed refractory multiple myeloma (RRMM) patients receiving bispecific antibodies (BsAbs). Notably, cytomegalovirus (CMV) infection has been reported in patients receiving BsAbs. However, the incidence and clinical significance of CMV infection remain poorly understood among these patients. This study presents our findings on CMV infection among RRMM patients receiving BsAbs at our institution. **Methods:** We conducted a retrospective single-center study of CMV infection in RRMM patients during treatment with commercial BsAbs (teclistamab, elranatamab, or talquetamab) at between 11/2022 and 1/2024. Patients with positive serum CMV IgG detected before treatment were included in this study. CMV reactivation was defined as serum CMV PCR >34.5IU/ml detected during treatment therefore we excluded patients with a baseline serum CMV PCR >34.5IU/ml. Serum CMV PCR monitoring during BsAb therapy was determined by the treating clinician. The estimated cumulative incidence of CMV reactivation was measured during the treatment period. **Results:** Seventy one patients with pre-treatment CMV serology were identified, of those 41 patients with positive CMV IgG, with baseline CMV PCR<34.5IU/ml, were included in the analysis. The median age was 69 (range 51-81), 56% were female, 65% were White (23% Black, 7.5% Asian), 42% had extramedullary disease, and 45% had high-risk cytogenetics. Patients had a median of 6 prior lines of therapy including BsAbs and CAR-T therapy (7.3% and 24% respectively). 29 (71%) were treated with teclistamab, 11 (27%) with talquetamab, and 1 (2.4%) with elranatamab. Median follow-up was 6.9 months.

5 (12.2%) patients had a baseline CMV PCR< 34.5, 22 (53.7%) had a negative baseline CMV PCR, and 14 (34.1%) did not have baseline CMV PCR testing. The estimated cumulative incidence of CMV reactivation was 28% (95% CI: 15-42) at 3 months and 37% (95% CI: 21-52) at 6 months. Only two patients with CMV reactivation required anti-viral therapy. One patient was treated with valganciclovir for CMV viremia (peak serum viral load 43700IU copies/ml) 4.6mo after starting teclistamab. The second patient was treated with valganciclovir for biopsy-confirmed CMV esophagitis 3.1mo after starting teclistamab. No significant differences in CMV reactivation were seen between BsAbs. Age was associated with an increased risk of CMV reactivation (HR = 1.11, 95% CI: 1.01-1.23, p = 0.02) in multivariable analysis adjusting for prior autologous stem cell transplant. **Conclusions:** This is the largest real-world analysis of CMV reactivation in patients with RRMM treated with commercial BsAb therapy. While very few patients required anti-viral therapy within the short follow-up period, CMV reactivation is estimated to occur in over one-third of seropositive patients within 6 months of BsAb treatment. CMV monitoring should be considered in seropositive patients, especially in the first months, regardless of the BsAb used.

P-040

Study of iCasp9 Transfected Anti-ROR1 CAR-T Cells for Multiple Myeloma and Mantle-Cell Lymphoma

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Introduction: Clinical trials and real-world data have shown that CAR T-cell therapy is highly effective in the treatment of B-cell malignancies and multiple myeloma. However, side effects, such as cytokine release syndrome (CRS) or immune effector cell-mediated neurotoxicity syndrome (ICANS), are frequently observed. Addressing those side effects is critical for solidifying the efficacy of CAR T-cells in hematologic malignancies and potentially broadening its indications for use. **Methods:** Our group investigated a novel anti-ROR1 CAR model for multiple myeloma and mantle cell lymphoma by assessing efficacy and safety profile both in vitro and in vivo. We lentivirally transduced two plasmids (CAR and iCasp9) and double selected the cells with hygromycin and puromycin. We confirmed the presence of GFP-positive CARs by flow cytometry. We cocultured CARs with mantle cell-lymphoma and multiple myeloma cell lines. Cytotoxicity assays have been performed. Following confirmation of the efficacy of the iCasp9 system by adding the suicide gene activator in the culture medium, we performed in vivo experiments to assess the toxicity and efficacy of the iCasp9 system. **Results:** A selection rate of 90% has been obtained after lentiviral transduction. The presence of the iCasp9 suicide gene did not demonstrate any cytotoxicity, no statistically significant difference has been obtained compared to the controls. Activation of iCasp9 led to apoptosis of more than 80% of the cells. In vitro results correlated with the data obtained from in vivo mice experiments. **Conclusions:** The iCasp9 suicide gene system is one approach for more effective and rapid control of adverse effects. iCasp9 has been shown to be an effective "safety switch" for the treatment of Graft versus Host Disease (GvHD) in haploidentical stem cell transplantation, activating the apoptotic pathway. Based on these factors, we merged two clinically validated technologies (iCasp9 and CAR-T) and investigated the efficacy of the resulting system. We demonstrated that this suicide gene system successfully induced apoptosis in our in vitro experiments and we observed ni significant toxicities in our mice models after administration of the CAR T-cells and the activator drug of iCasp9.

P-041

Exploring MAGE-A1 as a Therapeutic Target in Advanced Multiple Myeloma: Expression Analysis and Phase 1 Clinical Trial of MAGE-A1-Directed TCR-1367 T Cells

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Introduction: T cell-based adoptive cell therapies represent an expanding area in multiple myeloma (MM) treatment, with numerous approvals for Bi-specific T-cell engagers (BiTEs) and chimeric antigen receptor T (CAR-T) cells. These therapies commonly target B cell maturation antigen (BCMA) and G protein-coupled receptor, class C, group 5, member D (GPRC5D). However, patients eventually relapse after these therapies, occasionally exhibiting antigen loss (Lee et al., Nat Med 2023). Consequently, new therapeutic targets are required. MAGE-A1, a cancer/testis antigen expressed in various cancers, offers a promising target for T cell receptors (TCRs). Previously, we described TCR-1367, which targets MAGE-A1 (Obenaus et al., Nat Biotechnol 2015). **Methods:** We assessed MAGE-A1 expression frequency in 252 histological samples from 213 MM patients at Charité Berlin, Germany. MAGE-A1 expression, assessed via immunohistochemistry (IHC), was correlated with patients' clinical characteristics and survival data.

To explore MAGE-A1 as a therapeutic target, we initiated a one-armed, single-center, open-label, phase 1 clinical trial (EudraCT: 2017-001208-30) of MAGE-A1-specific TCR-1367 T cells. Main inclusion criteria were at least 3 prior lines of therapy, HLA-A*02:01 genotype and at least 30% of myeloma cells with MAGE-A1 expression. **Results:** Analysis revealed that 32% of samples exhibited >10% MAGE-A1 expressing MM cells, with 27% displaying ≥30% positive cells. Relapsed/refractory patients (RRMM, n=150) demonstrated higher mean MAGE-A1 expression compared to newly diagnosed (NDMM, n=102) patients (26% vs. 15%; p=0.0002). MAGE-A1 expression did not correlate with high-risk cytogenetic aberrations (del(17p), t(4;14), t(14;16), gain or amplification (1q21)), but showed an association with extramedullary disease (EMD). EMD samples exhibited significantly higher MAGE-A1 expression compared to bone marrow (BM) samples in both NDMM and RRMM (p< 0.0001 and p=0.0020). Furthermore, patients with >10% MAGE-A1 expressing MM cells at diagnosis had significantly lower median overall survival compared to MAGE-A1 negative patients (59 months vs. not reached; HR 0.2, p=0.0011). In our phase 1 trial, MAGE-A1-specific TCR-1367 T cells were administered to 2 patients. The trial aimed to enroll 12 patients; however, the trial was closed by the sponsor after enrolling 2 patients due to a lack of enrollment. Both patients had advanced disease, and both received the lowest dose of 1x105 cells per kg body weight. Cell production at academic institution was feasible and no unexpected toxicity was reported. Mean time to next treatment was 87 days, with TCR-1367 T cells undetectable in pharmacokinetic samples via flow cytometry and qPCR, likely due to the low administered cell number in the first dosing group. **Conclusions:** Our data highlight the frequent occurrence of MAGE-A1 in advanced and extramedullary MM. Further investigation of MAGE-A1-directed TCR-1367 T cells in clinical trials is warranted.

P-042

SWASTH: Phase 1/2 Study of Ribrecabtagene Autoleucel, a BCMA–Directed CAR-T Cell Therapy, in Relapsed-Refractory Multiple Myeloma

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Introduction: Introduction: Anti BCMA CAR-T cell therapy has demonstrated benefit in relapsed /refractory Myeloma (RRMM). While two different anti-BCMA CAR-T products are approved in the developed world, no CAR-T therapy is yet approved in India. Ribrecabtagene Autoleucel (also known as Ribre-cel as well as DRL-1801 / PRG-1801) is the first anti BCMA CAR-T cell therapy in India under clinical trials. It is a CAR-T having a single domain nanobody. The initial Phase 1 study was done in China in relapsed RRMM (NCT03661554). The current phase 1/2 SWASTH study (CTRI Registry India CTRI/2023/11/059795) is further evaluating Ribre-cel in RRMM. We present the initial data from the study. **Methods:** Methods: Eligible pts (aged ≥18 y) for the SWASTH trial were those diagnosed with RRMM with measurable disease and with ECOG performance status ≤ 1. Cyclophosphamide and fludarabine were used for lymphodepletion. Ribre-cel was administered IV, ranging from 2.5 to 10 x106 CAR+ T cells / Kg, 5 days after start of lymphodepletion. Response was assessed per IMWG criteria and MRD by Flow Cytometry. CTCAE v5.0 is used for grading of AEs and ASTCT criteria for CRS and ICANS. PK and PD parameters and RCL are also assessed. **Results:** Results: As of May 29, 2024, 7 pts (57.14.% female; median age 60 y [range 51–66]) with RRMM received Ribre-cel. The median vein to vein time was 26 days (range 25 to 29). Pts had received a median of 5 prior lines of therapy (range 4–7); 71.4% (5/7) had previously received autologous transplant with one having received double transplant. 71.4 % (5/7) patients were penta-refractory, with 100% being triple refractory. First efficacy evaluation was done at 6 weeks and was available for 5 patients. The ORR was 100 % (5/5), with CR of 40% (2/5; 1 MRD-negative and 2nd under evaluation), VGPR of 20% (1/5) and PR of 40% (2/5). All patients responded at the first evaluation (at 6 weeks) itself. In 3 patients, the follow up evaluation (beyond the initial 6 weeks evaluation) also occurred. In those without CR at initial evaluation, the responses further deepened over time. All patients continue to be responding and the median duration of response has not been reached. With respect to safety, no deaths or infections occurred, though one patient developed an SAE of "dengue fever"on follow up. All patients developed Grade 3 /4 neutropenia and 1 patient developed a grade 3 thrombocytopenia. CRS was reported in 57.14% (4/7), all Grade 1. The median onset of CRS was 1 day (range 0 to 6 days). One patient (14.28%) developed Grade 2 ICANS on day 2, requiring short duration steroids with complete resolution within 48 hours. The CAR+T cells peaked on Day 14 followed by a slow decline, demonstrated by flow cytometry and by qPCR. The complete PK and PD data will be presented at the conference. **Conclusions:** Conclusions: The preliminary data from SWASTH indicates that a single dose infusion of Ribre-cel has a very manageable safety profile with early responses seen in heavily pretreated pts with RRMM.

P-043

Stem Cell Boost for Persistent Cytopenias After BCMA-Directed Chimeric Antigen Receptor (CAR)-T Cell Therapy

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Introduction: Hematological toxicity after CAR-T is common and often prolonged, resulting in transfusion and growth factor

dependence. Emerging data has demonstrated that the infusion of autologous banked CD34+ stem cells can expedite hematological recovery. **Methods:** We performed a retrospective review of all myeloma patients receiving autologous stem support after CAR-T across three institutions from 2020-2024. Dose and timing of administration of boost was determined by the treating physician. We included controls who were transfusion dependent at day ≥60 after CAR-T. This project was conducted as part of the IMF Immunotherapy Registry. **Results:** Twenty-three patients received CD34+ stem cells between 2020-2024 after CAR-T therapy (8 ide-cel, 14 cilta-cel, 1 study drug). Median age at CAR-T was 65 years; 39% were women and 78% were White. Fourteen (61%) had at least one high-risk cytogenetic feature. Patients received a median of 6 prior lines of therapy (2-11); 43% received high-dose cyclophosphamide, 13% received bendamustine, and 30% received radiation within 3 months of CAR-T. At time of lymphodepletion, median blood counts were: absolute neutrophil count 2.0 x 109/L (0.5- 3.2), hemoglobin 8.7 g/dL (6.2-12.2), platelet (Plt) 62 (8-201) x 109/L. Median CD34+ boost dose was 3.29 x 106/kg (1.08– 23.55 x 106/kg), administered at a median of 62.5 days (14-263) after CAR-T, with variations across institutions (median of 49, 61.5, and 122 days, respectively). Median time post-boost to resolution of cytopenias was 8 days (1-161) for red blood cell (RBC) transfusion, 11 days (1-146) for Plt transfusion, 24 days (0-252) for Plt growth factors, and 13 days (2-86) for WBC growth factors (Table 1). Patients required a median of 4.5 RBC transfusions and 8 Plt transfusions pre-boost, compared to 0 RBC transfusions and 0.5 Plt transfusions post-boost. Those in the control arm required a median of 10 RBC transfusions and 9 Plt transfusions. At present, 57% of those who received stem cell support after cilta-cel and 88% who received stem cell support after ide-cel have relapsed, at a median of 295 days (179-1164) and 154 days (78-230), respectively. **Conclusions:** We demonstrate that most patients had rapid resolution of transfusion and growth factor needs after receiving autologous CD34+ stem cells. This strategy may be particularly useful in patients with pre-existing cytopenias or recent exposure to cytotoxic chemotherapy or radiation.

Table 1 (abstract P-043)

	Median Days (Range), from Boost	Median Days (Range), from CAR-T
Resolution of RBC transfusions		
Boost Arm (N=11)	8 (1-161)	57 (33-254)
Control Arm (N=13)	n/a	61 (2-447)
Resolution of Plt transfusions		
Boost Arm (N=12)	11 (1-146)	61.5 (25-199)
Control Arm (N=13)	n/a	73 (27-449)
Resolution of Plt growth factor need		
Boost Arm (N=9)	24 (0-252)	122 (54-370)
Control Arm (N=13)	n/a	138 (61-311)
Resolution of WBC growth factor need		
Boost Arm (N=9)	13 (2-86)	64 (34-258)
Control Arm (N=13)	n/a	55 (24-1437)

P-044

External Control Analysis for KarMMa-3: Idecabtagene Vicleucel (ide-cel) vs Real-World Standard of Care (RW SoC; COTA) for Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: KarMMa-3 (NCT03651128) is a phase III randomized controlled trial that demonstrated ide-cel (a chimeric antigen receptor [CAR] T therapy) extended progression-free survival (PFS) versus SoC in patients with TCE RRMM (hazard ratio [HR] 0.49 [95% CI: 0.38, 0.65]). Evaluating overall survival (OS) in KarMMa-3 is challenging given that 62% of patients in the SoC arm crossed over to ide-cel upon disease progression (i.e., OS estimates for SoC were confounded by subsequent ide-cel use). An external control arm (ECA) based on RW SoC from the COTA Vantage MM electronic health records database provides OS estimates from the United States, which can supplement the comparative effectiveness of ide-cel versus SoC. The aim of this study was to evaluate the comparative effectiveness of ide-cel versus RW SoC in terms of OS and PFS in patients with TCE RRMM. **Methods:** Individual patient data for ide-cel from KarMMa-3 (April 2023 cutoff date; intention-to-treat population) and RW SoC from COTA (March 2023 cutoff date) were used. To align with KarMMa-3, COTA patients with TCE RRMM (November 2015 to March 2021) were restricted to those who 1) received a non-CAR T index therapy in the 3-5L setting, 2) had no prior CAR T therapy nor allogeneic stem cell transplantation (SCT), and 3) had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1. Inverse probability of treatment weighting (IPTW) was used to balance pre-specified patient characteristics. Weights from propensity scores (average treatment effect on the treated) were applied to the SoC cohort (KarMMa-3 as the target population). Model covariates included were selected based on published rank-ordering of prognostic factors and data availability: triple-class refractory status, high-risk cytogenetics, duration of last regimen, number of prior lines, time since diagnosis, age, hemoglobin, lactate dehydrogenase, prior autologous SCT, ECOG, race, and sex. Multiple imputation was performed for covariates with ≤30% missing data. Relative treatment effects from Cox proportional hazards models were summarized as HRs with 95% CIs. Regression models were performed as a sensitivity analysis. **Results:** Following IPTW adjustment, model covariates were balanced between the KarMMa-3 ide-cel cohort (N=254 patients) and COTA RW SoC cohort (N=502 patients). Median OS was 41.4 months for ide-cel and 25.7 months for RW SoC, while median

PFS was 13.8 months for ide-cel and 6.1 months for RW SoC. Ide-cel demonstrated improvement versus RW SoC in OS (adjusted HR 0.69 [95% CI: 0.53, 0.90]), which was more precise than the KarMMa-3 crossover-adjusted HR. Additionally, ide-cel extended PFS versus RW SoC (adjusted HR 0.64 [95% CI: 0.53, 0.79]), leading to consistent estimates with KarMMa-3. Consistent OS and PFS results were obtained from the sensitivity analysis. **Conclusions:** Ide-cel was associated with improved OS and PFS compared to RW SoC, providing evidence regarding the clinical benefit of ide-cel in patients with TCE RRMM.

P-045

Idecabtagene Vicleucel (ide-cel) in Patients (pts) With Clinical High-Risk Early Relapse Multiple Myeloma (MM) Without Front-Line (1L) Autologous Stem Cell Transplantation (ASCT): KarMMA-2 Cohort 2B

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Introduction: Despite improvements with triplet regimens in 1L MM treatment (tx), pts develop disease refractory to these agents, necessitating txs with novel mechanisms of action. The CAR T cell therapy ide-cel significantly improved median progression-free survival (mPFS) vs standard regimens in KarMMa-3 in triple-class–exposed relapsed and refractory MM (RRMM). KarMMa-2 (NCT03601078) is a multicohort, phase 2, multicenter trial of ide-cel in clinical high-risk MM (early relapse after 1L tx including [cohort 2a] or excluding ASCT [2b] or inadequate response post-1L ASCT [2c]). In cohort 2a (median follow-up, 21.5mo), 24-mo PFS rate was 26% and incidences of grade (gr) 3/4 cytokine release syndrome (CRS) and investigator-identified neurotoxicity (iiNT) were numerically lower vs later tx lines in KarMMa. We report results from KarMMa-2 cohort 2b. **Methods:** Adults with disease progression < 18mo post-1L tx (no ASCT; at least IMiD agent, proteasome inhibitor, dexamethasone) received one ide-cel infusion (150–450×106 CAR+ T cells). Primary endpoint: complete response (CR) rate. Secondary endpoints: ORR, duration of response (DOR), PFS, overall survival (OS), safety, pharmacokinetics, health-related quality of life (QOL). Exploratory endpoint: minimal residual disease (MRD) negativity (neg; < 10-5). **Results:** Of 35 enrolled pts, 31 (89%) received ide-cel. At data cutoff (Dec 13, 2023), median follow-up was 30.1 (range 1.0–51.4) mo; 20/31 (65%) pts were ongoing in study and 11 discontinued, mostly due to death (n=7 [23%]; none considered ide-cel-related by investigator). At baseline, median age was 60 (range 32–77) y, 39% of pts had high-risk (HR) cytogenetics, 16% had ultra-HR cytogenetics, 68% had double-class–refractory MM, and 16% had triple-class–refractory MM. ORR (95% CI) was 94% (79–99). CR rate was 71% (52–86); 16 (52%) pts had ongoing CR. High rates of MRD neg were achieved by evaluable pts with ≥ partial response (12mo, 14/18 [78%]; 24mo, 10/12 [83%]) and with ≥CR (12mo, 13/16 [81%]; 24mo, 9/11 [82%]). Median DOR was not reached (NR); 24mo rate was 65%. Median PFS and OS were NR (PFS rate, 70% at 12mo, 63% at 24mo; OS rate, 90% at 12mo, 79% at 24mo).Gr 3/4 adverse events (AEs) occurred in 29 (94%) pts, gr 5 AEs in 2 (6%) pts (both MM progression). Gr 3/4 neutropenia and thrombocytopenia occurred in 29 (94%) and 11 (35%) pts, respectively; time to recovery was 1.5 and 2.0mo. Gr 3/4 infections occurred in 6 (19%) pts. CRS occurred in 26 (84%) pts and iiNT in 3 (10%) pts; none were gr ≥3. Robust CAR+ T cell expansion was seen in 31 pts (4.3-fold higher in pts with ≥CR vs < CR [AUC0–28d]). Pts showed sustained QOL improvement; 75% achieved meaningful improvement by 3mo post-infusion. **Conclusions:** In newly diagnosed MM that progressed < 18mo of tx initiation, a single ide-cel infusion demonstrated a favorable benefit–risk profile with frequent, deep, durable responses and a manageable safety profile, consistent with KarMMa-2 cohorts 2a and 2c.Previously presented at EHA 2024.

P-046

Identifying immune checkpoints on dysregulated T-cells as prognostic biomarkers for multiple myeloma patients with COVID-19

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Introduction: Broad T cell phenotypic alterations and potential dysfunctions were prominent in COVID-19. There are few and inconclusive data about the role of immune checkpoints for T cell exhaustion/activation during SARS-CoV-2 infection in multiple myeloma (MM) patients. **Methods:** Peripheral blood specimens were prospectively collected from MM patients and healthy controls (HCs) at 2-4, 8-10 and 14-16 weeks after infection with COVID-19. The percentage of CD4+ and CD8+ subpopulation and immune checkpoints (PD-1, TIGIT, TIM-3, LAG-3, CTLA-4, OX40, and 4-1BB) were evaluated by flow cytometry. **Results:** A total of 177 MM patients with COVID-19, 32 healthy infected controls and 42 uninfected MM patients were included. We have found that pronounced lymphopenia and inverted CD4/CD8 ratio in severe COVID-19 patients were especially developed within the first month after infection. And T cell subset dysregulation was persistent

in severe patients recovering from SARS-CoV-2 infection. Immune checkpoints on CD4+ T cells were variable and uncorrelated with the level of adaptive immunity, while the proportion of CD4+ T cells was positively correlated with humoral immune response. PD-1 and TIGIT on CD8+ T cells were significantly elevated in severe patients and sustained for more than 2 months, which was associated with impaired cellular immune function. Moreover, exhausted molecules PD-1 and TIGIT on T cells were reduced in immunotherapy patients. **Conclusions:** The prolonged T cell dysregulation after severe SARS-CoV-2 infection highlights the close surveillance from reinfection in MM patients even during convalescence. PD-1 and TIGIT on CD8+ T cells could be important prognostic factors to stratify prognosis in MM patients with COVID-19. Moreover, immunotherapy may downregulate the expression of exhausted checkpoints PD-1 and TIGIT, leading to T cell overactivation and severe COVID-19.

P-047

Characteristics of Clinicopathological Features of 17 Patients Who Had Relapsed Myeloma After Anti-BCMA CAR-T Therapy

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Introduction: CART therapy targeting BCMA is increasingly employed in myeloma patients who have failed other lines of therapy. Despite remarkable improvement in response rate and survival, a subset of patients still suffers from relapsed disease. We performed this study to analyze the clinicopathological features of patients who had relapsed diseases after CART therapy against BCMA. **Methods:** Patients who were treated with ide-cel (Abecma®) or cilta-cel (Carvykti™) and subsequently relapsed were identified from our database during the period of January 2020 to January 2024. Patients who had sufficient biopsy materials analyzed by morphology and ancillary studies including karyotyping or/and FISH using a panel for myeloma (9 probes) as well as flow cytometry using BCMA (clone 19F2, PE, Bio Legend) in combination with 8 other markers (CD38, CD138, CD45, CD19, CD27, CD56 and CD81) or immunohistochemistry for BCMA expression were included. **Results:** We identified 17 patients, age ranged from 58-91 yrs old (median 68), 10 men and 7 women. Two patients received Cilta-cel and the remaining 15 patients received Idel-cel. The interval from CAR-T infusion to relapse ranged from 3-38 months (median 12 months). The relapse was diagnosed in a bone marrow biopsy in 11 patients with tumor estimated to be 10-90% (median 70%) of total cellularity. The relapse was confirmed at extramedullary sites in 6 patients, involving soft tissue (n=3), skin (n=2), CSF (n=1). BCMA assessed in the relapsed samples was strongly positive (n=4), weakly/partially positive (n=3) and negative (n=3). Two cases were not assessed for BCMA. Four patients had a complex karyotype with loss of 17p/TP53 in 3. FISH found CKS1B amplification in 9 patients, including 2 with additional FGFR3::IGH, TP53 deletion (n=2) and MYC rearrangement (n=2). Four of 6 patients whose samples were analyzed by next generation sequencing found TP53 mutations with VAF ranging from < 5-30%. The relapsed diseases were treated with additional therapy, including stem cell transplant, Teclistamab, anti-CD70 CAR-NK or other chemoimmunotherapy. With a median follow up of 19 months (range 3.5-58.4), Five patients died and the remaining 12 were still alive at the last FU, the median OS has not reached yet. **Conclusions:** BCMA expression varied from bright to diminished or absent with majority retained in the relapse samples after the patients failed CART therapy suggesting immune evasion as a mechanism of resistance in majority. About 1/3 of patients suffered from extramedullary relapse despite negative bone marrow. The recurrent tumor cells typically harbored high risk genetic aberrations with a high frequency of CKS1B amplification, FGFR3::IGH, TP53 deletion or/and mutation, or MYC rearrangement.

P-048

Barriers to the Implementation of Bispecific Antibodies for Patient With Relapsed and Refractory Myeloma in the UK: Results of a National Survey

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Introduction: Bispecific T cell antibodies (BsAb) are an important treatment for patients with Relapsed Refractory Multiple Myeloma (RRMM). However, implementation poses challenges which may lead to inequities in access. To address these, a UK national multi-professional steering group was formed to improve, standardise processes and deliver education. This project sought to understand the key barriers to BsAb treatment. **Methods:** An on-line questionnaire of 22 questions was developed by a steering group composed of a mix of multiple-choice; Likert scale; and open-ended formats to allow quantitative and qualitative data collection. The questionnaire was distributed between January to March 2024 via the UK Myeloma Society and the British Oncology Pharmacy Association. **Results:** 85 completed responses were obtained from a variety of healthcare professionals (Clinicians (39), Pharmacists (28), Nurses (16), other allied healthcare professionals (HCPs) (2)) across 44 UK hospitals. Most responders were from transplant (ASCT) centres (n=41), with the rest from community hospitals that deliver chemotherapy (n=35). There were no responses from centres delivering limited out-patient treatment. All had access to in-patient beds (median 10-30, range 1- >50). 29% of patients travelled >60 minutes to reach their specialist centre. 39% had prior experience with BsAbs (27% were from ASCT centres, 12% were from chemotherapy centres). 28% had experience through a clinical trial. 78% were aware of BsAb trial data in myeloma (49%

ASCT centres; 29% chemotherapy centres). Haematologists were most likely to be aware of BsAb trial data (79%), although 21% reported either not being aware or were unsure. 57% pharmacists were aware, with 43% reporting limitations. 31% nurses were aware of data although were mainly clinical nurse specialists, with 69% of other nurses lacking knowledge. Overall, 64% were aware of the adverse events associated with BsAbs (42% ASCT centres; 22% chemotherapy centres) with 36% not reporting knowledge (6% ASCT centres; 30% chemotherapy centres). Haematologists were generally aware of adverse events (64%) as were pharmacists (57%), although nurses generally less so (31%). 58% had difficulty accessing immunoglobulin (Ig) due to restricted commissioning (44%), administrative issues (37%) and resource restrictions such as infusion capacity (19%). 29% reported prescribing systems were not a barrier to implementation, whilst 47% were unsure. Qualitative thematic analysis identified the need to streamline IVIG approval processes and improve capacity and resources to access Ig. Additionally, there was a need to develop outpatient/ ambulatory pathways. **Conclusions:** Whilst BsAbs have significant activity for patients with RRMM, this survey highlighted areas requiring improvement to implement this treatment in the UK. Further educational activity is essential for all HCPs, particularly nurses. Additionally, development of pathways to improve access and capacity for Ig administration is required.

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Teclistamab in Real Life: Can We Shorten the Ramp-Up?

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Introduction: Teclistamab (TEC) is a bispecific BCMA-CD3 directed T-cell antibody (BsAb) approved from the MajesTEC-1 study with high overall response rates(ORR)≥ 63.0% in refractory/ relapsed multiple myeloma (RRMM) patients(pts). The very low rate of ICANS (3.0%; all grade (G) 1 or 2) and CRS (G 3 : 0,6% no G 4) was also observed in our center which motivated us to shorten the dose escalation schedule. Thus we report the first results of modified ramp-up of TEC. **Methods:** We enrolled all pts with RRMM from a single institution after at least two lines of therapy including triple-class exposure to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody ; 13 pts had standard ramp-up (Gp1) over 5 days accorded to the guidelines ; 27 pts had received a shortened ramp-up (Gp2) over 4 days (Day(D)1 : 0.06mg/kg, D2 : 0.3 mg/kg, D4 : 1.5 mg/Kg) with no pause between the 1st and the 2nd dose. Data was collected from medical records between september 2022 until 01/05/2024. **Results:** Between September 2022 and May 2024 , 40 patients were included; median age was 68 (range 37-84); 16 pts (40 %) had >75 years; 14 pts (35 %) were males. Patients received a median of 4 of lines of previous therapy (range 2-8); 28,1% were refractory to last line of therapy; 9 pts (22.5%) had high-risk cytogenetics/FISH. In the total population CRS was seen in 24 (60%) (all G1: except 2 G2, 1 G3), all resolved within 24 hours and was managed with acetaminophen alone (n=17); tocilizumab(toci) alone (n= 1) ; dexamethasone(dex) alone (n=3) or dex- toci (n=2). CRS was observed by 9 pts (69,23 %) in the Gp 1 (77,8 % G1, 22,2% G2), 22,2 % at D2; 44,4% at D4; 33,3% at D6 vs 14 pts (51,85%) in the Gp 2 (78,5% G1, 14,2% G2, 7,1% G3) 78% at D3, this may be due to the premedication of 2nd dose with dex which probably avoids the CRS after D1; and 21,4% at D5. ICANS was infrequent (n=2 ; 5 %) all G1. The overall response rate for evaluable patients (n=39) was 61.53%; (≥VGPR in 22; PR in 2; PD in 15). With a median follow-up of 11,7 months(m), the median PFS and OS were 12,14 m and 13,04 m respectively. The median of duration of response (mDOR) is 12,47 months. Efficacy were similar in the two groups. Most common reason for treatment discontinuation was PD (38,4%). 15 pts have died by 01/05/24. Most common cause of death was disease progression. Infections were common, seen in 19 (48,7%) of pts, the majority were viral Infections or Pneumonia. IVIG was given in 19 pts (48,7%). There was no difference between the two groups. **Conclusions:** In this study, results of adverse events (CRS, ICANS), ORR and PFS were similar to MajesTEC-1. The rates of CRS in Gp2 was low compared to the Gp1 and occured at D3 or less frequently at D5 i.e. one day less CRS. Moreover, shortened Ramp-up do not compromise pts outcome and toxicity. Since 02/23 we used only the shortened ramp-up. Finally manageable, predictable toxicity show that it could be a good schedule for an outpatient setting.

P-050

Talquetamab vs Real-World Physician's Choice in Patients With Relapsed/Refractory Multiple Myeloma and Prior B-Cell Maturation Antigen Therapy: Analyses of MonumenTAL-1 vs LocoMMotion/MoMMent

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Introduction: T-cell redirection therapies (TCR), including B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR)-T cells and bispecific antibodies (BsAbs), are new treatment (tx) options for patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) but result in an unmet need for pts who relapse after these txs. Talquetamab is the first G protein–coupled receptor family C group 5 member D-targeting BsAb approved for the tx of pts with TCE RRMM and showed overall response rates (ORRs) of 72.9% and 56.5% in pts with prior BCMA CAR-T and prior BCMA BsAb tx, respectively, in MonumenTAL-1 (NCT03399799/NCT04634552). LocoMMotion (NCT04035226) and MoMMent (NCT05160584) are prospective observational studies of clinical outcomes with real-world physician's choice (RWPC) therapies. As MonumenTAL-1 is a single-arm study, adjusted comparisons can help determine the relative efficacy of talquetamab vs other txs. Here, we present results of talquetamab vs RWPC in pts with prior BCMA TCR. **Methods:** An adjusted tx comparison was performed using individual pt data (IPD) for pts with prior BCMA TCR and who received subcutaneous talquetamab 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W) dosing (MonumenTAL-1; data cut-off [DCO]: Jan 2024) or RWPC therapies (LocoMMotion; final data, and MoMMent; DCO: Aug 2023). IPD from talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W dosing are pooled for this analysis. For the base case analysis, multivariable regression was used to adjust for imbalances in refractory status, ISS stage, time to progression on prior line of therapy (LOT), number of prior LOTs, time since diagnosis, presence of extramedullary disease, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase levels, hemoglobin levels, and creatinine clearance. A sensitivity analysis, including additional adjustments for age, sex, MM type, average duration of prior LOTs, and prior autologous stem cell transplantation, was also performed. ORR was analyzed using multivariable logistic regression to estimate odds ratios, relative risk (RR), and 95% confidence intervals (CIs). Progression-free survival (PFS) and overall survival (OS) were analyzed using multivariable proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs. **Results:** The base case analysis showed superior efficacy of talquetamab (n=74) vs RWPC (n=36) after BCMA TCR for ORR (64.9% vs 11.1%, RR=6.42; 95% CI, 2.54–16.25; P< 0.0001), PFS (median: 6.0 vs 2.5 months, HR=0.53; 95% CI, 0.29–0.98; P=0.0423), and OS (median: 27.1 vs 8.5 months, HR=0.32; 95% CI, 0.17–0.63; P=0.0008). Results of the sensitivity analysis were consistent with the base case analysis. **Conclusions:** These analyses demonstrate clinical benefit and superior efficacy of talquetamab vs RWPC for ORR, PFS, and OS, and highlight talquetamab as a novel, highly effective tx option for pts with TCE RRMM and prior BCMA TCR exposure.

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iMMagine-3: A Phase 3, Randomized Study to Compare the Efficacy and Safety of Anitocabtagene Autoleucel (Anito-Cel) With Standard of Care in Patients With Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Anito-cel, formerly CART-ddBCMA, is an autologous anti-BCMA CAR T-cell therapy with a novel synthetic D-Domain binder that facilitates high CAR transduction efficiency and surface expression with low tonic signaling (Buonato, et al. Mol Cancer Ther, 2022). In a Phase 1 expansion study, anito-cel demonstrated an overall response rate of 100% including a 76% complete response (CR)/stringent CR (sCR) rate in 38 patients (pts) with RRMM who had ≥3 prior lines of therapy. With median follow-up of 26.5 months, median progression-free survival (PFS) was not reached and estimated 24-month PFS rate was 56%. At 100×106 CAR+ T cells (n=32), no pt had Gr ≥3 CRS, 1 pt (3%) had Gr 3 ICANS, and there were no delayed neurotoxicities (Frigault, et al. ASH, 2023). An ongoing Phase 2 study, iMMagine-1, is investigating anito-cel in pts with RRMM who had ≥3 prior therapies including a proteasome inhibitor, an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody (mAb; NCT05396885). The randomized, open-label, Phase 3 study iMMagine-3 (NCT06413498) will assess the efficacy and safety of anito-cel compared with standard of care (SOC) in pts with RRMM who received 1-3 prior lines of therapy including an IMiD and an anti-CD38 mAb. **Methods:** iMMagine-3 will enroll ~450 patients randomized 1:1 to anito-cel or SOC. Before randomization, investigators will select one of the following SOC regimens: pomalidomide (P), bortezomib (V), and dexamethasone (d; PVd); daratumumab (D), P, and d (DPd); carfilzomib (K), D, and d (KDd); or K and d (Kd). Pts in the SOC arm will receive the selected SOC regimen (21-d cycles of PVd or 28-d cycles of DPd, KDd, or Kd) until unacceptable toxicity, progression, death, or withdrawal of consent. Pts in the anito-cel arm will undergo leukapheresis and optional bridging therapy (with the

selected SOC regimen at discretion of the investigator) followed by lymphodepleting chemotherapy (fludarabine 30 mg/m2/d and cyclophosphamide 300 mg/m2/d for 3 d) and one infusion of anito-cel (115×106 CAR+ T cells) on D1. Additional key inclusion criteria are ECOG score 0-1, progressive disease within 12 mo of the last dose of the last regimen, and measurable disease at screening per 2016 IMWG criteria. Key exclusion criteria include prior BCMA-targeted therapy, T-cell engager therapy, genetically modified T-cell therapy, prior autologous stem cell transplant (SCT) within 12 wk before randomization, prior allogeneic SCT, and active or history of central nervous system or meningeal involvement of MM. The primary endpoint is PFS per independent review (time from randomization to disease progression per the 2016 IMWG criteria or death by any cause) with the hypothesis that anito-cel will prolong PFS compared with SOC. Key secondary endpoints include CR rate (CR/sCR), overall minimal residual disease negativity, overall survival, and safety. **Results:** iMMagine-3 will have ~130 sites in North America, Europe, and rest of world. **Conclusions:** iMMagine-3 is enrolling soon.

P-052

Efficacy and Safety of ide-cel with Lenalidomide (R) Maintenance Versus R Maintenance Alone in Adult Patients (pts) with NDMM Who Have Suboptimal Response to ASCT: Phase 3 KarMMa-9 Trial

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Introduction: Trial in Progress. Despite treatment (tx) advancements for transplant-eligible NDMM with triplet and quadruplet induction tx, including immunomodulatory (IMiD®) agents, proteasome inhibitors (PIs), and anti-CD38 antibodies followed by ASCT, pts who achieve < complete response (CR) post-ASCT have poorer prognosis than pts who achieve ≥CR. R maintenance post-ASCT is the standard of care in NDMM, but risk of disease progression is higher in pts who have suboptimal response to ASCT. Tx optimization is warranted to reduce residual disease post-ASCT and extend response duration in these pts.Ide-cel, a BCMA-directed CAR T cell therapy, significantly improved median PFS and ORR versus standard regimens in pts with triple-class–exposed early-line relapsed and refractory multiple myeloma. Ide-cel also showed deep and durable responses in pts with NDMM who had inadequate response to front-line ASCT in phase 2 KarMMa-2 trial cohort 2c at a median follow-up of 39.4 months. Of 8 pts who received R maintenance after ide-cel at investigator discretion in this cohort, 6 achieved ≥CR and 2 achieved very good partial response (VGPR); none experienced progressive disease (PD) or death at data cutoff, and the safety profile of R maintenance after ide-cel was favorable. There were no second primary malignancies in pts who received R maintenance after ide-cel.This multicenter, randomized, controlled, phase 3 KarMMa-9 trial (NCT06045806) will compare efficacy and safety of ide-cel and R maintenance versus R maintenance alone in adults with NDMM who had partial response (PR) or VGPR to ASCT. **Methods:** Adults with NDMM who had 4–6 induction tx cycles, including an IMiD agent and a PI followed by high-dose chemotherapy and a single ASCT, and had achieved PR or VGPR post-ASCT were eligible. Pts could not have PD since commencing induction nor received consolidation or maintenance tx.Patients (N≈618) will be randomized 1:1 to receive R maintenance alone or ide-cel and R maintenance. Randomization will be stratified by revised International Staging System stage III disease at diagnosis, anti-CD38 induction, and response post-ASCT. Ide-cel and R group will receive 1 cycle (28 days) of R (10 mg daily) ≤7 days post-randomization followed by leukapheresis (14–42 days after last dose of R) and lymphodepleting chemotherapy before ide-cel infusion (target dose: 300–460 x 106 CAR+ T cells). R maintenance will resume at 1 month post–ide-cel contingent on blood cell count recovery. Pts will receive R at 5 mg once daily for the first cycle post-infusion; if tolerated, subsequent dosing will follow prescribing information. Both groups will receive R maintenance until PD/unacceptable toxicity.Primary endpoint: PFS. Key secondary endpoint: overall survival. Other secondary endpoints: sustained MRD-negative CR for 12 months, MRD-negative CR rate, event-free survival, DOR, CR rate, time to progression, PFS2, safety, pharmacokinetics, HRQoL. **Results:** Not applicable. **Conclusions:** Not applicable.

P-053

Early Absolute Lymphocyte Count after BCMA CAR-T as a Surrogate for CAR-T Expansion, Response, and Progression Free Survival in Multiple Myeloma

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Introduction: Expansion of chimeric receptor antibody (CAR)-T cells after infusion has previously been described across CAR-T products; however, peripheral blood expansion and absolute lymphocyte dynamics and their clinical and biological significance have not been studied after CAR-T infusion in multiple myeloma (MM). **Methods:** 156 patients (pts) with relapsed MM (91 pts ciltacabtagene autoleucel (cilta-cel) and 65 pts idecabtagene vicleucel (ide-cel) were included. Baseline characteristics, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), ALC on day -5 through 15, and outcomes were collected. ALCmax was defined as the highest ALC on day 0 to 15. **Results:** Early ALC increase after BCMA CAR-T was common, with a median ALCmax of 1.26 x103/uL (IQR 0.6-2.7) from a median baseline of 0. Patients with CRS had higher ALC max (1.4 vs 0.5, $p < 0.001$). Similarly, patients with ICANS had higher ALCmax (2.17 vs 1.1, $p < 0.01$), while the use of any cytotoxic chemotherapy or bendamustine as the last line of therapy before leukapheresis had lower ALCmax (0.8 vs 1.4, $p = 0.03$ and 0.55 vs 1.3, $p = 0.007$, respectively). There was a significant positive correlation of ALCmax with the maximum ferritin within 30 days post-infusion, while there was no correlation for baseline ALC and ferritin. ALCmax was associated with deeper (CR/VGPR vs ≤PR), and improved duration of response (DoR) and PFS. In contrast, non-paraskeletal EMD, baseline ferritin, high-risk cytogenetics (HRCG), and number of previous lines of therapy were associated with worse PFS in univariable analysis. Patients with ALCmax >1.0 x103/uL had prolonged PFS (median 33.5 vs 6 months, $p < 0.0001$), while those with ≤0.5x103/uL had a poor prognosis (median PFS 3.6 vs 24 months, $p < 0.0001$). Similar results were seen when each BCMA CAR-T product was assessed individually. ALCmax > 1 x103/uL (HR 0.35, 0.2-0.6, $p < 0.001$) and non-paraskeletal EMD (HR 2.2, 1.3-3.6, $p < 0.01$) were the only independent factors associated with PFS/DoR in the multivariable model after adjusting for CAR-T Product, HRCG, and the number of previous lines. PB flow cytometry in 3 patients with VGPR/CR and ALCmax range 2-14 x103/uL, showed expansion of CD3+ BCMA CAR+ cells from day 7 (< 0.2% of CD3+ cells) into day 14 (range 54-88.6%) of total T cells. However, a non-responder patient with ALCmax of 0.4 x103/uL had minimal expansion of CD3+ BCMA CAR+ (2%) at days 14 and 21—ongoing analysis of 9 other cases in underway. **Conclusions:** Early Post-CAR-T lymphocytosis is common following BCMA CAR-T in MM. After adjusting for other prognostic variables, it is strongly associated with depth of response, PFS, and DoR. A cut-off of ALCmax > 1 x103 identified patients with prolonged PFS, while ALC max < 0.5 x103 was prognostic for poor response and early progression. ALC kinetics correlated with BCMA CAR-T expansion, thus ALCmax is a clinically accessible biomarker for response in patients receiving BCMA CAR-T in MM.

P-054

Abnormal Serum Fixation Pattern 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 the appearance of a monoclonal band with a different isotype than that of the multiple myeloma (MM), is seen in 30-60% of MM patients (pts) who undergo autologous stem cell transplantation (ASCT) and other treatment modalities and is associated with better outcomes. We describe the presence of ASIP in MM pts following BCMA CAR T-cell therapy. **Methods:** Pts with relapsed MM who received BCMA CAR-T at two institutions were included. Clinical characteristics, serum protein electrophoresis/immunofixation (SPEP/sIFE), quantitative immunoglobulin, immune-related events such as vaccinations and infections were collected. **Results:** 51 pts were included (15 idecabtagene vicleucel and 36 ciltacabtagene autoleucel). ASIP was seen in 9 pts (25%) before the progression of the disease, including 2 pts with 2 independent ASIP events. The median time to ASIP was 9.5 months and lasted a median of 2 consecutive SPEP/sIFE assessments (range 1-12). 6 out of 9 (67%) of ASIP were preceded within 60 days by an immunological event (5 infections, 2 vaccination events). 100% of ASIP cases occurred after achieving pts best response (7 pts CR, 2 pts VGPR). There were no differences in the proportion of pts who had an immunological event (67% vs 68%, $p = 0.9$) or the median number of events (2 (1 – 3) vs 2 (1 – 3), $p = 0.9$) in ASIP vs no ASIP. Similarly, there were no differences in the proportion or median number of infectious events (any infection: 67% vs 51%, $p = 0.5$, median 1 (1 – 2) vs 1 (1 – 2) $p = 0.9$) or vaccination events (any vaccination: 22% vs 38%, $p = 0.5$, median 1 (1 – 1) vs 1 (1 – 2), p 0.4). At the time of ASIP, 100%, 67%, and 56% of pts had serum IgA, IgG, and IgM below the lower limit of normal (LLN). However, when comparing to pts without ASIP, those with ASIP had higher median IgG (603 vs 443 mg/dL, $p < 0.01$) and IgM (29 vs 11 mg/dL, $p < 0.01$), whereas IgA was higher but not significant (29 vs 11 mg/dL, $p = 0.052$). Pts with ASIP had lower rates of immunoglobulins below the LLN throughout their course (IgG: 50% vs 88%, IgA: 83% vs 100%, IgM: 72% vs 100%). Pts with ASIP had more SPEP/sIFE assessments (7 vs 21 < 0.1). **Conclusions:** ASIP was a frequent event following BCMA CAR-T, with 13 (25%) ASIP events in the cohort, including 9 (17%) with ASIP. ASIP uniformly occurred after achieving a deep response (≥ VGPR) and was often associated with hypogammaglobulinemia at the time of ASIP appearance. However, patients with ASIP had lower rates of hypogammaglobulinemia throughout their course, along with a similar rate of immunological events, suggesting ASIP may occur in patients with deep response and relatively more

preserved residual non-neoplastic plasma cell compartment in response to an immunological stimulus. The implication of ASIP on the loss of CAR-T on target effect or outcomes cannot be assessed due to the sample size, but it represents an important next step given the implication of ASIP in other treatment modalities.

P-055

Conserved and Unique Pathways of Natural Killer Cell Resistance in Multiple Myeloma Cell Lines

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Introduction: Multiple myeloma (MM) displays heterogeneity in gene expression profiles (GEP) at the cellular level that contributes to variable sensitivity to therapeutic agents. We used MM cell lines with variable sensitivity to natural killer (NK) cell-mediated cytotoxicity to determine if common pathways of resistance to cellular therapy could be identified. We utilized an induced pluripotent stem cell derived NK product expressing a chimeric antigen receptor (CAR) against B cell maturation antigen (BCMA) that is currently in Phase 2 trial for relapsed MM. In addition to engagement of the CAR, CAR-NK cells retain the ability to recognize MM cells through natural cytotoxicity or CD16 engagement. **Methods:** MM cell lines (n=4) were stained with an antibody against BCMA. Flow cytometry showed greater than 85% expression of BCMA on U266, H929, and MM1S but only 40% expression on RPMI-8226. MM were incubated with CAR-NK cells at 1:1 ratio and samples at 0 and 24 hours used for genome wide transcriptome analysis. In parallel, fluorescently labelled MM cells were incubated with NK cells for 48 hours and killing was measured by live cell imaging (4 replicates per condition). **Results:** RPMI-8226 were most resistant to CAR-NK cells (< 10% killing at 24 hours). H929, MM1S, and U266 showed 20-35% killing at 24 hours. Hierarchical clustering of the top genes with differential expression between pre-NK treatment and post-NK treatment showed 85 genes shared by all 4 cell lines that exhibited a 2-fold difference in gene expression after CAR-NK cell therapy. Genes highly expressed by all cell lines were HLA-B, TAP1, and TAP2, all of which suppress NK cell cytotoxicity through HLA engagement of inhibitory receptors. KEGG pathway analysis confirmed that genes in the NK cell cytotoxicity and cytokine receptor interaction pathways were enriched in the NK-resistant MM cells. Other genes upregulated in all 4 lines were PARP14, encoding a poly (ADP-ribose) polymerase and regulator of survival in MM cells as well as DTX3L, which encodes a ubiquitin ligase known to play a role in proliferation and drug resistance in MM. Significantly more genes were altered in the most resistant cell line, RPMI-8226, compared to the more NK-sensitive cell lines. The gene encoding TRAIL, TNFSF10, was significantly upregulated and may directly modulate NK cell function through regulation of interferon-g signaling. The upregulated metalloproteases ADAM8 and MMP25 may promote RPMI-8226 resistance by clipping activating receptors from the NK cell surface. **Conclusions:** Our data provide initial insights into the pathways that promote resistance to NK cell-mediated killing in MM. We are using human bone marrow samples before and after BCMA CAR-NK therapy to validate these findings in patients. These results will eventually identify novel targets that can improve cellular therapies and eliminate resistant MM.

P-056

Bispecific Antibodies Improve Outcomes in Patients With Relapsed or Refractory Multiple Myeloma After Car-T Cell Therapy

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Introduction: Despite the unprecedented rates of deep remissions in relapsed/refractory multiple myeloma (RRMM), virtually all patients experience relapse after CAR T-cell therapy. Although advances have been made in identifying risk factors for poor outcome after CAR T-cell therapy, the role of salvage treatments is uncertain. In the current study, we analyzed a large, international cohort of patients treated for relapse after BCMA-directed CAR T-cell therapies for RRMM. **Methods:** We collected detailed data on disease-, treatment-, and patient-related factors of 12 centers from Europe and the United States. In addition, data on treatment sequences and responses were collected. Primary objective was to describe response to salvage practices for relapsed myeloma after CAR T and to identify regimen offering optimal outcomes. **Results:** We included a cohort of 142 patients with relapse after commercial CAR T cell products who received salvage therapies. The median time from CAR T infusion to relapse/progression was 5 months (range, 0.4-33 months). 50% of patients experienced relapse with extramedullary disease (EMD). Patients received the following salvage treatments for first relapse/progression: Talquetamab (20%), Teclistamab (26%), combinations of IMiDs or CD38 monoclonal antibodies (31%), chemotherapy (11%), radiotherapy (4%), autologous or allogeneic transplant (3%), and others. Median time to first relapse was 5 months for the talquetamab group, 7 months for the teclistamab group, 4 months for the IMiDs/CD38 group, and 3 months for all others (P=0.04). Response to first salvage treatment was significantly different, with talquetamab and teclistamab showing better responses (P< 0.001). Overall response rate was 77% for talquetamab, 62% for teclistamab, 26% for IMiDs/

CD38, and 25% for the rest. Complete responses were seen in 32% of the talquetamab group, 33% of the teclistamab group, 3% of the IMiDs/CD38 group, and 0% of the rest. Very good partial responses were highest for talquetamab (27%), followed by teclistamab (15%). Median follow-up of survivors after relapse was 8 months (95% CI, 7-9 months). Overall survival after relapse was significantly improved with bispecific antibodies (P< 0.001), showing 83% for talquetamab, 75% for teclistamab, 40% for IMiDs/CD38, and 23% for the rest at 8 months. Poorer prognosis was seen for EMD relapse with overall survival of 43% versus 67% for non-EMD relapse (P< 0.001) at 8 months. Importantly, both talquetamab and teclistamab appeared to be able to overcome the poorer prognosis of EMD relapse, showing promising survival and no significant difference between EMD vs non-EMD relapse (P=0.43 for talquetamab and P=0.86 for teclistamab). **Conclusions:** Talquetamab and teclistamab improved outcomes for patients with relapse/progression after CAR T cell therapy. Both agents might overcome the dismal prognosis of EMD relapse. Final analyses including subgroups will be presented at the meeting.

P-057

Comparative Efficacy of Cilta-Cel vs Approved Comparator Treatments for Patients With Relapsed/Refractory Multiple Myeloma With 1–3 Prior Lines of Therapy: A Network Meta-Analysis

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Introduction: In the phase 3 CARTITUDE-4 trial, ciltacabtagene autoleucel (cilta-cel) prolonged progression-free survival (PFS) vs standard of care (SOC) (HR [weighted], 0.26; P< 0.0001; HR [unweighted], 0.40; P< 0.0001) in patients with lenalidomide (len)-refractory multiple myeloma (MM) and 1–3 prior lines of therapy (LOT), including a proteasome inhibitor and an immunomodulatory drug. We report the results of a network meta-analysis (NMA) that compared cilta-cel efficacy vs relevant SOC comparators based on target trial populations, including len-refractory patients who received 1–3 prior LOT. **Methods:** Comparators of interest were identified a priori based on approved and commonly used SOC regimens in the United States, United Kingdom, Spain, France, Germany, Italy, Canada, and the Netherlands. A systematic literature review was conducted, and a total of 22 trials were assessed for feasibility by comparing the study design and degree of overlap with the CARTITUDE-4 population. The comparator arm in CARTITUDE-4 is SOC treatment with physician's choice of daratumumab, pomalidomide, dexamethasone (DPd) or pomalidomide, bortezomib, dexamethasone (PVd). DPd was the most common treatment in the SOC arm of CARTITUDE-4 (87% of patients), and PFS results for the DPd cohort were similar to the intent-to-treat (ITT) population; therefore, the assumption that the SOC arm was comparable to the DPd arm in APOLLO was made to form a network of trials. This network was centralized around pomalidomide in combination with dexamethasone (Pd) and included the CARTITUDE-4 (cilta-cel), APOLLO (DPd + Pd), ELOQUENT-3 (elotuzumab, pomalidomide, dexamethasone [EloPd]), ICARIA-MM (isatuximab, pomalidomide, dexamethasone [IsaPd]), and OCEAN (melflufen, dexamethasone [Md]) trials. NMAs were performed using fixed-effects Bayesian models to assess the outcome of PFS in the ITT and subgroups, including len-refractory and patients with 2–3 prior LOT. **Results:** The NMA showed cilta-cel had a statistically significant PFS benefit vs all comparators of interest and across all populations analyzed. Results favored cilta-cel across all comparator regimens in the full ITT populations (HR range, 0.25–0.49), the len-refractory subgroup (HR range, 0.27–0.45 [EloPd was excluded because data for this subgroup were not reported in ELOQUENT-3]), and the 2–3 prior LOT subgroup (HR range, 0.26–0.47). **Conclusions:** These comparisons provide valuable information to contextualize the efficacy of cilta-cel in which treatment for these patients may be different from DPd or PVd. The NMA showed that cilta-cel had a statistically significant PFS benefit vs all feasible comparators (Pd, EloPd, IsaPd, Md). Results of the NMA should be supplemented with matching-adjusted indirect comparisons given key differences across the included trials with regard to effect modifiers (eg, number of prior LOT, ISS stage, cytogenetic risk).

P-058

Cytokine Release Syndrome in Patients Receiving Alternative Step-Up Doses of Talquetamab for Relapsed/Refractory Multiple Myeloma: Results from the Phase 1/2 MonumenTAL-1 Study

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Introduction: Talquetamab (tal) is the first GPRC5D×CD3 bispecific antibody approved for the treatment of patients (pts) with relapsed/refractory multiple myeloma (RRMM). Cytokine release

syndrome (CRS) is a common adverse event reported with T-cell redirecting bispecific antibodies. To mitigate the risk of CRS, pts receive step-up doses (SUDs); for the tal 0.4 mg/kg weekly (QW) and 0.8 mg/kg every other week (Q2W) approved doses, pts receive 2 (0.01 and 0.06 mg/kg) or 3 (0.01, 0.06, and 0.4 mg/kg) SUDs, respectively. With 3 SUDs in the tal Q2W cohort, CRS occurred in 74.5% and immune effector cell–associated neurotoxicity syndrome occurred in 11.0% of pts. While receiving SUDs, pts should be hospitalized and monitored for ~10 days. This analysis evaluated the impact of alternative, fewer SUDs in the tal Q2W schedule on key parameters of CRS. **Methods:** Alternative SUD cohorts were added to phase 1 of MonumenTAL-1 (NCT03399799) for the Q2W schedule. Eligible pts had RRMM and were intolerant to or progressed on available established therapies. Pts received either 0.03 mg/kg followed by 0.2 mg/kg (cohort 34; n=6) or 0.06 mg/kg followed by 0.4 mg/kg (cohort 35; n=10) SUDs. Administration was 24–72 hours between SUDs and first treatment dose, with inpatient monitoring through 48 hours after the first treatment dose. CRS was graded per Lee criteria (Lee et al 2014). Other AEs were graded per CTCAE v4.03. **Results:** Across cohorts (N=16), median follow-up was 3.4 months (range, 0.03–6.21). Median age was 71.0 years (range, 43–80), 9/14 pts had high-risk cytogenetics, 2/16 had extramedullary disease, 2/16 had ISS stage III disease, and none had bone marrow plasma cells ≥60%. In cohorts 34 and 35, CRS occurred in 6/6 (3 grade [gr] 1, 3 gr 2) and 8/10 (7 gr 1, 1 gr 2) pts, respectively. No pts had gr ≥3 CRS. Multiple CRS events occurred in 1/6 and 3/10 pts, respectively. In cohort 34, 3 CRS events occurred after SUD1 and 4 after SUD2; in cohort 35, 6 CRS events occurred after SUD1, 5 after SUD2, and 1 after cycle 1 day 1. No CRS events occurred from cycle 1 day 15 onwards. Across cohorts, median time to onset and median duration of CRS were each 2.0 days. All pts received treatment for CRS, mainly paracetamol and tocilizumab. No pts experienced neurotoxicity. CRS data were generally consistent with the MonumenTAL-1 Q2W cohort with 3 SUDs, whereas fewer neurotoxicity events were reported in the alternative SUD cohorts. Preliminary pharmacokinetics data suggested that tal serum exposure after the first full treatment dose in cycle 1 was comparable between the alternative SUD cohorts and the MonumenTAL-1 Q2W cohort with 3 SUDs. **Conclusions:** These data show that compressing the total period of step-up dosing had minimal impact on CRS. This has the potential to improve patient experience with tal by shortening the time for which intense CRS monitoring is needed, including inpatient/hospital-based monitoring.

P-059

Ferritin Dynamics are Associated with Clinical Outcomes of Multiple Myeloma Patients Receiving Bispecific Antibodies

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Introduction: Bispecific antibodies (BiAbs) have demonstrated response rates of 60-70% and provided nearly 1 year of progression-free survival (PFS) in relapsed refractory MM patients. Current research aims to identify factors influencing response to BiAbs. Based on our findings on ferritin's prognostic significance in CAR-T therapy (Pan et al., ASH 2023), we investigated ferritin's utility in predicting long-term outcomes for MM patients treated with BiAbs. **Methods:** We identified 198 MM patients who received a BiAb at Mount Sinai through clinical trials or commercially. Descriptive analyses summarized baseline characteristics and ferritin dynamics. Kaplan-Meier (KM) method estimated survival outcomes. Group-based trajectory modeling (GBTM) identified clusters of patients with similar ferritin trends. **Results:** Patients were followed for a median of 25.13 months. The median age at BiAb initiation was 66 years. Of 198 patients, 99 (50%) received anti-BCMA BiAb, 80 (40.4%) talquetamab, and 18 (9.1%) cevostamab. Moreover, 36 (18.2%) received a BiAb with daratumumab, pomalidomide, or both, and 164 (82.8%) received the RP2D. They had a median of 6 prior lines of therapy. Furthermore, 150 (76%) achieved a partial response (PR) or better, including 128 (62.6%) who achieved a deep response (very good PR or better). The median baseline ferritin level for patients was 530.24ng/mL. Patients with PFS ≥1 year had lower baseline ferritin (113.5ng/mL) compared to those with PFS < 1 year (189ng/mL, p=0.006). Patients with PFS ≥1 year had lower maximum ferritin level during the first 2 weeks of BiAb therapy (214ng/mL vs 305.5ng/mL, p=0.038) and within 6 months of initiating BiAbs (309ng/mL vs 696ng/mL, p=0.005). Similarly, patients with OS ≥2 years had lower baseline ferritin (91ng/mL vs 173ng/mL, p=0.007). They also had lower maximum ferritin levels during the first 2 weeks (191ng/mL vs 374ng/mL, p=0.02) and 6 months (255.5ng/mL vs 678.5ng/mL, p=0.004) of initiating BiAbs. A deep response was also associated with lower ferritin at baseline (p=0.01), during the first 2 weeks (p=0.05) and the first 6 months (p< 0.001). Using GBTM, we identified 3 distinct ferritin % change trends throughout therapy. Most patients (71.6%) followed a trend of a minor increase followed by a 42.5% decrease in ferritin within 6 months. Trend 2 showed a steep ferritin peak at 2 months before returning to baseline at 6 months. Trend 3 had a slower rise but remained elevated beyond 6 months. PFS and OS were similar for trends 1 and trend 2 (PFS: 23 months; OS: not reached), while patients following trend 3 experienced a shorter PFS (9 months) and OS (26 months). Further, trend 2 was associated with a higher tumor burden (p=0.022) whereas trend 3 was associated with more prior lines of therapy (7 vs 5; p=0.038). **Conclusions:** Our study highlights that patients with higher ferritin at baseline and during BiAb therapy demonstrate less favorable outcomes, suggesting ferritin as a potential prognostic biomarker for BiAb therapy in MM.

P-060

Heme Attenuates T Cell Exhaustion in Multiple Myeloma

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Introduction: Multiple myeloma (MM), is an incurable plasma cell malignancy. B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T therapy is a promising therapeutic strategy for MM. Modulating the manufacturing process to produce CAR T cells with less-exhausted phenotypes associated with durable treatment responses, is an active area of research. Mitochondrial function and energetics play a central role in regulating T cell fate and function, and heme is an essential co-factor critical for maintaining electron transport chain activity and oxidative phosphorylation. In the present study, we investigate the effects of hemin (oxidized heme) supplementation on T cell metabolism and CAR T cell efficacy. **Methods:** Human healthy donor and MM patient T cells were activated and expanded with α-CD3/CD28 and IL-2 for 7 days +/- hemin, after which immunostaining and metabolic assays were conducted. For CAR T manufacture, T cells were transduced with CAR construct starting on day 3 and were co-cultured with antigen-expressing tumor cells in vitro on day 7-8. Cytotoxicity and cytokine production were assayed after 24 hours of co-culture. **Results:** We identified hemin supplementation reduces dysfunction-related triplet-expressing T cell phenotypes (PD1+/LAG3+/TIM3+) and increased enrichment of effector memory cells (CD62L-CD45RA-) in both CD4+ and CD8+ subsets isolated from normal human donor PBMC, MM patient bone marrow-derived T cells and CAR T cells. Conversely, inhibition of de novo heme biosynthesis reversed these effects. Inquiry of cellular energetics of hemin-supplemented CAR T cells reveals reduced reactive oxygen species(ROS) and increased spare respiratory capacity and mitochondrial membrane potential, characteristic of effector T cells. Preliminary analysis of metabolite profiling of hemin-expanded T cells suggests elevated pyrimidine synthesis. Hemin supplementation induced activation of pAKT/p-mTOR/p-S6 and pro-survival MCL-1. In co-culture with tumor cells, heme-CAR T cells have higher tumor-specific lysis and production of TNFα and IL-2. CAR T-tumor cell engagement in the presence of hemin resulted in significantly decreased proportions of exhausted CAR T cells and increased production of TNFα. Lastly, hemin treatment also increases BCMA surface expression in several MM cell lines, highlighting a viable strategy for enhancing BCMA CAR T engagement with MM. **Conclusions:** We show that heme increases effector T and CAR T cell function and decreases T cell exhaustion. Increased cytotoxicity of hemin-supplemented CAR T cells was associated with activation of AKT and mTOR-signaling, pyrimidine biosynthesis, increased membrane potential and reduced ROS. Overall, our studies have broader implications for investigating heme supplementation in ex vivo CAR T manufacturing for a wide range of hematological cancers for strategic enhancement of T-cell based immunotherapies.

P-061

Incidence and Clinical Impact of Acute Kidney Injury: A Comparison of CAR T-Cell and Bispecific Antibody Therapies

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Introduction: Chimeric antigen receptor (CAR)-T cell therapy and bispecific antibodies (BsAb) therapy have shown high response rates in relapsed/refractory multiple myeloma (RRMM), yet patients often experience significant toxicities. There is a scarcity of data on the incidence, risk factors, and outcomes of acute kidney injury (AKI) following CAR T cell and BsAb therapies in RRMM. **Methods:** This retrospective study included 238 patients (pts) with RRMM who received their first CAR-T cell therapy (n=149) or BsAb therapy (n=89) at our institution between March 2017 and December 2023. Pts who received a second or subsequent dose of either CAR-T/BsAb therapy were excluded. Both commercially available (ciltacabtagene autoleucel and idecabtagene vicleucel) and investigational CAR-T therapies were included, while all BsAb therapies used were commercial products. Creatinine clearance (CrCl) were calculated via Cockcroft-Gault equation. AKI rates were estimated using cumulative incidence with new therapy or death as a competing risk. **Results:** Patients treated with BsAb were older (median age: 73 years vs. 70 years) and had a lower creatinine clearance (CrCl < 60mL/min: 47% vs. 19%), and M-spike burden under 1.5g/dL (70% vs. 83%). Both groups had similar rates of extramedullary disease (45% vs. 47%) and high-risk cytogenetics (55% vs. 52%). Our analysis showed that pre-treatment CrCl was not associated with the incidence of AKI (p >0.9). The cumulative incidence of grade 1, grade 2, and grade 3 AKI within 90 days was 14%, 4.0%, and 0.93%, respectively, for the entire cohort. There is no significant difference for the incidence of any-grade AKI by 90 days between CAR-T or BsAb treated patients (13% vs. 16%, p=0.8). Additionally, all patients that developed AKI recovered within 30 days. Univariable time-to-AKI (any-grade) analysis showed higher baseline albumin level (HR: 0.45, 95% CI: 0.24-0.83, p=0.014) and M-spike below 1.5g/dL (HR: 0.36, 95% CI: 0.18-0.71, p=0.005) were associated with a lower risk of AKI. In a multivariable model, M-spike above 1.5g/dL emerged as a significant predictor of AKI (HR: 2.56, 95% CI: 1.08-6.11, p=0.039). Importantly, patients who developed any AKI had significantly lower OS (HR 2.30; 95% CI, 1.21-4.38,

p=0.01) with a median follow-up duration of 14 months for CAR-T and 8.4 months for BsAb. **Conclusions:** Our study found that AKI post-infusion was reversible after BsAb and CAR-T therapies, regardless of pre-existing renal impairment. However, patients who developed AKI post-treatment had significantly inferior survival after adjusting for other variables, highlighting transient AKI as a clinically and prognostically significant complication. Furthermore, our results suggest that a higher tumor burden, as indicated by a higher M-spike, increases the risk of renal injury after BsAb and CAR T-cell therapies. PFS data and causes of death will be explored and presented in an updated analysis at the meeting.

P-062

QUINTESSENTIAL: A Multicenter Phase 2 Study Evaluating the Efficacy and Safety of BMS-986393 in Patients With Quadruple-Class Exposed Relapsed or Refractory Multiple Myeloma

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Introduction: Despite advances in the treatment of multiple myeloma (MM), relapses are common and there are no approved therapies for patients (pts) who continue to show disease progression after receiving four classes of treatment (immunomodulatory drug [IMiD™] therapy, anti-CD38 antibodies, proteasome inhibitors [PIs], and B-cell maturation antigen [BCMA]-targeted therapy). As BCMA-targeted therapies are being approved earlier in the treatment course, the population of quadruple class-exposed pts is expected to grow, and new treatment options are needed. 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 clinical trial (NCT04674813) suggested that BMS-986393, a GPRC5D-directed autologous chimeric antigen receptor (CAR) T cell therapy, is safe and efficacious in pts with triple class-exposed relapsed or refractory (RR) MM, including pts who received prior BCMA-targeted therapy. At the recommended phase 2 dose (RP2D) of 150 × 106 CAR T cells, the overall response rate (ORR) was 91% (21/23), including a very good partial response or better in 8/8 pts previously exposed to BCMA-targeted therapies (Bal S et al. ASH 2023. Presentation 219). Here, we present the study design of QUINTESSENTIAL, an open-label, multicenter, phase 2 study (NCT06297226) evaluating BMS-986393 in pts with quadruple class-exposed RRMM. **Methods:** Enrollment is planned at ~150 pts; ~135 pts are expected to receive therapy. Key inclusion criteria include age ≥ 18 years, confirmed diagnosis of MM as per IMWG criteria, ≥ 4 classes of MM treatment (including IMiD, PI, anti-CD38 and anti-BCMA therapy) and ≥ 3 prior lines of therapy (LOTs). Pts must also have documented disease progression during or after the most recent regimen as per IMWG, measurable disease during screening, and an ECOG performance status of 0 or 1. Pts who received previous treatment with a GPRC5D-targeted therapy are excluded. After screening, pts will undergo leukapheresis followed by bridging therapy (excluding any experimental therapy, GPRC5D-directed agents, or T-cell engagers). Pts will then receive lymphodepleting chemotherapy (LDC) followed by a single infusion of BMS-986393 at the RP2D dose of 150 × 106 CAR T cells (range 120–180 × 106 CAR T cells) ≥ 48 h post LDC. The primary objective is ORR by IMWG response criteria per an independent review committee in pts who received ≥ 4 prior LOTs. Secondary objectives include complete response rate, time to response, duration of response, progression-free survival, overall survival, minimal residual disease-negative status, and safety. Pts will be followed for ≤ 5 years after the last pt receives BMS-986393, with a subsequent long-term follow-up study continuing for ≤ 15 years. This study will recruit at 36 centers across the USA and Canada. The first pt first visit was achieved on March 21, 2024. **Results:** N/A. **Conclusions:** N/A.

P-063

Systematic Literature Review and Meta-Analysis of Clinical Trials of Fourth Line or Higher Treatment for Relapsed/Refractory Multiple Myeloma Patients

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Introduction: Treatment options for relapsed/refractory multiple myeloma (RRMM) have expanded, but clinical burden remains high, particularly for heavily pretreated patients. This systematic literature review and meta-analysis was conducted to synthesize outcomes from clinical trials evaluating fourth line or higher (4L+) treatment regimens. **Methods:** Searches using Embase, MEDLINE, and CENTRAL were conducted (January 2012-March 2024), and publications from key conferences were hand-searched. Eligible

studies were clinical trials that included the Phase II dose of a National Comprehensive Cancer Network recommended intervention and whose population was ≥80% 4L+. Meta-analyses were conducted to synthesize outcomes by treatment class (CAR T-cell therapies [CAR T], bispecific antibodies [BsAb], and Other) using random effects models where possible. For outcomes where Kaplan-Meier (KM) curves were available, meta-analyses were conducted using survival function parameters fitted to each curve. **Results:** The meta-analysis included 34 trials (5 CAR T, 3 BsAb, and 26 Other). All CAR T and two BsAb trials investigated BCMA-targeting interventions. The estimated overall response rate for CAR T, BsAb, and Other was 85.5% (95% confidence interval: 72.7, 92.9), 67.6% (62.0, 72.8) and 40.5% (33.3, 48.1), respectively. The 1-year overall survival was 84.4% (79.1, 88.4) for CAR T, 70.4% (66.6, 73.9) for BsAb, and 59.5% (55.8, 63.1) for Other. The 1-year progression-free survival was 59.0% (53.7, 64.0) for CAR T, 48.4% (44.2, 52.3) for BsAb, and 20.9% (17.9, 24.0) for Other. Infections occurred in 67.1% (59.6, 73.8) with CAR T, 69.2% (60.9, 76.5) with BsAb, and 60.2% (48.6, 70.9) with Other. For adverse events specific to the immune effector cell therapies of CAR T and BsAb, overall neurotoxicity occurred in 18.8% (10.0, 32.3) and 10.2% (7.2, 14.2), and cytokine release syndrome (CRS) in 92.3% (85.2, 96.2) and 71.4% (63.4, 78.3), respectively. Additional outcomes data will be presented. **Conclusions:** This study offers a comprehensive and up-to-date synthesis of clinical trial outcomes for recommended interventions in 4L+ treatments for RRMM. While efficacy outcomes are improving with more recently approved interventions, there remains an unmet need for durable treatments with an improved safety profile in this population.

P-064

Trial in Progress: A Retrospective Multi-Country Study of Clinical Outcomes in Patients with R/R Multiple Myeloma Treated with Teclistamab Outside of Clinical Trials

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Introduction: Teclistamab is a T cell redirecting bispecific monoclonal antibody that has shown promising results in triple-class exposed patients with relapsed/refractory multiple myeloma (RRMM) in the MajesTEC-1 clinical trial[1]. In a recent analysis of the CONNECT MM registry, it was reported that up to 40% of patients treated in routine care would be ineligible for enrollment in randomized trials due to stringent eligibility criteria[2]. Therefore, there is a growing demand from healthcare providers for data outside of clinical trials that provide a better understanding of the safety and effectiveness of emerging antimyeloma treatments in these patient populations. This data can be partly obtained from pre-approval access programs and/or early phases of commercialization but for interpretation, it needs to be considered that the majority of patients treated in this setting are heavily pre-treated and in an advanced stage of disease. Nevertheless, studies conducted in this setting are useful to address areas of unmet medical need, evidence gaps, results in populations underrepresented in clinical trials, management of adverse events and sequencing of therapies. **Methods:** REALiTEC is a retrospective, non-interventional, international study to describe the use of teclistamab in patients with RRMM outside of clinical trials. Data from patient´s medical records will be collected to assess their characteristics and demography, history of prior antimyeloma treatments, teclistamab treatment patterns (healthcare setting, dosing frequency), effectiveness parameters (progression free survival, overall survival, response rates, duration of response, time to response, time to next treatment), safety, medical resource utilization and subsequent therapies. To be eligible, patients included in this study will need to have received at least one dose of teclistamab on/before 31st of December 2022, either in pre-approval access programs and/or the health care system, to ensure sufficient data availability at the time of enrollment in the study. Since there is no formal statistical hypothesis and study objectives are of descriptive nature, based on feasibilities, a sample size of 180 patients has been established. 27 sites from 10 countries have been approached to participate in this study and enrollment began in December 2023 and is currently ongoing. **Results:** N/A. **Conclusions:** Non-trial patient populations represent a considerable proportion of patients seen in clinics and may have substantially different patient/disease characteristics compared with clinical trial cohorts. Information on the management and outcomes of these patients is limited. Hence, this study will provide valuable data in RRMM patients treated in early access programs and early commercial phases to complement data from clinical trials and potentially inform future management of teclistamab by the medical community. [1]Moreau P et al, NEJM 2022;387:495-505. [2]Shah JJ et al, Clin Lymphoma Myeloma Leuk 2017;17:575-83.e2.

P-065

Effectiveness and Safety of Teclistamab in Triple-Class Exposed Relapsed/Refractory Multiple Myeloma: Results of the French Real-World RetrosTECtive Study

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Introduction: Teclistamab, a B-cell maturation antigen (BCMA) x CD3 directed bispecific antibody, has demonstrated high response rates and prolonged survivals in patients with relapsed/refractory multiple myeloma. FDA and EMA approved teclistamab based on the phase I/II MajesTEC-1 trial. Teclistamab was available in France since October 2022 through an early access. Most previous studies of real-world use have reported the results of cohorts of smaller numbers of patients than the original trial, often with a shorter follow-up. We report here the French real-world experience of teclistamab in triple-class exposed multiple myeloma patients. **Methods:** Data of all patients who initiated teclistamab in 31 IFM centers between October 14, 2022 and September 14, 2023, and did not object, were retrospectively collected. The study was submitted to the French Health Data Hub. Teclistamab was administered every week at 1.5 mg/kg after two step-up doses of 0.06 and 0.3 mg/kg including premedication according the EMA recommendations. More than 300 patients were included in the IFM2024-09 RetrosTECtive study. This analysis focused on the first 274 patients with a median follow-up of 12.1 months. **Results:** The median age was 70 years [range 37-88] and 26% of the patients had more than 75 years. All patients were triple-class exposed; they had received a median of 4 previous lines of therapy [range 2-10]. To note, 70% of them were IMiDs-refractory and 55% were refractory to anti-CD38 antibody(ies). Cytogenetics was evaluated in 172 patients: 45 had del(17p) and/or TP53 mutation. When assessed, 26 patients had EMD (11%), 63 had PMD (28%). At the initiation of teclistamab, 24 patients had an ECOG 3 or 4, 28 had severe renal insufficiency and 28 were previously exposed to anti-BCMA agents. Taking it all in, 69 patients (25%) would have been ineligible to MajesTEC-1. The ORR rate is 69%, the VGPR or better rate was 61%. The median PFS (mPFS) was 10.81 months (95%CI 7.98-14.88). The 1-year PFS rate in responder patients was 76% (95%CI 68.8-83.9). In contrast, mPFS was less than 3 months in patients with EMD. Interestingly, PFS did not differ in patients aged more than 75 years. At the data cut-off, 106 patients died, mostly due to progressive disease (63%) and 45% of patients were still receiving the treatment. Median OS was not reached; the 1y-OS rate was 61.2% (95%CI 55.2 -67.9). No new toxicity signals was observed: 85 patients (36%) received Tocilizumab and/or Dexamethasone for CRS/ICANS. Among 238 patients with informative data, 144 (60%) received polyvalent immunoglobulins, including 92 as a primary prophylaxis; 13% of the patients definitely stopped teclistamab due to infections and 29% of patients were readmitted to the hospital at least once for infectious adverse event. **Conclusions:** In our real-world experience, effectiveness and safety of teclistamab seem comparable to those of the original MajesTEC-1 trial. Data of the whole cohort will be presented at the meeting.

P-066

Prophylactic Interventions for Oral Toxicities With the GPRC5D×CD3 Bispecific Antibody Talquetamab in Relapsed/Refractory Multiple Myeloma: An Open-Label, Phase 2, Randomized Study (TALISMAN)

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Introduction: GPRC5D, a novel antigen, has limited expression in normal tissue but is highly expressed on malignant plasma cells, making it a promising target in multiple myeloma (MM). On-target off-tumor adverse events (eg, oral toxicities) have been reported with GPRC5D-targeted therapies, including talquetamab (tal), the first GPRC5D×CD3 bispecific antibody approved for patients (pts) with relapsed/refractory MM (RRMM). Although tal demonstrated high ORRs of >71% and durable responses in the MonumenTAL-1 study, early-onset oral toxicities (eg, dysgeusia) can impact pts' quality of life. This study aims to better understand oral toxicities and investigate prophylactic interventions to prevent and/or limit the severity of tal-related oral toxicities. **Methods:** This phase 2, multicenter, open-label, randomized study will enroll pts aged ≥18 years with RRMM and prior exposure to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody; prior GPRC5D-directed therapy will not be permitted. At screening, pts must have an ECOG PS 0/1 (ECOG PS 2/3 permitted once physical limitations are stable) and cannot have a "severe" score for hypogeusia or ageusia per the Waterless Empirical Taste Test (WETT) scale. Pts will be randomized to 1 of 4 cohorts: 1 control cohort

and 3 experimental cohorts receiving the following prophylaxis: dexamethasone mouthwash, oral pregabalin, or clonazepam orally dissolving tablets. Pts will receive their prophylaxis 1 week before starting tal, which will be administered at 0.8 mg/kg every other week after 3 step-up doses; a dose frequency reduction to every 4 weeks is permitted if the pt achieves a ≥VGPR or ≥PR starting at cycle 5 or 7, respectively. Procedures include: taste assessment using WETT strips; smell assessment using the University of Pennsylvania Smell Identification Test and threshold testing; patient-reported outcomes (PROs; including PRO-CTCAE); optional tongue and/or salivary gland biopsies (only at selected sites); microbiome analysis via tongue swab (control cohort only); and salivary flow and specific protein content assessments. The primary endpoint will be the incidence, severity, onset, and resolution/improvement of hypogeusia/ageusia determined by the total WETT score. Key secondary endpoints will include change from baseline in WETT score, body weight, and sense of smell over time; safety, efficacy, and PRO (including impact of oral toxicities) assessments; and frequency of dose modifications. In addition, qualitative pt interviews in the US will be conducted to better understand pt experience. Enrollment is expected to begin in August 2024 (target N=120, 6 countries). **Results:** Trial in progress. Not applicable. **Conclusions:** This study will provide needed data on smell- and taste-related assessment tools; potential strategies to manage, prevent, and decrease the severity of tal-related oral toxicities; and assessments of the potential impact of toxicities on pt treatment experience.

P-067

Long-Term Follow-Up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab, the first approved B-cell maturation antigen × CD3 bispecific antibody (BsAb) with weight-based dosing for the treatment of patients (pts) with triple-class exposed relapsed/refractory multiple myeloma (RRMM), demonstrated rapid, deep, and durable responses in the pivotal MajesTEC-1 study. Here, we report updated results from MajesTEC-1. **Methods:** Eligible pts received teclistamab at the recommended phase 2 dose (RP2D; 1.5 mg/kg subcutaneous QW preceded by step-up dosing) with the option to switch to Q2W dosing if a partial response or better after ≥4 cycles of therapy (phase 1) or complete response or better (≥CR) for ≥6 mo (phase 2) was achieved; pts not in ≥CR could switch due to adverse events (AEs). Pts could subsequently switch to less frequent dosing if they continued to demonstrate a response. The primary endpoint was overall response rate (ORR) assessed by independent review committee per International Myeloma Working Group 2016 criteria. AEs were graded per Common Terminology Criteria for Adverse Events v4.03. Cytokine release syndrome (CRS) was graded per American Society for Transplantation and Cellular Therapy guidelines. **Results:** At median follow-up of 30.4 mo, 165 pts had received teclistamab at the RP2D. ORR was 63.0%, and responses continued to deepen, with 46.1% achieving ≥CR. 85.7% (48/56) of MRD-evaluable pts were MRD negative (10-5 threshold). Median duration of response (mDOR) increased to 24.0 mo; median progression-free survival (mPFS) and overall survival (mOS) improved to 11.4 and 22.2 mo, respectively. For pts with ≥CR, mDOR, mPFS, and mOS were not yet reached, and estimated 30-mo DOR, PFS, and OS rates were 60.8%, 61.0%, and 74.2%, respectively. Of the 38 pts who remain on treatment, 37 have switched to a less frequent dosing schedule (eg, Q2W), all of whom maintained responses. Hematologic AEs (any grade/grade 3/4) included neutropenia (72%/65%), anemia (55%/38%), thrombocytopenia (42%/23%), and lymphopenia (36%/35%). Infections occurred in 79% of pts (55% grade 3/4). Of grade 5 infections, 18/22 were due to COVID-19, reflecting study conduct during the COVID-19 pandemic. Onset of new grade ≥3 infections generally decreased over time, which aligned approximately with the median time of switch to Q2W dosing; other factors, such as increasing use of IVIG, may also contribute to this trend. AEs leading to dose reduction (n=1) or discontinuation (n=8; 5 due to infection) were infrequent. No new safety signals were reported. **Conclusions:** With the longest follow-up of any BsAb in MM, teclistamab continues to demonstrate deep and durable responses, including in pts who switch to less frequent dosing. The safety profile of teclistamab remains consistent with that of BCMA-targeted bispecific therapies, with a notable decrease in new onset of severe infections with time.

P-068

Developing Novel DKK1-A2 CAR-T Cell Therapy for Myeloma and Other Hematologic Malignancies

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Introduction: Hematologic malignancies (HMs), including leukemia, multiple myeloma (MM), and lymphoma, account for 9% of all newly diagnosed cancers. Although immunotherapies using mAbs or CAR-T cells specific for CD19, CD20, or BCMA are FDA-approved for the treatment of B-cell malignancies and MM, no effective immunotherapy has been developed for other types of HMs. Moreover, patients with B-cell malignancies or MM receiving immunotherapy relapse during or after the treatment, indicating that more effective and less toxic CAR-T cell therapy is urgently needed for patients. We have been exploring whether targeting Dickkpf-1 (DKK1), a secreted protein and tumor-associated antigen, can be applied to treat HM patients. DKK1 mRNA is absent from most human normal tissues but high levels of DKK1 mRNA and protein are found in many human HMs including MM, follicular lymphoma, T-cell prolymphocytic leukemia, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and others. **Methods:** We generated T-cell receptor-like murine and humanized mAbs recognizing the DKK1 (P20) peptide in the context of human HLA-A2 (DKK1-A2 complex), because HLA-A2 is the most frequent serologic type in all ethnic groups and expressed in 47.6% of human populations. These mAbs bind with high affinity to all tested HLA-A2+(DKK1+) human HM cell lines and to >95% tumor cells of examined HLA-A2+ HM (MM, AML, CML) patients, but not to (HLA-A2+) normal human tissues except tonsil, indicating that high levels of the DKK1-A2 complexes exist on HLA-A2+ HM tumor cells but not normal cells and thus are an excellent and safe target for immunotherapy. **Results:** Using the mAb sequences, we generated human DKK1-A2 CAR-T cells that specifically lysed DKK1+HLA-A2+ HM cell lines but not normal cells in vitro. More importantly, DKK1-A2 CAR-T cells are highly therapeutic against established human HMs (MM and AML) in NSG mice. We also discovered that adoptive T-cell therapy can be significantly improved to treat tumors by polarizing T cells under Th9 condition. Th9-polarized murine and human CD4+ or CD8+ T cells, now expressing IL-9 receptor (IL-9R) and secreting mainly IL-9, exert greater antitumor efficacy in vivo compared to the classical Th1/Th17 or Tc1/CTL cells, due to their long-persistence, highly proliferative and cytolytic, and better tumor-infiltrating/survival capacities. In line with our findings, a recent study published in Nature by Ribas, June, Garcia, and others reports that repurposing IL-9R signaling in T cells leads to significantly improved antitumor activity for hard-to-treat solid tumors. **Conclusions:** In this study, we developed DKK1-A2 CAR-T cells that specifically recognize and kill DKK1-expressing, HLA-A2+ MM and leukemia cells. Our study suggests that Th9-polarized DKK1-A2 CAR-T cells may be potent and safe effector T cells for the treatment of HLA-A2+DKK1+ HM patients such as relapsed MM and myeloid leukemia.

P-069

Idecabtagene Vicleucel (ide-cel) in Patients (pts) with Triple-Class–Exposed (TCE) Relapsed and Refractory Multiple Myeloma (RRMM): the 5-year Follow-Up Analysis from KarMMa

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Introduction: Pts with RRMM have poor survival outcomes once they become TCE to immunomodulatory agents, proteasome inhibitors, and anti-CD38 mAbs. In a prior analysis (median follow-up: 24.8 mo) of the KarMMa trial (NCT03361748), in pts with TCE RRMM who received ≥3 prior lines of treatment (LoTs), treatment (tx) with ide-cel resulted in deep, durable responses (ORR 73%, median DOR [mDOR] 10.9 mo, median PFS [mPFS] 8.6 mo, and median OS [mOS] 24.8 mo; Anderson. ASCO 2021). Correlative analysis showed that lower soluble BCMA (sBCMA) levels at infusion were associated with better outcomes (Rytlewski. ASCO 2022). In the phase 3 KarMMa-3 trial (NCT03651128), ide-cel significantly improved mPFS and ORR vs standard regimens (Rodríguez-Otero. NEJM 2023) in pts with TCE RRMM who received 2–4 prior LoTs. The KarMMa 5-y median follow-up analysis is presented here. **Methods:** Pts with heavily pretreated RRMM who were TCE and had disease refractory to the last tx received a single infusion of ide-cel at a dose range of 150–450×106 CAR+ T cells. Primary endpoint: ORR. Key secondary endpoint: complete response rate (CRR). Other secondary endpoints: PFS, OS, DOR, and safety. **Results:** Of 149 pts enrolled, 137 pts who received ide-cel infusion were included in this analysis, including 9 pts from the Japanese cohort. At a median follow-up of 63.6 mo (range 48.4–70.5; data cutoff Dec 20, 2023), ORR was 76.6% (95%CI 69.6–83.7), CRR was 34.3% (95%CI 26.4–42.3), and mDOR was 11.3 mo (range 10.0–12.6). mPFS was 10.8 mo (95%CI 6.1–11.9); mOS was 28.2 mo (20.2–38.1). A subset of pts (n=9; 6.6%) who attained a stringent complete response (sCR; n=7), CR (n=1), and very good partial response (n=1) with a single infusion of ide-cel were still in remission at this data cutoff (DOR: 48.8–64.9

mo) despite being heavily pretreated and having high-risk features. Seventy-six (55.5%) pts received ≥1 subsequent anti-MM tx and had PFS2 of 15.2 mo (95%CI 12.8–18.7). Ide-cel safety profile was consistent with prior reports; no new safety signals were observed. No long-term investigator-identified neurotoxicity, Guillain–Barré syndrome, or parkinsonism events were reported. Incidence rate (% per 100 pt-y, 95%CI) of second primary malignancies (SPMs) was 3.7 (2.0–6.9). Hematologic SPMs were observed in 3 pts (2 myelodysplastic syndrome, 1 plasmablastic lymphoma); none were T-cell related. The strongest correlate of prolonged PFS was lower pre-infusion sBCMA level, which is an indicator of tumor burden. **Conclusions:** In this 5-y median follow-up analysis of the KarMMa trial, a single infusion of ide-cel continued to show deep and durable responses in pts with TCE RRMM. The correlation of lower pre-infusion sBCMA levels with better PFS highlights the need for managing tumor burden before ide-cel tx. Safety profile of ide-cel was consistent with previous reports; no new safety signals observed. This analysis supports the use of ide-cel in TCE RRMM to achieve long-term survival outcomes with a favorable safety profile.

P-070

Safety Profiles of Novel Myeloma Therapies: A Comprehensive FAERS Analysis (Q1 2020 - Q1 2024)

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Introduction: Understanding the safety profiles and better selection of patients for new therapies for multiple myeloma is crucial for optimizing patient care. This study examines adverse event (AE) reports associated with hospitalization (HO) and death (DE) and toxicities for several novel anti-myeloma therapies using data from the FDA Adverse Event Reporting System (FAERS). **Methods:** Methods: FAERS data collected between Q1 2020 and Q1 2024 for teclistamab, elranatamab, ciltacabtagene autoleucel (cilta-cel), idecabtagene vicleucel (ide-cel), and talquetamab were analyzed. We calculated the percentages of HO and DE for each drug based on the number of AEs reported and the total number of cases for each drug. Additionally, Proportional Reporting Ratio (PRR) values were calculated to analyze the toxicities associated with each drug. **Results:** Total reported cases for each drug were: teclistamab (n=2681), elranatamab (n=782), cilta-cel (n=1277), ide-cel (n=822), and talquetamab (n=474). The percentages of hospitalizations and deaths were as follows: teclistamab: 37.0% HO, 28.5% DE; elranatamab: 62.0% HO, 22.6% DE; cilta-cel: 33.3% HO, 13.6% DE; ide-cel: 30.2% HO, 11.3% DE; and talquetamab: 38.8% HO, 9.1% DE. Notably, PRR values elucidated significant associations between specific adverse events and drug therapies. Below, we provided top 10 serious toxicities: Hepatocellular damage/hepatitis: Associated with cilta-cel, ide-cel. Encephalopathies: Linked to cilta-cel, elranatamab, ide-cel. Seizures: Observed with cilta-cel , ide-cel. Renal failure: Seen in cilta-cel, elranatamab, ide-cel, teclistamab. Sepsis: Reported with cilta-cel, elranatamab, teclistamab. Respiratory failure: Associated with ide-cel. Cardiac disorders: Linked to teclistamab. Anemia: Observed with elranatamab, ide-cel, talquetamab, teclistamab. Neutropenia: Reported with elranatamab, ide-cel, talquetamab, teclistamab. **Conclusions:** This analysis reveals significant variation in the AE profiles of different anti-myeloma therapies, highlighting the need for careful patient selection, appropriate prophylaxis and close clinical monitoring. In heavily treated patients with advanced disease, Elranatamab and Teclistamab exhibited high rate of hospitalizations, and deaths. These observatiions are most likely suggestive for selection bias as many of these patients are sick and require urgent treatments. In contrast, patients who receive CAR-T therapy are fit enough to withstand the procedure duration. Our findings are limited by the retrospective nature of the analysis but nonetheless underscore the importance of careful patient selection and continuous AE monitoring to enhance patient safety and inform clinical decision-making in multiple myeloma treatment.

P-071

Real-World Experience with Teclistamab for Relapsed/ Refractory Multiple Myeloma from the U.S. Myeloma Immunotherapy Consortium

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Introduction: Teclistamab is a T-cell-redirecting anti-BCMA bispecific antibody approved in relapsed/refractory multiple myeloma (RRMM) based on the MajesTEC-1 trial, which demonstrated a 63% overall response rate (ORR) and 59% ≥VGPR rate in the main cohort of patients with no prior anti-BCMA

therapy (N=165); in a separate cohort of BCMA-exposed patients (N=40), ORR was 53% and ≥VGPR rate was 48%. Here, we report the real-world safety and efficacy of commercial teclistamab in a cohort of 391 patients from 14 United States institutions. **Methods:** Patients with RRMM who initiated teclistamab by 31 July 2023 or 31 Oct 2023, depending on institution, were included; follow-up data cutoff was 15 Nov 2023. Thirteen patients initiated teclistamab in an expanded access program. Data on 83 patients were previously reported with earlier follow-up cutoff of 15 Aug 2023 (Transplant Cell Ther 2024 Mar;30(3):308.e1). CRS and ICANS were graded according to ASTCT criteria, and responses were evaluated by IMWG criteria. **Results:** Teclistamab was initiated in 391 patients by the cutoff. Among 236 patients with available refractoriness data, median number of prior lines of therapy was 6 (range 2-18); 94% were refractory to IMiDs, 90% to proteasome inhibitors, and 96% to anti-CD38 antibodies; 85% were triple-class refractory and 35% penta-refractory. High-risk cytogenetics (HRC) (including 1q gain) were present in 55%. Median time from MM diagnosis was 5.9 years. Racial/ethnic representation included 23% Black, 8% Hispanic, and 5% Asian. Three hundred five (79%) would have been ineligible for the main MajesTEC-1 BCMA-unexposed cohort, predominantly due to prior BCMA-targeting therapies (N=188, 116 Ide-cel or Cilta-cel and 78 belantamab mafodotin) or cytopenias (N=108). CRS occurred in 57% (1.3% grade ≥3), and ICANS in 14% (2.6% grade ≥3). Infections were reported in 168 (43%) and led to hospitalization or IV antibiotic use in 86 (22%). The ORR was 55% and ≥VGPR rate was 45%. ORR did not significantly differ by HRC status but was lower in BCMA-exposed patients (47% vs 62%, p=0.0042), as was ≥VGPR rate (37% vs 52%, p=0.0030). At a median potential follow-up of 8.4 months, the median estimated progression-free survival (PFS) was 7.4 months (95% CI, 5.8 to 9.1). Among ≥VGPR patients, PFS probability at 1 year was 75%. PFS was shorter in patients with HRC (median 5.6 vs 9.8 months, p=0.0073) and in those with prior anti-BCMA therapy, though the difference was not significant (median 6.0 vs 8.9 months, p=0.061) and not apparent if ≥VGPR (p=0.43). ORR and mPFS did not significantly differ according to MajesTEC-1 main cohort eligibility status. The median overall survival was 14.3 months (95% CI 13.4-not reached). **Conclusions:** The real-world safety and efficacy of teclistamab is comparable to that observed among both BCMA-unexposed and BCMA-exposed patients on MajesTEC-1. Though response rates were lower in BCMA-exposed patients, PFS was similar to BCMA-unexposed patients among those achieving ≥VGPR.

P-072

Health Care Resource Utilization and Economic Burden of Cytokine Release Syndrome Management in Patients With Multiple Myeloma Receiving CAR-T Cell and Bispecific Antibody Therapies

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Introduction: The multiple myeloma (MM) treatment landscape was transformed by chimeric antigen receptor (CAR)-T cell therapies and T-cell engaging bispecific antibodies (BsAbs); however, these immunotherapies can lead to cytokine release syndrome (CRS) resulting in substantial health care resource utilization (HCRU) and economic burden. We assessed real-world HCRU and costs among patients (pts) with MM with or without CRS post CAR-T/BsAb therapy. **Methods:** This retrospective study using data from the Optum® Market Clarity Dataset (2020–2023) included adult pts in the United States who received CAR-T/BsAb therapy, had continuous enrollment ≥90 days pre- and post-index treatment date, and had an MM diagnosis during the 90-day baseline (BL) period. Two cohorts were evaluated: 1) pts experiencing any grade CRS (based on ICD-10 diagnosis codes) ≤30 days post-index, and 2) pts without CRS diagnosis nor severe CRS-associated symptoms/procedures post-index through follow-up. For the latter cohort, a randomly selected date using the same distribution of time to CRS as in the CRS cohort was designated as the start of the 30-day observation period for HCRU and costs. Outcomes included: hospitalizations, length of stay (LOS), emergency room (ER) and intensive care unit (ICU) visits, outpatient visits, and all-cause total (medication + medical) costs per-patient-per-month (PPPM). HCRU and costs were compared between cohorts using count data models and a generalized linear model with gamma distribution and log link, respectively. BL prognostic factors were balanced between cohorts using inverse probability of treatment weighting (IPTW). **Results:** Of 219 eligible pts, 172 received CAR-T and 47 received BsAb therapy, of whom 118 (69%) and 18 (38%) experienced CRS, respectively. Among the 136 pts with CRS and 83 pts without CRS, 88% vs 59% were hospitalized; 21% vs 17% had ER visits; and 29% vs 13% were admitted to ICU. On a PPPM basis, pts experiencing CRS had 1.1 hospitalizations, 10.0 days LOS, and 0.5 ICU days, while pts without CRS had 0.7 hospitalizations, 6.7 days LOS, and 0.1 ICU days. Among pts with CRS, those treated with BsAb had fewer ICU days and lower total costs vs those treated with CAR-T. Regression with IPTW showed that, pts with CRS vs without CRS had 50% more hospitalizations with 4.7 days longer LOS and 3.7 times more ICU days PPPM; significant differences remain in sensitivity analysis adjusting for specific MM therapies. No significant differences were observed in other HCRU types evaluated. Total costs PPPM were significantly higher for the CRS vs no-CRS cohort after IPTW ($28,052 or 50% higher). **Conclusions:** CRS following CAR-T/BsAb therapy led to higher HCRU and costs, mainly driven by inpatient and ICU admissions. CRS management imposes substantial economic burden on pts, treatment centers, and the healthcare system. Effective management of CRS that reduces duration or necessity of hospitalizations could save costs and inform decision-making in MM treatment.

P-073

Identification and Validation of Factors Promoting Resistance to CAR-T Therapy in Multiple Myeloma by Genome-Wide CRISPR Screenings

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Introduction: CAR-T cells have revolutionized cancer immunotherapy, representing a promising option for relapsed/refractory Multiple Myeloma (MM) patients. Despite high remission rates observed after BCMA CAR-T therapy, there is a lack of long-term responses since most of the patients relapse within the first year after treatment (media PFS 13.8 months for ide-cel and 34.9 months for cilta-cel). Development of primary, and especially, secondary resistance to CAR-T therapies, mainly due to antigen scape mechanisms, is still a relevant clinical problem. The main aim of this work was to identify new mechanisms of resistance to CAR-T therapies in MM beyond antigen loss. **Methods:** We performed a genome wide CRISPR screening in MM cell lines using the CRISPR Brunello library, containing 76456 sgRNAs targeting 19114 coding genes. MM1S and KMS11 cell lines were engineered to express Cas9 and then transduced with Brunello library at MOI of 0.2 to ensure individual sgRNA transduction. MM1S and KMS11 cells were then cocultured with BCMA CAR-T cells at a E:T ratio of 1:25. We used MAGeCK algorithm, that evaluates the statistical significance of individual sgRNA abundance changes using a negative binomial model, to identify top sgRNA hits by comparing samples after 14 days of cocultured with initial controls. Cytotoxicity was evaluated by using Bright-Glo™ Luciferase Assay System. In vivo antitumoral efficacy was evaluated using xenograft MM models in NSG mice. **Results:** Genome-wide CRISPR screening allowed the identification of 5 targets (undisclosed) whose absence conferred resistance to BCMA CAR-T cells. Individual target validation was performed in both MM1S and KMS11 cells, generating at least 3 independent clonal cell lines depleted of each of the identified factors (MMKO cells). Disruption of the corresponding target in each MMKO cells was confirmed by WB. Additionally, we corroborated that target depletion did not affect neither BCMA expression nor cell growth capacity. Interestingly, coculture of the generated MMKO cell lines with BCMA CAR-T cells showed that depletion of one of the 5 identified factors improved MM cell survival. Moreover, in vivo analysis in NSG mice showed a reduced antitumoral efficacy of BCMA CAR-T cells in animals injected with MMKO cell depleted from that specific factor, validating their capacity to promote resistance to BCMA CAR-T cells. Additional transcriptional and functional analyses are being performed to fully characterize pathways involved in resistance induction after inhibition of that specific target. **Conclusions:** Overall, our genome-wide CRISPR screening allowed the identification and validation of undisclosed targets whose inhibition provide resistance to CAR-T cell treatment in MM, representing a potential target for the development of improved CAR-T therapies.

P-074

Longer-Term Follow-Up of Patients Receiving Prophylactic Tocilizumab for Cytokine Release Syndrome in the Phase 1/2 MajesTEC-1 Study of Teclistamab in Relapsed/Refractory Multiple Myeloma

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Introduction: Emerging data suggest that administering tocilizumab (toci) prior to bispecific antibodies reduces the incidence of cytokine release syndrome (CRS), which may support outpatient therapy initiation. We previously showed that the incidence of CRS with teclistamab, the first approved BCMA×CD3 bispecific antibody with weight-based dosing for the treatment of patients (pts) with triple-class exposed RRMM, was reduced from 72% in the overall MajesTEC-1 study population to 26% in a cohort receiving a single dose of toci before the first teclistamab step-up dose. Here, we present an updated analysis with longer-term follow-up. **Methods:** Pts with triple-class exposed RRMM received subcutaneous teclistamab 1.5 mg/kg weekly in a prospective exploratory cohort or at a comparable fixed dose, following 2 step-up doses. Toci 8 mg/kg was given intravenously ≤4 hours before the first teclistamab step-up dose. CRS was graded per Lee et al (Blood 2014;124:188-95) and managed per the study protocol. **Results:** This analysis included 24 pts with median follow-up 8.1 months (range, 0.9–13.2). Median age was 72 years (range, 50–82); 100% had ECOG PS score ≤1; 96% had International Staging System stage I/II; 74% had standard-risk cytogenetics; 21% had extramedullary plasmacytomas; 33%

had ≥30% bone marrow plasma cells (biopsy or aspirate). Pts had a median of 4 prior lines of therapy (range, 2–9); 58% were triple-class refractory. CRS occurred in 6 pts (25%; 2 grade 1, 4 grade 2, no grade ≥3); 3 pts each had 1 recurrent CRS event. Median time to CRS onset was 2 days (range, 1–3); median duration was 2 days (range, 2–4). CRS was managed with additional toci in 5/6 pts and steroids in 1/6; all CRS events resolved and none led to teclistamab discontinuation. Most common adverse events (AEs; any grade/grade 3/4) were infections (79%/25%), neutropenia (63%/63%), and anemia (58%/25%); 5 pts had a neurotoxicity AE (grade 1 dizziness; grade 1 headache; grade 1 insomnia; grade 2 headache; grade 2 immune effector cell-associated neurotoxicity syndrome). Overall response rate (n=22) was 73% (59% very good partial response or better). Timing of interleukin (IL)-6 induction in the prophylactic toci cohort was consistent with the phase 1 MajesTEC-1 population, with higher IL-6 levels as observed in other studies of IL-6 receptor-blocking antibodies. **Conclusions:** Prophylactic toci reduced the incidence of CRS with teclistamab, with a 65% relative reduction vs the overall MajesTEC-1 population (grade 1, 8% vs 50%; grade 2, 17% vs 21%). No new safety signals or impact on response to teclistamab was observed with longer follow-up. Prophylactic toci may be a useful measure to consider when selecting pts for outpatient administration of teclistamab in the future. This approach is being evaluated in the phase 2, multicenter, prospective OPTec study (NCT05972135).

P-075

Development of a Quantitative Systems Pharmacology (QSP) model describing T-cell bispecific induced immune activation and Multiple Myeloma (MM) cell killing

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Introduction: Forimtamig, a GPRC5DxCD3 T-cell-engaging bispecific antibody, is currently being evaluated in patients with relapsed/refractory multiple myeloma (RRMM). In a first-in-human Phase I dose escalation study (BP42233; NCT04557150), forimtamig induced deep and durable responses, with high objective response rates in all patient subgroups and a safety profile consistent with its mechanism of action (MoA) and target expression (Carlo-Stella et al. ASH 2022; Harrison et al. IMS 2023). We performed an in-silico evaluation of soluble B-cell maturation antigen (sBCMA) dynamics and of IL-8 release using a QSP model, with sBCMA representing tumor burden and probability of clinical response and with IL-8 being used as a surrogate for immune activation and probability of cytokine release syndrome (CRS). Initially performed for the intravenous (IV) route of administration (Santini et al. AACR 2023), here we extended this in-silico evaluation by incorporating the subcutaneous (SC) route of administration and calibrated the model with clinical data from 144 RRMM patients treated either IV or SC. The model was set up to perform patient-specific calibrations and characterize the population with regard to patients' sensitivity to tumor killing and immune activation, allowing for the analysis of patient subgroups. Here, we discuss the model development and calibration results for both IV and SC forimtamig dosing. **Methods:** The QSP model is a minimal mechanistic model integrating key elements of the MoA of forimtamig describing immune activation by forimtamig and resulting MM cell killing. It comprises a system of two ordinary differential equations and 14 parameters, two of which are fitted to longitudinal clinical data (sBCMA and IL-8). Assumptions regarding the MM disease and the MoA of forimtamig are represented in the model and supported by clinical or preclinical evidence. **Results:** The calibrated model showed an accuracy of 89% in recapitulating partial response or better, demonstrating its appropriateness to address clinical pharmacology questions. Patient-specific model calibrations revealed that the treated RRMM population showed greater heterogeneity with regard to its sensitivity to forimtamig-induced MM cell killing as compared to immune activation. In addition, an analysis of the fitted model parameter representing forimtamig-induced MM cell killing and patient-related factors indicated that patients with extramedullary disease showed lower sensitivity to forimtamig, reflecting clinical observations (Harrison et al. IMS 2023). **Conclusions:** The mechanistic model is able to describe forimtamig-induced immune activation and T cell-mediated MM cell killing in patients. It may therefore be utilized to predict response in virtual populations at different dosing regimens and for different patient subgroups. This example illustrates that in-silico modeling of T cell-engaging bispecific antibody MoA may support more accurate dose finding in Phase 1 studies.

P-076

Early Free Light-Chain Suppression After CAR-T Therapy is Predictive for Progression-Free and Overall Survival

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Introduction: CAR-T cells directed against BCMA have demonstrated remarkable efficacy and were recently approved by FDA and EMA for second or third line therapy. Only a minority of patients are primary refractory to CAR-T cells, however early relapse remains a challenge and is correlated with poor overall survival. Recently the MyCARe score has been proposed to predict PFS and OS based on the presence of extramedullary disease, plasma cell leukemia, high-risk cytogenetics, elevated ferritin and lenalidomide-refractoriness. While the number of these risk factors clearly predicted inferior PFS and OS after CAR-T therapy, it will be difficult to withhold CAR-T cells from patients with high MyCARe scores, since they have the highest medical need and most likely the worst outcome with any alternative therapy. Another option to address

early treatment failure after CAR-T would be to define a biomarker for progression very early after CAR-T treatment. **Methods:** Patients with myeloma and treatment with commercial CAR-T cells at a large academic institution from 1/2022 to 12/2023 were analyzed for PFS and OS. Minimum follow up was 3 months. Free light-chain (FLC) suppression was assessed on day 28 after CAR-T infusion and defined as undetectable serum levels of both FLC kappa and lambda. FLC suppression was tested as biomarker to predict PFS and OS after CAR-T therapy. **Results:** 43 patients received either ide-cel (n= 22) or cilta-cel (n=21) as standard therapy for relapsed/refractory myeloma. Median follow up was 9.8 (range 3-32) months and median PFS was 11.5 (range 6.3-16.7) months. Twenty-nine patients showed FLC suppression on day 28 and 11 have progressed so far, showing a median PFS of 14.5 (range 10.9-18.1) months and an OS of 88,1% at 12 months (median not reached). In contrast, of the 14 patients with no FLC suppression on day 28 after CAR-T infusion, 12 progressed with a median PFS of 2.3 (range 0.2-4.3) months and a median OS of 12.7 (3,73-21,6) months. By log rank test achieving FLC suppression was significant for PFS (log-rank p< 0.001) and OS (p=0.002). **Conclusions:** Based on our results the failure to achieve FLC suppression on day 28 after CAR-T therapy is highly predictive for a markedly inferior PFS and OS. This simple biomarker could help to identify patients with a suboptimal early response and a high risk of dying within 12 months. These patients may benefit from early additional intervention with agents such as bi-specific antibodies, IMIDs or CELMODs.

P-077

Prophylactic Tocilizumab to Mitigate Cytokine Release Syndrome in Patients Receiving Talquetamab for Relapsed/Refractory Multiple Myeloma: Results From the Phase 1/2 MonumenTAL-1 Study

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Introduction: Talquetamab (tal) is the first approved GPRC5D-targeting bispecific antibody (BsAb) for the treatment of patients (pts) with relapsed/refractory multiple myeloma (RRMM). In the MonumenTAL-1 study, cytokine release syndrome (CRS) occurred in 73.1–79.0% of pts, among whom, 35.0–47.4% were treated with tocilizumab (toci; ± other interventions). Data suggest that prophylactic toci before BsAb treatment may reduce the incidence and severity of CRS, which may facilitate outpatient administration of priming doses and improve pt experience. The current analysis evaluated the effects of prophylactic toci on CRS following tal treatment. **Methods:** Eligible pts were from phase 2 of MonumenTAL-1 (NCT04634552). Pts had RRMM and received ≥3 prior lines of therapy (≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 antibody). Pts received subcutaneous tal 0.8 mg/kg every other week preceded by step-up (priming) doses of 0.01, 0.06, and 0.3 mg/kg in a prospective exploratory cohort. Toci (8 mg/kg IV) was given ~3 hours before the first tal step-up dose (SUD) together with required pretreatments (glucocorticoid, antihistamine, and antipyretic). Dexamethasone (dex; 8 mg PO/IV) was given daily for 2 days after each SUD and first full treatment dose. If post-treatment dex was scheduled on a day when premedication with dex was required, only the premedication dose was given. CRS was graded by ASTCT criteria; other adverse events were graded by CTCAE v4.03. **Results:** Nine pts were included in the analysis, with median follow-up of 2.6 months (range, 0.4–5.9). Median age was 68 years (range, 51–76); no pts had high-risk cytogenetics, 1 (11.1%) had extramedullary disease, 1 (11.1%) had ISS stage III disease, and 2 (22.2%) had ≥60% bone marrow plasma cells (BMPCs). CRS occurred during priming through cycle 1 in 2 (22.2%; all grade [gr] 1) pts; CRS occurred at any time in 3 (33.3%; all gr 1) pts. One (11.1%) pt with CRS had a second event (gr 1) during priming. Median time to CRS onset was 3.5 days (range 2–12) and median duration was 2 days (range 1–6). All 3 pts received treatment for CRS, including toci (n=2, 22.2%) and paracetamol (n=3, 33.3%). One (11.1%) pt with 80% BMPCs developed immune effector cell–associated neurotoxicity syndrome (gr 2; concomitant with CRS). Three (33.3%) pts had infections (2 gr 3/4 [22.2%]). No pts had neutropenia. No notable elevations in alanine minotransferase/aspartate aminotransferase were observed. **Conclusions:** A single dose of toci before tal and increased dex use post dose appeared to reduce the incidence and severity of CRS compared with the overall MonumenTAL-1 population. No neutropenia, a common side effect of toci, and no increase in rates of infection were observed. These data support the exploration of outpatient administration of tal priming doses to reduce the burden of hospitalization during initial tal treatment. This study continues to recruit, with subsequent pts treated on an outpatient basis.

P-078

Prompt and Profound Responses with Talquetamab in Patients with Heavily Pretreated Relapsed-Refractory Multiple Myeloma – Another Bridging Therapy

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Introduction: Talquetamab is a G protein-coupled receptor class C group 5 member D (GPRC5D) targeting bispecific T-cell engager approved in August 2023 for patients with relapsed-refractory multiple myeloma (RRMM) who have received at least 4 prior lines of therapy (LOT) including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody based on the results of the pivotal MonumenTAL-1 trial. Maintaining disease control during the manufacturing process of commercially available anti-BCMA chimeric antigen receptor (CAR) T cell therapies is an area of unmet need, as most patients undergoing CAR T cell therapy have highly refractory disease. Because talquetamab targets a distinct epitope from the CAR T cell therapies, it is an attractive option to maintain disease control during this period. In this multicenter retrospective study, we evaluated the safety and efficacy of talquetamab as a bridging therapy. **Methods:** Patients who received talquetamab monotherapy as of April 5th, 2024, at one of five U.S. academic medical centers participating in the US Myeloma Research Innovations Research Collaborative (USMIRC) were included. Patients receiving talquetamab after leukapheresis for either idecabtagene vicleucel or ciltacabtagene autoleucel therapy, but before CAR T infusion were included. All patients included in the analysis had received at least the first full dose of talquetamab. Responses to therapy were evaluated using the International Myeloma Working Group (IMWG) criteria. Adverse events were graded based on the CTCAE v5.0 criteria. **Results:** In the total cohort, seven received talquetamab as a bridging therapy to chimeric antigen receptor therapy (CART). The patients had received a median of 4 (3-10) prior LOT. Most were triple class (86%), penta-drug (43%), and BCMA directed therapy (14%) refractory, and 29% had extramedullary disease (EMD). The median duration of exposure to talquetamab was 24 days (7-92). One patient failed to manufacture cells despite multiple attempts. The best ORR was 57% (4/7), with 3 VGPR, 1 stringent CR (sCR), and 1 partial response (PR). No patients exhibited progressive disease, none developed new end-organ damage during the period of bridging therapy. The median time to first response was 8 days (7-28) and 18 days (12-30) to best ORR. At the final data cutoff (May 1st, 2024), all patients were alive. Cytokine release syndrome (CRS) was observed in 71%, all grade I events, median duration 1 day (1-3). None of the patients encountered Immune effector cell-associated neurotoxicity syndrome (ICANS). Dysgeusia (43%), dry mouth (57%), and weight loss ≥10% (14%) were common. Nail changes (14%), skin rash (14%), and other skin changes (29%) such as peeling and dryness were also noted. **Conclusions:** This study demonstrates rapid and profound responses to talquetamab, with no patients exhibiting disease progression or new end organ damage, providing an option for bridge to CART.

P-079

Real-World Safety and Efficacy of Talquetamab for Patients with Heavily Pretreated Relapsed-Refractory Multiple Myeloma

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Introduction: Talquetamab is a G protein-coupled receptor class C group 5 member D (GPRC5D) targeting bispecific T-cell engager approved in August 2023 for patients with relapsed-refractory multiple myeloma (RRMM) who have received at least 4 prior lines of therapy (LOT) including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody based on the results of the pivotal MonumenTAL-1 trial. In this multicenter study, we evaluated the real-world safety and efficacy of talquetamab, including patients who would have been ineligible for the MonumenTAL-1 trial. **Methods:** RRMM patients who received at least the first full dose of talquetamab monotherapy at one of five U.S. academic institutions as of 4/5/24 were included in this US Myeloma Research Innovations Research Collaborative (USMIRC) analysis. Responses to therapy were evaluated using the International Myeloma Working Group (IMWG) criteria. Adverse events were graded based on the CTCAE v5.0 criteria. Kaplan-Meier methods were used for progression-free (PFS) and overall survival (OS) calculations. **Results:** The 43 patients included in this analysis received a median of 6 (3–15) prior LOT and 51% had extramedullary disease (EMD). Most were triple class (93%), penta-drug (60%), and ≥1 B cell maturation antigen (BCMA) directed therapy (BDT) (69%, 25/36) refractory. Any grade cytokine release syndrome (CRS) was observed in 63%, with 1 grade III/IV event (2.3%). Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 12%, with 1 grade III/IV event (2.3%). The most common grade III/IV hematological toxicities were thrombocytopenia (30%) and anemia (21%). Dysgeusia (70%), dry mouth (56%), and weight loss ≥10% (30%) were common. Nail changes (56%), skin-related events (42%), prominently rash, peeling, and dryness were also noted. Infections occurred in 37% of patients, most (63%) involving the respiratory tract. No treatment-related mortality was observed; 26% of the patients had died at the time of data cut-off (5/1/24) with 88% of deaths attributed to disease progression. At a median follow-up of 4.9 (0.5–17.5) months, the best overall response rate (ORR) was 63%. Responses were deep: 53% very good partial response or better (>VGPR), 26% complete response or better (>CR). The median time to first response was 20

days (2-57) and 1 month (0.4-5.5) to best response. ORR was 56%, 58%, and 50% for BDT-refractory, penta-refractory, or those with EMD, respectively. The estimated 6-month PFS was 35% (95% CI 12-59) and OS was 72% (95% CI 60-98), respectively. Of the patients included in our analysis, 50% (17/34) would have been deemed ineligible for the MonumenTAL-1 trial, due to ECOG>2 (24%), grade 3-4 anemia (47%), or thrombocytopenia (41%). ORR in this sub-group was 65%. **Conclusions:** In this real-world experience of the safety and efficacy of talquetamab for RRMM, results were comparable to that of the MonumenTAL-1 trial even though 50% of patients would not have been eligible.

P-080

Sequencing of Bispecific Antibodies in Relapsed Refractory Multiple Myeloma

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Introduction: Therapeutic options for relapsed refractory multiple myeloma (RRMM) are limited, and outcomes remain poor. The introduction of T-cell-directed therapies such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies (BsAb) have led to improved survival in this difficult to treat population. To date, 3 BsAB have been approved for RRMM, two of which – Teclistamab (tec) and elranatamab (elra) target BCMA, while talquetamab (talq) targets the GPRC5D protein. Despite the promising outcomes seen with these agents the optimal sequencing strategy is yet to be defined. Herein, we aim to describe the sequencing trends and associated outcomes in RRMM patients treated with multiple BsAbs at our center. **Methods:** IRB-approved, retrospective study of RRMM patients treated at Huntsman Cancer Institute with >1 commercial or investigational BsAb between August 2021 and May 2024. Time-to-event analyses were performed from BsAb initiation, and disease response was assessed using the IMWG criteria. **Results:** Sixteen patients received >1 BsAb. Fourteen patients (88%) received 2 BsAb, and 2 patients (13%) received ≥3 BsAb. The most utilized first BsAb was tec (56%), followed by elra (19%), AMG 701 (13%), talq (6%), and cevostamab (cevo) (6%). Similarly, talq was the most utilized second BsAb (81%), followed by tec (13%) and cevo (6%). One patient received three BsAbs (elra-cevo-talq). One patient received four BsAbs (AMG 701-tec-cevo-talq). The overall response rate (ORR) to the first BsAb was 56%. All responders achieved a VGPR or better, and 5 patients (31%) achieved minimal residual disease (MRD) negativity by flow (10-5). ORR to a second BsAb was 38%, 31% of patients achieved a VGPR or better and one patient (6%) achieved MRD negativity. The median PFS seen after the first and second BsAb was 262 days and 119 days, respectively. At data collection five patients remain on second BsAb with average duration of treatment of 232 days. Infectious complications were common; the most common being Rhinovirus/Enterovirus URI (69%), COVID 19 (38%), bacterial pneumonia (31%), UTI (31%) and RSV(25%). Five patients (31%) experienced one or more ≥ Grade 3 infectious complications accounting for 18 instances of hospital admission. Indication for admission included neutropenic fever, bacteremia, and fungal pneumonia. **Conclusions:** Treatment of RRMM remains challenging given the limited options and poor outcomes seen in this population. Our results support the sequential use of BsAbs with an ORR of 38% to second BsAb with an average duration of treatment of 232 days for those remaining on their second BsAb at time of analysis. Despite the clinical benefit observed, infectious complications remain a significant risk of this strategy, requiring close and frequent monitoring. A limitation of this analysis is the heterogeneity of treatment between sequenced BsAbs. Further research efforts are needed to determine optimal sequencing of BsAb in this population.

P-081

Talquetamab, a GPRC5DXCD3 Bispecific Antibody, for Treatment of Relapsed/Refractory Multiple Myeloma in Patients With Prior Exposure to BCMA Targeted Therapies – a "Real World" Study

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Introduction: After the failure of B-cell maturation antigen (BCMA) directed therapy for relapsed refractory multiple myeloma (RRMM), retreatment with a different anti-BCMA therapy remains a viable option. Emerging therapies targeting novel non-BCMA pathways offer alternative treatment possibilities. Talquetamab is a T cell-redirecting bispecific antibody that targets CD3 expressed on T cells, and G protein-coupled receptor class C group 5 member D (GPRC5D) which is overexpressed on myeloma cells. Targeting a different antigen makes talquetamab a compelling treatment option for anti BCMA-refractory patients, as previously demonstrated in the MonumentAL-1 study (NEJM, 2022). To date, no "real-world" data on the safety and efficacy of talquetamab in patients with RRMM have been reported. Here, we present the outcomes of 10 patients receiving talquetamab in non-clinical trial settings, all of whom had previously received anti-BCMA therapy. **Methods:** N/A. **Results:** Since 07/2023, 10 patients with RRMM (median age 61.8, IQR 55.5-67.3) were treated with talquetamab at our center. The median number of prior therapies was 6 (IQR 5-6), with 80% and 10% of the patients being penta and quad-refractory, respectively. Median time from previous treatment to initiation of talquetamab was 60.5 days (IQR 30.5-97.5). All patients had at least one recent prior exposure to BCMA-targeted therapy (60% CAR-T, 40% teclistamab, 30% belantamab mafodotin), 4 patients (40%) had prior exposure to 2 different anti-BCMA treatment modalities. Only 2 patients (20%) from this cohort were eligible to enroll in the MonumenTAL-1 study, ineligibility was mostly due to ECOG >1 (6, 75%) and cytopenias (7, 87.5%). Median time to

response was 13 days (IQR 7-29). The overall response rate (at least partial response) was 70%, with 60% of patients achieving a very good partial response (VGPR) or better. At a median follow-up of 58.5 days (IQR 40-119), 6 patients (60%) were progression-free. Seven patients (70%) had cytokine release syndrome (CRS) grade 1, one patient (10%) had grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS). No serious adverse events were noted and neither treatment discontinuation nor dose reduction was observed. Five patients (50%) experienced grade 2-3 infections. One fatal adverse event occurred (sepsis and multi-organ failure) and was considered unrelated to talquetamab. **Conclusions:** In this cohort, we describe 10 heavily pretreated RRMM patients, all of whom were refractory to a recent anti-BCMA therapy and had progressive disease at enrolment. The response rates observed in our "real-world" setting are comparable to those of the pivotal trial. The safety profile remains favorable, marked by low occurrence of CRS and ICANS as well as manageable burden of infectious toxicities. It appears that in real world setting, talquetamab maintains both its safety and efficacy in this heavily pretreated cohort of anti BCMA-refractory patients.

P-082

Ciltacabtagene Autoleucel vs Standard of Care in Patients With Functionally High-Risk Multiple Myeloma: CARTITUDE-4 Subgroup Analysis

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Introduction: Functionally high-risk (FHR) multiple myeloma (MM) is associated with poor prognosis. In CARTITUDE-4, a single ciltacabtagene autoleucel (cilta-cel) infusion significantly improved progression-free survival (PFS) vs established standard of care (SOC; P< .0001) in patients (pts) with lenalidomide (len)-refractory MM after 1–3 prior lines of treatment (tx; LOT). This post hoc subgroup analysis of CARTITUDE-4 reports outcomes for pts who received cilta-cel vs SOC as second-line (2L) tx, including pts with FHR MM. **Methods:** Pts randomized to cilta-cel underwent apheresis, received PVd or DPd bridging tx, and then cilta-cel infusion (target dose, 0.75×106 CAR+ viable T cells/kg) 5–7 d after the start of lymphodepletion. Pts randomized to SOC received PVd or DPd until progressive disease (PD). FHR was defined as PD within 18 mo after receiving autologous SCT or the start of initial frontline tx. Efficacy was assessed in randomized pts (intent to treat) and safety in pts who received any part of study tx. **Results:** 136 pts received cilta-cel (n=68) or SOC (n=68) as 2L tx. Of these, 79 had FHR MM (cilta-cel, n=40; SOC, n=39). Median PFS was longer in pts who received cilta-cel (not reached [NR]; 95% CI not evaluable [NE]–NE) vs SOC (17 mo; 95% CI 11–NE; hazard ratio [HR] 0.35; 95% CI 0.2–0.7; P=.0007) as 2L tx including the FHR subset (NR; 95% CI 18–NE, vs 12 mo; 95% CI 8–NE; HR 0.27; 95% CI 0.1–0.6; P=.0006). The 12-mo PFS rate was also longer for pts receiving cilta-cel vs SOC as 2L tx (78%; 95% CI 66–86 vs 59%; 95% CI 46–69) and included the FHR subset (77%; 95% CI 60–87 vs 49%; 95% CI 32–64). Overall survival was immature at the time of this analysis. The overall response rate of pts who received 2L cilta-cel (90%) was greater than SOC (79%; odds ratio [OR] 2.3; 95% CI 0.8–6.0; P=.0979), similar to FHR pts (88% vs 80%; OR 1.8; 95% CI 0.5–6.1; P=.3400). Complete response or better was achieved in 71% of pts receiving cilta-cel vs 35% with SOC (OR 4.4; 95% CI 2.1–9.0; P< .0001) as 2L tx and 68% vs 39% in those with FHR (OR 3.3; 95% CI 1.3–8.4; P=.0102). More pts achieved minimal residual disease negativity at a 10–5 threshold with cilta-cel (63%) vs SOC (19%; OR 7.3; 95% CI 3.3–15.9; P< .0001) as 2L tx and with FHR pts (65% vs 10%; OR 16.3; 95% CI 4.8–55.1; P< .0001). A longer median duration of response was achieved in all pts receiving cilta-cel (NR; 95% CI NE–NE) vs SOC (20 mo; 95% CI 14–NE) and in FHR pts (NR; 95% CI 16–NE vs 16 mo; 95% CI 8–NE). Pts with grade ≥3 TEAEs who received cilta-cel vs SOC as 2L tx were comparable (96% vs 96%) including the subset with FHR MM (100% vs 97%). Among pts who received 2L tx, 22 died (cilta-cel, n=11; SOC, n=11), 16 of whom had FHR MM (n=7; n=9). **Conclusions:** In pts with len-refractory FHR MM after 1 prior LOT, cilta-cel improved outcomes vs SOC and had a safety profile consistent with the known mechanism of action of CAR-T tx, suggesting cilta-cel may overcome the poor prognosis associated with FHR MM.

P-083

Simultaneous Progressive Multifocal Leukoencephalopathy and BK Virus-Nephropathy Associated with Bispecific Antibody Therapy in Multiple Myeloma

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Introduction: Progressive multifocal leukoencephalopathy (PML) is a rare and devastating demyelinating disease of the central nervous system caused by the reactivation of the JC polyomavirus 2 (JCV) in the setting of severe immunosuppression. Similarly, BK polyomavirus 1 (BKV) associated nephropathy occurs most commonly in solid organ transplant recipients. Humoral immune response alone is insufficient in preventing PML or BKV nephritis and adequate cellular immunity is required to suppress viral reactivation. Grade 3 or higher infectious complications have been described in 16-45% of multiple myeloma (MM) patients treated with bispecific antibodies. Here we describe a unique case of a patient with MM treated sequentially with teclistamab (anti-BCMA) and talquetamab (anti-GPRC5D) bispecific antibodies who developed renal failure from BKV nephritis and ultimately fatal neurologic decline from PML. **Methods:** n/a. **Results:** We present a 66-year-old female with heavily treated IgG kappa MM who received teclistamab in her eighth line and later developed progressive renal dysfunction, diagnosed with BK nephropathy by electron microscopy of renal tissue. On progression of disease, the patient received chemotherapy (DCEP), subsequently requiring talquetamab salvage therapy. She then developed progressive decline in mental status, requiring hospitalization. She ultimately became unresponsive and required intubation for airway protection. Workup was notable for new white matter hypodensities in the temporal and occipital lobes on MRI consistent with PML. CSF showed marked elevation of BK and JC virus PCRs (BK virus 54,700 copies/mL, JC virus 120,000 copies/mL), confirming the diagnosis of PML. Autopsy was performed with the family's consent, which showed atypically high viral burden by immunohistochemistry in the affected brain regions. **Conclusions:** As the use of bispecific antibodies becomes more mainstream in the treatment of MM, it is crucial to better understand their impact on T cell fitness and the downstream infectious consequences. It has been readily demonstrated that T cell dysfunction is key in the development of polyomavirus infections. JC virus-specific CD8+ cytotoxic T cells are commonly detected in the blood of PML survivors and are notably absent in those with fatal disease within one year. Early renal biopsy and serum and CSF PCR studies can aid in the diagnosis of polyomavirus-associated nephropathy or PML. This case highlights the devastating impact of defective cellular immunity that can be seen in MM patients treated with T cell-diverting immunotherapies.

P-084

Efficacy of Linvoseltamab in Prespecified High Risk Subgroups of Patients with Relapsed/Refractory Multiple Myeloma: Results from LINKER-MM1

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Introduction: LINKER-MM1 is a Phase 1/2 study of the safety and efficacy of linvoseltamab (a B-cell maturation antigen×CD3 bispecific antibody) in patients with relapsed/refractory multiple myeloma (RRMM; NCT03761108). We report durability and depth of response for linvoseltamab 200 mg including new data in prespecified patient subgroups. **Methods:** Eligibility criteria and study design have been previously reported: patients with triple-class exposed or triple-class refractory RRMM received intravenous linvoseltamab once weekly through Week 14, then once every 2 weeks, then every 4 weeks if they reached ≥very good partial response (VGPR) and were still on treatment at ≥24 weeks. The primary endpoint was objective response rate (ORR). Secondary endpoints included safety, duration of response, progression-free survival (PFS), overall survival (OS), and minimal residual disease. **Results:** As of Jan 6, 2024, median duration of follow-up in the 200 mg dosing cohorts (Phase 1+2; n=117) was 14.3 months; all patients were ≥triple-class exposed and 82% were ≥triple-class refractory. Linvoseltamab treatment was highly effective in the overall population, with an ORR of 71%, including ≥VGPR rate of 63% and complete response or better (≥CR) rate of 50%. Deep responses and high ORR were also seen across prespecified subgroups associated with high disease burden and poor outcomes including: age ≥75 years (ORR 71%; ≥CR 55%), presence of extramedullary plasmacytoma (ORR 50%; ≥CR 33%), or presence of high-risk cytogenetic abnormality (ORR 67%; ≥CR 48%). The overall response rate in Black/African American patients was also high (ORR 85%; ≥CR 45%). Median time to ≥CR in the overall population was 8.3 months (range 1.9–13.9). Patients with baseline EMP, who typically have a longer time to response, had a median time to ≥CR of 8.6 months (5.8–11.8) vs 8.2 months (1.9–13.9) for patients without baseline EMP. Median PFS was not reached (NR) in the overall population, was 14.7 months (95% confidence interval

[CI] 11.4–NR) in patients with high-risk cytogenetics and NR in patients standard-risk. Median OS was NR in the overall population and inpatients with standard cytogenetic risk and was 31.4 months (95% CI 21.6-NR) in patients with high-risk cytogenetics. New data on depth and durability of response and PFS in additional subgroups will be presented. The most common treatment emergent adverse event (TEAE) was cytokine release syndrome (46% [Gr ≥3: 1%]); other common TEAEs (>30%) were neutropenia (43%), anemia (39%), diarrhea (38%), cough (37%), and fatigue (33%). **Conclusions:** Linvoseltamab 200 mg induced high rates of deep and durable responses in patients with RRMM, including those in high-risk subgroups. Analysis of outcomes in patients with high-risk cytogenetics showed frequent, deep, and durable responses, which is noteworthy in the context of available treatment options.

P-085

Overcoming Challenges: Development of Two Potent, Domestic BCMA-targeted CAR-T Cell Products for the Treatment of Multiple Myeloma in Brazil

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Introduction: B cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR)-T cell therapy has emerged as a breakthrough treatment for multiple myeloma. However, disease relapse is still a major issue after treatment. In this context, 4th generation CAR-T cells with cytokine production came up as an alternative to enhance tumor cell killing as well as CAR-T cells' persistence. In Brazil, access to CAR-T cell therapy is hampered by extremely high costs and long waiting times for CAR-T cell production. In this work, we aimed to produce BCMA-targeted 2nd and 4th-generation CARs for future use in the treatment of multiple myeloma patients. **Methods:** We developed two BCMA-targeted CAR constructs, a 2nd-generation one (BCMA-4-1BB-CD3z, named CAR-BCMA) and its 4th-generation counterpart with soluble IL-15 (sIL-15) production (BCMA-4-1BB-CD3z-IL-15, named CAR-BCMA-IL15). Lentiviral particles containing the CAR sequences were produced by transfection of HEK293T cells and primary T cells were transduced with the lentiviral particles. CAR-T cells were tested regarding cytotoxicity and cytokine production (TNFα and IFNγ) against BCMA+ (MM1.S, U266) and BCMA- (K562) cell lines. In addition, CAR-T cells' memory and exhaustion profiling tests are underway. **Results:** Both 2nd and 4th generation BCMA-targeted CARs were transduced into primary T cells from healthy donors with high transduction rates (75-85% for CAR-BCMA and 35-55% for CAR-BCMA-IL15, n=3) and were able to proliferate in culture (up to 400-fold expansion in 14 days) with high viability rates (>90%). When tested regarding cytotoxicity and cytokine production, both CAR-T cells showed BCMA-specific action, as they were able to kill the BCMA+ target cell lines MM1.S and U266 and to produce TNFα and IFNγ cytokines when co-cultured with these cell lines. In contrast, CAR-T cells either produced TNFα and IFNγ or were able to kill the BCMA- K562 cell line. Initial tests show no evidence of increase in T cell exhaustion markers (PD-1, TIM-3, LAG-3) on CAR-T cells when compared to non-transduced T cells as well as a tendency of larger proportions of memory T cell populations on IL-15 producing CAR-T cells. Additional tests are being performed and will be presented at the meeting. **Conclusions:** In this work, we developed two new BCMA-targeted CAR-T cell products, including a 2nd-generation CAR and its 4th-generation version with sIL-15 production. Both CARs revealed cytotoxic action and cytokine production restricted to BCMA+ target cells as well as appropriate memory and exhaustion profiling. Additionally, CAR-T cell production, testing, and profiling were performed as short as 10 days. Benefits from IL-15 incorporation into CAR's structure are expected to be clearer in in vivo experiments, so we are importing the animals. In conclusion, our work shows hope for the enhancement of access to Brazilian multiple myeloma patients for CAR-T cell therapy.

P-086

Clinical Outcomes of Teclistamab among MajesTEC-1 Eligible and Ineligible Population in the Real-World Setting for the Treatment of Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab (Tec) is the first BCMAxCD3 bispecific antibody approved for relapsed/refractory multiple myeloma (RRMM). The MajesTEC-1 (TEC-1) study demonstrated promising outcomes with Tec (overall response rate [ORR] of 63%, median progression-free survival [PFS] of 11.4 months [mos], and median duration of response [mDoR] of 24.0 mos at 30.4-mo median follow-up [mFU]). Existing evidence showed that majority of the real-world (RW) patients (pts) treated with Tec would not have met TEC-1 eligibility. Herein, we examined RW clinical outcomes of pts with RRMM treated with Tec, stratified by TEC-1 eligibility. **Methods:** This is a retrospective study of pts treated with Tec for RRMM at Memorial Sloan Kettering from November 29, 2022, to March 1, 2024, with an analysis cut-off of April 17,

2024. Responses were assessed by IMWG Criteria. TEC-1 eligibility was based off trial pt criteria. Pt characteristics were summarized by frequency (percentage) or median (interquartile range [IQR]) and compared. PFS, DoR and overall survival (OS) were evaluated using the Kaplan-Meier method. **Results:** In 86 pts with ≥1 Tec dose, the median age was 71 (64-78); 49% male; 16% Black; 10% had ECOG 2; 71% had high-risk cytogenetic abnormalities (HRCA); and 38% had extramedullary disease (EMD). ORR was 61% for 77 response-evaluable pts (43% ≥VGPR). Median time to first response was 1.3 mos (0.9-2.6). After a mFU of 9.5 mos, 6-mo PFS rate was 52.4% (95%CI 42.4-64.7%). The 6-mo DoR rate was 76.1% (95%CI 64.2-90.3%); mDoR was not reached. In this cohort, 20 pts met TEC-1 eligibility criteria, and 66 (77%) did not. Most common reasons for ineligibility were cytopenias (61%), prior BCMA-directed therapy (48%), CrCl < 40 mL/min (27%), and prior T-cell redirecting therapy (15%). The ineligible cohort was numerically older (median age 71 [64-77] vs 67 [60-78]), had more pts with EMD (40% vs 31%) and HRCA (76% vs 55%), more prior LOT (median 6 [4-9] vs 4 [4-5]), and higher rate of triple-class (80% vs 75%) and penta-drug (38% vs 25%) refractory, as compared to the eligible cohort. The unadjusted best ORR was 78% and 56% for the 18 and 59 response-evaluable TEC-1 eligible and ineligible pts, respectively. Half (50%) of the eligible pts and 33% of the ineligible pts were able to transition to less frequent dosing schedules (e.g., every two weeks). After a mFU of 9.5 mos, unadjusted 6-mo PFS rate was 70.0% (95%CI, 52.5-93.3%) and 46.3% (95% CI, 35.1%-61.1%), and unadjusted 6-mo OS rate was 80% (95%CI, 64.3-99.6%) and 65.5% (95% CI, 54.2-79.1%), for the eligible and ineligible cohorts, respectively. **Conclusions:** In the RW setting, TEC-1 eligible pts demonstrated impressive ORR, 6-mo PFS and OS. In pts who would not have met TEC-1 eligibility, despite significant disease burden and high-risk features, the unadjusted ORR still appears to be comparable with TEC-1 trial. Updated findings with longer follow-up and larger sample size are warranted and will be presented at the meeting.

P-087

Real-World Clinical Outcomes of Teclistamab and Talquetamab in Relapsed/Refractory Multiple Myeloma (RRMM): A UK Single-Centre Experience

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Introduction: Patients with RRMM have historically faced an adverse prognosis with limited alternatives. Recent advancements have introduced bispecific antibodies such as teclistamab and talquetamab as feasible options. These agents have shown an acceptable safety profile and have opened an encouraging path to address unmet treatment needs with promising rates of response and survival. However, there is still limited real-world data available on the clinical outcomes of these treatments. **Methods:** In this UK single-centre study, we conducted a retrospective review of 7 patients treated with teclistamab and 6 with talquetamab. All were part of the pre-approval access program, which made these drugs available in the UK from February 2022 to September 2023. Variables assessed included PFS, OS, ORR, very good partial response or better (≥VGPR), complete response or better (≥CR) and duration of response (DOR). We also evaluated common complications, such as CRS and haematological toxicity. These results were compared with data from the phase I/II MajesTEC-1 study and the phase I MonumenTAL-1 study. The main limitation of our study was the sample size. **Results:** Our analysis of patients treated with teclistamab revealed response rates lower than those reported in the MajesTEC-1 study, with an ORR of 42% vs 63%. The consistency and durability of response were also lower in our study, with ≥VGPR at 42% vs 58.8%, ≥CR at 14% vs 39.4% and a median DOR of 8 months vs 18.43 months. CRS rate was similar and did not exceed grade 2. Haematological toxicity was below expected except for thrombocytopenia, which had a similar rate (43% vs 40%). Nonetheless, in our cohort poor prognosis features were more prevalent. Regarding talquetamab, our data showed better response rates compared to the MonumenTAL-1 trial, with an ORR 100% vs 64%. These responses were more consistent and durable, with ≥VGPR at 50% vs 52%, ≥CR at 33% vs 23% and a median DOR that has not been reached yet after a median follow-up of 9 months compared to 7.8 months previously reported. The CRS rate was lower than expected (50% vs 80%), and never surpassed grade 2. Haematological toxicity was higher than reported for anaemia and thrombocytopenia (66% vs 43% and 50% vs 23%) while neutropenia rates were similar. As additional findings, no discontinuations were related to AEs or drug intolerance and none of the reported deaths were associated with the use of any of the drugs. **Conclusions:** Aligning with previous results, both agents were well-tolerated and showed manageable safety profiles. In terms of outcomes, in our experience teclistamab showed lower response rates and durability compared to trial data (possibly biased by the characteristics of our cohort), while talquetamab exhibited higher response rates and promising durability. These findings emphasize the importance of further real-world data with larger samples to overcome the main weakness of our study and obtain robust evidence to complement clinical trials and optimize strategies for RRMM.

P-088

Evaluating T-cell Fitness Pre B-Cell Maturation Antigen (BCMA)-Targeted T-Cell Redirection Therapies (TRT) as a Predictive Marker for Efficacy/Toxicity in Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: BCMA-targeted chimeric antigen receptor T-cell (CART) and bispecific T-cell engager (BiTE) therapies have led to unprecedented responses in RRMM. There are currently no predictive markers of response to these TRT. We hypothesized that pretreatment T-cell fitness as measured by Polyfunctional Strength Index (PSI) may predict efficacy/toxicity to TRT. **Methods:** We analyzed PBMCs from 20 RRMM pts prior to treatment with idecabtagene vicleucel or teclistamab at Yale Cancer Center. PSI, a metric for T-cell fitness combining polyfunctional T-cells % with the intensity of secreted cytokines, was obtained using the IsoPlexis' Single-Cell Secretome Platform. PSI was an average of CD4+ and CD8+ PSIs. Response was assessed by the International Myeloma Working Group criteria and response duration was defined as time from response to disease progression. Responder (R) was defined as ≥very good partial response for ≥5 mos. Non-responder (NR) was defined as stable or progressive disease ≤3 mos. Cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS) were graded using the American Society for Transplantation & Cellular Therapy system. Statistics were performed with Mann-Whitney U test using GraphPad PRISM v.9. **Results:** There were 10 pts in R group (5 BiTE & 5 CART) and 10 pts in NR group (5 BiTE & 5 CART). Median follow-up time was 13 mos. Median age at TRT was 65.5 years in both R(56-71) and NR(52-73). Median years from MM diagnosis to TRT was 8(6-16) in R and 8.5(1-17) in NR. Extramedullary disease (EM) was present in 10%(n=1) in R and 60%(n=6) in NR. High-risk cytogenetics, defined as del17p, t(4;14), t(14;16), t(14;20), 1q gain/amplification or del1p, were seen in 50%(n=5) in R and 70%(n=7) in NR. Median lines of prior therapy was 5.5 in both R(4-9) and NR(3-10). CRS/ICANS occurred 80%(n=8) in R and 30%(n=3) in NR. In all pts, PSI was 265 in R and 164 in NR(p=0.063). In CART pts, PSI was 279 in R and 205 in NR(p=0.6905). In BiTE pts, PSI was 252 in R and 123 in NR(p=0.0556). PSI was 211 in CRS and 220 in no CRS(p=0.882). PSI was 287 in ICANS and 191 in no ICANS(p=0.1974). We observed the greatest fold change of PSI from baseline in CD8+ T-cells in CART group and observed increase in granzyme B, IFN-γ, TNF-α, and TNF-β cytokines in R and ICANS groups. **Conclusions:** There is a trend towards higher PSI in R compared to NR, and higher PSI with ICANS but not with CRS. One limitation was a small sample size and thus testing PSI in a larger cohort might yield a statistically significant correlation and more granular data on T-cell profiles for each TRT. The NR group had more high-risk cytogenetics and higher EM. One confounder could be that measuring peripheral T-cell fitness may not be sufficient to predict response in EM where spatial determinants of T-cell influx play a role.

P-089

Impact of COVID-19 on Outcomes With Teclistamab in the Phase 1/2 MajesTEC-1 Study in Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: The COVID-19 pandemic disproportionately impacted patients (pts) with multiple myeloma (MM) with higher infection risk and mortality rate. Teclistamab is the first approved B-cell maturation antigen × CD3 bispecific antibody for the treatment of triple-class exposed (TCE) relapsed/refractory MM (RRMM). The MajesTEC-1 study of teclistamab enrolled most pts Mar 2020–Mar 2021, concurrent with the pandemic onset and overlapping with peak death rates worldwide. At that time, there was no approved COVID-19 treatment; vaccines were unavailable until ≥9 months into MajesTEC-1 recruitment. We report the impact of COVID-19 on teclistamab outcomes from a post hoc analysis of MajesTEC-1. **Methods:** Pts with TCE RRMM (N=165) received subcutaneous teclistamab 1.5 mg/kg weekly following step-up dosing. COVID-19 was managed per institutional guidelines and/or teclistamab interruption. COVID-19 vaccination was recommended when available. **Results:** By Jan 4, 2023 (median follow-up 22.8 months), COVID-19 was reported in 48 pts (29.1%; grade 3/4, 35 [21.2%]; deaths, 18 [10.9%]). 24.2% of pts received supportive therapies, (teclistamab interruption in 29/48 [60.4%]). Prior to teclistamab dosing, 13 pts (7.9%) received ≥1 vaccination, including 1/18 pts who died of COVID-19. On-study, 99 pts (60.0%) received ≥1 vaccination, including 13/18 pts who died of COVID-19. Never-vaccinated pts tended to die of COVID-19 earlier than vaccinated pts (0.7–5.9 vs 2.4–25.9 months after starting teclistamab, respectively). Overall, median (95% CI) progression-free survival (PFS), duration of response (DOR), and overall survival (OS) were 11.3 (8.8–16.4), 21.6 (16.2–not estimable [NE]), and 21.9 (15.1–NE) months, respectively. When censored for COVID-19 deaths, median PFS, DOR, and OS were 15.1 (9.9–22.8), 26.7 (21.6–NE), and 28.3 (21.9–NE) months, respectively. **Conclusions:** Survival with teclistamab in MajesTEC-1 was longer when censored for COVID-19 deaths. More data from pts treated with teclistamab in the era of both innate and vaccine-induced immunity are needed to further understand the impact of COVID-19 on outcomes.

P-090

Infections and Immune Reconstitution in the Phase 3 CARTITUDE-4 Trial of Ciltacabtagene Autoleucel vs Standard Care in Patients with Lenalidomide-Refractory Multiple Myeloma (MM) and 1–3 Prior Lines

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Introduction: Patients (pts) with MM have high risk of infection from underlying MM and treatment (tx). We characterize infections and immune reconstitution in pts who received ciltacabtagene autoleucel (cilta-cel) vs standard care (SOC) tx in CARTITUDE-4 (NCT04181827). **Methods:** Eligibility criteria were previously described. Cilta-cel arm pts underwent apheresis, received bridging tx (daratumumab-pomalidomide-dexamethasone [DPd]/pomalidomide-bortezomib-dexamethasone [PVd]), and then cilta-cel infusion 5–7 days [d] post lymphodepletion. SOC arm pts received DPd/PVd until progressive disease (PD). Infection was assessed in all pts (both arms) who received any part of study tx (safety set) and pts who received cilta-cel as study tx. Lymphocyte counts were derived by flow cytometry. **Results:** As of Apr 2023 (21.5 months [mo] median follow-up), 91% of pts in the cilta-cel arm (n=208) and 72% of the SOC arm (n=208) had either tx-emergent (≤112 d post cilta-cel, ≤30 d after last SOC tx, or until PD/subsequent tx) hypogammaglobulinemia or postbaseline IgG < 500 mg/dL. A respective 68% and 16% received intravenous immunoglobulin (IVIG). 30% of the cilta-cel arm and 23% of the SOC arm had grade (gr) 3/4 tx-emergent and non–tx-emergent infections. In mo 1–3, mo 4–6, mo 7–9, and mo 10–12 post study tx start, a respective 26, 18, 12, and 9 pts in the cilta-cel arm and 18, 9, 14, and 6 in the SOC arm had gr 3/4 infections. 11 (5%) pts in the cilta-cel arm and 6 (3%) in the SOC arm had fatal infections. Any gr viral infections occurred in 42% of the cilta-cel arm and 37% of the SOC arm, any gr bacterial infections in 17% and 18%, and any gr fungal infections in 6% and 7%.Most fatal infections were due to COVID-19 pneumonia (most occurred during the pandemic's omicron wave). 7 pts in the cilta-cel arm (0 were fully vaccinated) and 2 in the SOC arm died due to COVID-19. Among 176 pts who received cilta-cel as study tx, 24% had gr 3/4 infections. 11 had a fatal infection, including the 7 COVID-19–related deaths. Pts most often had gr 3/4 infections in the first 3 mo post infusion (23 in mo 1–3; 11 in mo 4–6; 8 in mo 7–9; 4 in mo 10–12). 8/11 deaths from infections occurred in the first 6 mo. Of pts who received cilta-cel as study tx, 85% had gr 3/4 neutropenia that recovered to gr ≤2 by d 60. B cells recovered to baseline % lymphocytes by ~6–7 mo in bone marrow (BM) and ~9 mo in blood; plasma cells recovered by ~9 mo in BM and blood. IgA and IgM recovery, surrogates for endogenous IgG, was seen in the cilta-cel arm but not the SOC arm. **Conclusions:** Pts in both the cilta-cel and SOC arms were at risk of severe and fatal infections. In the cilta-cel arm, most severe and fatal infections occurred early after infusion, with risk higher in the first 3–6 mo and decreasing over time. These results underscore the importance of monitoring, infection prophylaxis (eg, IVIG), and supportive care early following cilta-cel infusion and throughout for pts receiving continuous tx.

P-091

Talquetamab Versus Belgian Real-World Clinical Practice in Triple-Class Exposed Relapsed and Refractory Multiple Myeloma Patients Using Adjusted Comparison

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Introduction: Triple-class exposed (TCE) patients (pts) with relapsed and refractory multiple myeloma (RRMM) face a challenging outlook with limited treatment options, mainly consisting of recently approved B-cell maturation antigen-targeting

agents. Talquetamab, a bispecific antibody targeting GPRC5D and CD3, was granted an orphan drug designation and approved by EMA as of August 2023 as treatment for TCE RRMM pts based on the single-arm phase 1/2 MonumenTAL-1 trial. The effectiveness of talquetamab in this trial was compared against real-world clinical practice (RWCP), using individual patient data (IPD) from the retrospective Belgian patient cohort in BELCOMM (Belgium Comparator study in Multiple Myeloma). **Methods:** The external control arm for MonumenTAL-1 was constituted from TCE RRMM pts in BELCOMM treated with therapies used in RWCP. They had ECOG score ≤2, ≥ 3 prior lines of therapy (LOTs), and ≥1 subsequent active MM therapy after becoming TCE. IPD were available for MonumenTAL-1 pts (cut-off date January 17th, 2023) and RWCP pts in BELCOMM (data collection March 2017-May 2021). Inverse probability weighting (IPW) and multivariable regression were used to balance confounding factors between both patient cohorts. The comparative effectiveness of talquetamab vs RWCP was assessed for overall response rate (ORR), very good partial response rate or better (≥VGPR), progression-free survival (PFS), time to next treatment (TTNT) and overall survival (OS) in the treated population. For ORR and ≥VGPR, weighted logistic regression was used to estimate an odds ratio (OR) and 95% confidence interval (CI). The ORs were also transformed to estimate response rate ratios (RR). For PFS, TTNT and OS, weighted Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% CIs. **Results:** From MonumenTAL-1, 143 pts (143 LOTs) from the 0.4 mg/kg weekly cohort and 145 pts (145 LOTs) from the 0.8 mg/kg Q2W cohort and from BELCOMM 123 pts (268 LOTs) were included in the all-treated analyses. Comparisons of both the 0.4 mg/kg as well as the 0.8 mg/kg cohorts with the RWCP cohort demonstrated statistically significant results in favour of talquetamab with respect to all endpoints. For ORR, the RR [95% CI] for talquetamab vs RWCP were 2.51 [1.88, 3.36] with 0.4 mg/kg dosing and 2.34 [1.75, 3.13] with 0.8 mg/kg dosing. While for ≥VGPR these were 5.32 [3.51, 8.07] and 5.42 [3.58, 8.20], respectively. The HR [95% CI] for talquetamab vs RWPC were 0.47 [0.36, 0.61] and 0.35 [0.26, 0.47] for PFS, 0.42 [0.32, 0.54] and 0.34 [0.25, 0.45] for TTNT, and 0.34 [0.24, 0.49] and 0.32 [0.21, 0.47] for OS, respectively. **Conclusions:** Both talquetamab 0.4 mg/kg weekly and 0.8 mg/kg Q2W showed superior effectiveness compared to RWCP treatments administered for each measure of clinical effectiveness in Belgian TCE RRMM pts and indicate its potential as a novel and effective treatment in TCE RRMM pts.

P-092

Monitoring of Anti-BCMA CAR-T Cells and non-CAR-T Immune Subsets in Multiple Myeloma Patients

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Introduction: Chimeric antigen receptor (CAR) T cells targeting B-cell maturation antigen (BCMA) represent a groundbreaking therapeutic option for multiple myeloma (MM). Monitoring CAR-T cell expansion might play a role in the prediction of treatment efficacy and the severity of side effects. **Methods:** Peripheral blood (PB) samples (n = 73) from 12 MM patients in total were assessed at various timepoints starting at day 0 (D0)/day of infusion or D2, with resampling at D7, D10, D14, D21, D28 and M1-M6 each month. An 8-color flow cytometry panel (CD3, CD4, CD8, CD19, CD20, CD45, CD16+CD56, BCMA CAR) using dried reagent tubes was utilized to assess levels of BCMA CAR-T cells and other immune subsets. **Results:** Median number of assessed CD45+ leukocytes was 164 x 103 with median limit of detection 0.0122%. The presence of CAR-T cells was first detectable at D7 (median count/µl PB, min-max: 9, 0.55-2152) with maximum expansion at D10 (966, 222-11924). From D14 (937, 219-2800), the CAR-T cell counts gradually dropped to detectable levels in 3/5 patients at M1-2 and 1/4 patients at M2-3 (Figure 1). The CD4/CD8 ratio significantly decreased over time from D7 to D28 in the CAR-T cell compartment (median percentage in CAR-T fraction: CD4+, D7 = 74.20% vs. D28 = 54.08%, p = 0.0079; CD8+, D7 = 17.50% vs. D28 = 44.89%, p = 0.0016). A similar shift in the CD4/CD8 ratio was also observed in non-CAR T cells between D0 and M5-6. B cells were completely depleted from D7 to D28 with their first considerable reappearance in circulation at M1-2 in 3/5 patients. The monocyte percentage in the leukocyte fraction significantly increased from D2 to D7 (median: D2 = 2.15% vs. D7 = 25.60%, p = 0.0028). NK cell levels in the lymphocyte fraction were not significantly affected by the therapy in any of the timepoints. **Conclusions:** The data obtained from this multicentric collaboration describe the dynamics of CAR-T cell expansion as well as of non-CAR-T immune subsets

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Real World Data on Bispecific Antibodies in the Brazilian Setting

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Introduction: Bispecific antibodies (BsAbs) are a newly approved treatment for relapsed and refractory Multiple Myeloma (MM) in Brazil. They are expected to be widely used among patients previously exposed to anti-CD38, proteasome inhibitors, and immunomodulatory agents (triple class-exposed), as access and cost hinder the use of CAR-T cells for most of the population. Brazil's unique label for teclistamab and talquetamab allows for the possibility of prescription in the second line of treatment for

triple-class exposed patients, even though data is lacking in this setting. Here, we present initial data on twelve patients treated with commercially available BsAbs in our hospital. **Methods:** We collected data for patients treated with BsAbs at our Oncology Center (AC Camargo Cancer Center) in São Paulo, Brazil, between June 2023 and May 2024. Baseline characteristics were collected at baseline, and response and toxicity parameters were updated based on the last day of follow-up. **Results:** Twelve patients were identified, most were male (58%), and the median age was 67.5 years (CI 44-77), with 33.3% expressing IgG/Kappa and 33.3% expressing IgG/Lambda. ISS 1 was the most common staging (41.6%), followed by ISS 3 (33.3%). FISH was unavailable for most (66.6%). All patients were triple class exposed, with the majority having received lenalidomide and thalidomide as IMiDs (66.6%). The mean number of previous lines of treatment was 3 (CI 1-5), with one patient receiving treatment as a second line. The median follow-up was 4 months [CI 1-7]. Teclistamab was the most common BsAb (83.3%, n=10), followed by talquetamab (16.7%, n=2). Response was achieved in 10 patients, with 16% (2/12 pts) in stringent complete response, 33.3% (4/12 pts) in VGPR, and 25% (3/12 pts) in partial response. The median hospital stay for step-up dosing was 12 days [CI 9-56]. Cytokine release syndrome (CRS) occurred in most patients (83%, 10/12 pts), with most being grade 1 (50%, 6/12 pts). Tocilizumab was used in 41% (5/12 pts) of patients, and dipyrone was the most used antipyretic for CRS management (83%, 10/12 pts). Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in two patients (16%), and both had dialytic renal dysfunction due to MM activity. Infections were common (66.6%, 8/12 pts), with most being grade 3-4 (66.6%, 8/12pts) and lower respiratory tract infections (37.5%, 4/12 pts). Hypogammaglobulinemia occurred in 91.6% (n=11) of patients, and only one patient had not yet received intravenous human immunoglobulin. One patient died during the in-hospital stay for the step-up dosing due to infectious complications and renal dysfunction. **Conclusions:** BsAbs will be used as a mainstay treatment for most of the Brazilian patients for whom it is available. Responses and the toxicity profile seem to be in line with what was previously observed in pivotal studies, although more data and follow-up are necessary for definitive conclusions.

P-094

The Optimal Lymphodepletion Prior to Eque-cel in Patients with Refractory Relapsed Multiple Myeloma in FUMANBA-1 Study

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Introduction: The Lymphodepletion (LD) with the combined treatment of Cy/Flu has been associated with improved clinical outcomes. A higher exposure was reported to be associated with improved PFS. The LD dosages were Cy 500 mg/m2/day and Flu 30 mg/m2/day for 3 days in FUMANBA-1 study. Due to adverse effects associated with LD, dose adjustments were made for some patients. This analysis compares the outcomes of patients receiving Eque-cel treatment in the FUMANBA-1 study under different LD regimens. **Methods:** A retrospective analysis was conducted on data from CAR-T-naïve patients in the FUMANBA-1 study who received a dose of 1.0×10^6 BCMA CAR-T cells/kg. Patients were divided into an LD dose-adjusted group and a standard dose group based on whether the LD dose was adjusted. Baseline characteristics, efficacy, and safety were compared between the two groups. Log-rank tests and other methods were used for intergroup difference analysis. **Results:** Among the 91 CAR-T-naïve patients in FUMANBA-1, 33 patients underwent LD dose adjustment, with a median of 4 prior lines of therapy (range 3-6). In the dose-adjusted group, 29 cases (87.9%) involved a dose reduction, with the average doses of Cy and Flu administered being 88.7% and 90.8% of the theoretical doses, respectively. The two groups had similar distributions of baseline disease characteristics (P >0.05), including high-risk genetic factors (72% vs 66.7%), R-ISS stage III (3.4% vs 12.1%), screening bone marrow plasma cells ≥50% (15.5% vs 21.2%), double refractory (100% vs 100%), and triple refractory (17.2% vs 27.3%) disease. After a median follow-up of 18 months, the analysis showed that insufficient LD was associated with reduced efficacy. The 12-month PFS rate was 73.5% in the dose-adjusted group, while it was 92.2% in the standard dose group. The dose-adjusted group also took longer to achieve MRD negativity (22 days vs 15 days) and had a lower 12-month MRD negativity maintenance rate (63.7% vs 90.4%). CRS (grades 1-2) occurred in 94.8% of the standard dose group and 93.9% of the dose-adjusted group, with no severe CRS (≥grade 3) in either group. Median time to CRS onset was 6.0 days for both groups, with durations of 5 days for standard dose group and 6 days for adjusted group, respectively. Apart from one grade 2 ICANS case

in the adjusted group, no ICANS occurred in either group. Standard dose group did not show an increased risk of severe hematologic toxicity (P >0.05, grade 3 or higher hematologic toxicity occurring 28 days and 60 days and at the end of follow-up, including neutropenia, thrombocytopenia, lymphopenia). **Conclusions:** LD conditioning prior to CAR-T cell therapy is necessary for optimal CAR-T efficacy. Our study further confirms that the current adequate LD regimen and dosages are optimal for Eque-cel with improved disease remission and clinical outcomes. Administering full LD doses when possible can lead to greater benefits without increasing toxicity. Thanks to professor Chunrui Li, the corresponding author of this paper.

P-095

Impact of Granulocyte Colony-Stimulating Factor Exposure on Cytokine Release Syndrome During Bispecific Antibody Initiation in Relapsed/Refractory Multiple Myeloma

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Introduction: Bispecific antibodies (BsAb) are a novel class of immunotherapy agents used in the treatment of multiple myeloma. They are associated with notable adverse events including cytokine release syndrome (CRS), cytopenias, and infections. While granulocyte colony-stimulating factors (GCSF) can be used to treat neutropenia and reduce infection risk, little is known about their safety during the BsAb initiation period (during step up doses [SUD] and first treatment dose [FTD]), when patients are at highest risk of CRS. The objective of this study was to assess the impact of GCSF exposure on CRS rates during BsAb initiation. **Methods:** We included all patients who received at least one SUD of commercial teclistamab, elranatamab, or talquetamab between November 2022 and April 2024 at Memorial Sloan Kettering Cancer Center. Exposure to GCSF was defined as administration of at least one dose of filgrastim from 48 hours before up to 7 days after BsAb SUD or FTD, or one dose of peg-filgrastim between 7 days prior to up to 7 days after BsAb SUD or FTD. Data collection included patient demographics, disease characteristics/history, and CRS rates/grades. Baseline characteristics were compared using Fisher's exact or Wilcoxon rank sum tests. Association of CRS and GCSF exposure was evaluated with univariate cox proportional hazard model with GCSF as a time-dependent covariate. **Results:** A total of 126 patients were included, of which 18 were GCSF-exposed and 108 were non-exposed. Baseline characteristics were comparable except for baseline absolute neutrophil count/ANC (1.3 x 109/L [IQR 1-2] in GCSF-exposed vs 3 [2-4.4] in non-exposed; p< 0.001). Median prior lines of therapy were 7 (5-9) vs 6 (4-8), p=0.3. This included BCMA-directed therapy in 56% vs 47% (p=0.5) and BsAb therapy in 28% vs 11% (p=0.07). Extramedullary disease (EMD) was present in 54% vs 35% (p=0.2). Four (22%) patients received GCSF prior to first SUD at a median of 23 hours (14-31), 5 (28%) received GCSF in between SUD/FTD, and 9 (50%) received GCSF after FTD at a median of 75 hours (62-132). The median ANC at time of GCSF exposure was 0.5 (0.4-0.7). An increase in ANC after GCSF by at least 50% was observed in 11 (61%) patients. CRS occurred in 4 (22%) patients after GCSF exposure vs in 53 (49%) of non-exposed patients. There was a trend towards increased CRS after GCSF exposure, although not significant potentially due a limited number of patients in the GCSF-exposed cohort (HR 2.6, 95% CI 0.9-7.1, p=0.07). Grade 2 CRS occurred in 2 (50%) GCSF-exposed patients. No CRS occurred in patients exposed to GCSF after FTD. **Conclusions:** Exposure to GCSF during BsAb initiation was not significantly associated with increased risk of CRS. These results suggest that there are no major safety concerns with GCSF administration for neutropenia during BsAb initiation, although larger cohorts are needed to confirm these findings.

P-096

Patient-Reported Outcomes in the Phase 3 CARTITUDE-4 Study of Ciltacabtagene Autoleucel Vs Standard of Care in Patients With Lenalidomide-Refractory Multiple Myeloma After 1–3 Lines of Therapy

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Introduction: The phase 3 CARTITUDE-4 trial (NCT04181827) in patients (pts) with lenalidomide (len)–refractory multiple myeloma (MM) after 1–3 lines of therapy (LOT) showed significantly improved progression-free survival (hazard ratio [HR], weighted, 0.26; P< 0.0001) with ciltacabtagene autoleucel (cilta-cel) vs standard of care (SOC; pomalidomide, bortezomib, and dexamethasone or daratumumab, pomalidomide, and dexamethasone). We present comparisons of pt-reported outcomes (PROs) from pts randomized to cilta-cel vs SOC. **Methods:** 419 pts with len-refractory MM and 1–3 prior LOT, including a PI and an IMiD, were randomized to cilta-cel (N=208) or SOC (N=211). European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; 100-point scale), EuroQoL 5-Dimension 5-Level (EQ-5D-5L; 100-point scale), and MM Symptom and Impact Questionnaire (MySIm-Q; 5-point scale) questionnaires were administered to all pts until disease progression (PD). Compliance was calculated as the number received divided by the number expected. Mixed-model for repeated measures analyses were performed to analyze changes from baseline for each arm and included the baseline PRO score and prognostic characteristics as covariates to balance arms and adjust for confounders. Time to sustained symptom worsening, defined as a clinically meaningful increase (≥0.5 standard deviation of pooled baseline values) without a subsequent reduction in MM symptoms, was assessed using the Kaplan-Meier method. **Results:** As of Nov 2022, 99 pts in the cilta-cel arm and 66 in the SOC arm had both baseline and 12-mo PRO assessments prior to PD. PRO compliance was 100% at baseline and decreased to 74% (cilta-cel) and 81% (SOC) at mo 12. From baseline, functioning and symptom scores improved in the cilta-cel arm, while PRO scores in the SOC arm trended towards worsening or lower degrees of improvement for most domains and symptoms. Average improvement at mo 12 (least squares mean change) for pts who received cilta-cel was 10.1 points (global health status), −10.2 points (pain), 8.0 points (visual analogue scale), −9.1 points (fatigue), and 9.5 points (emotional functioning). Results numerically favored cilta-cel for all EORTC QLQ-C30 domains. On the MySIm-Q total symptom scale, the median time until MM symptom worsening in the cilta-cel arm was 23.7 mo (95% CI, 22.1–NE) vs 18.9 mo (95% CI, 16.8–NE) in the SOC arm (HR, 0.42). **Conclusions:** CARTITUDE-4 demonstrated improvements in health-related quality of life (HRQoL) and reductions in disease-specific symptoms on multiple PRO endpoints after a single cilta-cel infusion vs SOC. Improvements in HRQoL were numerically greater with cilta-cel versus SOC across all scales. With previously reported data showing significant clinical benefit of cilta-cel, these results strengthen cilta-cel's potential to be a new SOC for pts with len-refractory MM after first relapse.

P-097

Examining the impact of T-cell redirecting therapies in the treatment of ultra-high risk multiple myeloma and plasma cell leukemia

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Introduction: T-cell redirecting therapies have demonstrated efficacy in patients (pts) with MM in the 4th line of treatment or later; however, pts with ultra-HRMM and plasma cell leukemia (PCL) were largely excluded from registrational trials. Here we report response data and survival outcomes for a cohort of ultra-HRMM/PCL pts who either received cellular therapies (CT), including bispecific antibodies (BSAb) or CAR-T, or conventional treatment regimens. **Methods:** In this retrospective study, pts were required to have either PCL or at least two of the following cytogenetic abnormalities (CA) at the time of diagnosis: t(4;14), t(14;16), t(14;20), del(17p), del(1p32), and gain or amp 1q. Survival analysis was conducted using the Kaplan-Meier method with log-rank testing along with the Cox proportional hazards model for regression. 69 ultra-HRMM/PCL pts were identified. Of these, 30 pts received cellular therapies in the 4th line of therapy or later. **Results:** The overall patient cohort had a median age of 62.1 years. Those receiving CT were more likely to have PCL and EMD as well as lower LDH and B2M at the time of diagnosis. The most common CA were gain/amp of 1q, del17p, and t(4;14). In the CT group, 100% and 73% of pts were triple and penta-refractory compared to 75% and 41% among those not receiving CT. The median prior lines of therapy at the time of first treatment with CT was 7. 17 pts received CAR-T cells (8 Carvykti, 9 Abecma), 23 BSAb, and 10 pts multiple CT. ORR to first CT=40% (VGPR-10%, CR-23%), median DOR-6.5 mo.) MRD status was not available. CRS rate =82%, ICANS=35%, both of which were predominantly low grade. Overall, the median OS from 1st treatment was 51.8 months and 3-year OS was 61.0%. CT patients survived longer from 1st treatment: median OS=65.0 vs 32.2 mo. p=0.029. We then conducted a landmark 12-month OS analysis from the time of CT or last treatment for those note receiving CT. Overall the median OS was 6.3 months, 6-month OS was 51.8% and 12-month was 30.9%, however the survival curves exhibited a crossing hazards pattern with trends toward inferior survival for CT at one month and improved OS for CT at middle and later time (6-month OS: 63.9% with 95% CI 45.4-82.4 vs 45.6%, p= 0.16, 12-month OS: 40.7% vs 25.6, p = 0.18). Additional details of this analysis will be reported. **Conclusions:** Within the limits of this analysis, a substantial minority of heavily pretreated pts with ultra-HRMM or PCL responded to late-line treatment with CT. When compared with patients who did not receive CT, landmark OS analysis conducted from the time of receipt of CT or last line of therapy suggests that early post-treatment mortality may offset some survival benefit in the intermediate term. Given the potential morbidity of these treatments, care should be taken in the selection of ultra-HRMM/PCL pts when considering late-line cellular therapies. The use of CT in earlier lines of therapy may allow for improvement of these outcomes and warrants further study in this vulnerable population.

P-098

Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: Talquetamab (tal) is the first approved GPRC5D-targeting bispecific antibody (BsAb) for treatment of patients (pts) with relapsed/refractory multiple myeloma (RRMM). In the phase 1/2 MonumenTAL-1 study, tal demonstrated high ORRs in pts naive (>71%) and exposed (65%) to prior T-cell redirection therapy (TCR). We report efficacy and safety results across 3 RRMM cohorts in MonumenTAL-1 with a longer median follow-up (mFU) of 20–30 mo. **Methods:** Eligible pts were intolerant to or progressed on established therapies (phase 1, NCT03399799) or had ≥3 prior lines of therapy, including ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 Ab (phase 2, NCT04634552). Pts received RP2Ds of subcutaneous tal 0.4 mg/kg QW or 0.8 mg/kg Q2W, with step-up doses. Response was assessed by IRC based on IMWG criteria. AEs were graded by CTCAE v4.03. CRS and ICANS were graded by ASTCT criteria. **Results:** As of Jan 2024, 375 pts were enrolled: 143 pts in the QW cohort with mFU of 29.8 mo, 154 pts in the Q2W cohort with mFU of 23.4 mo, and 78 pts in the prior TCR cohort who received either RP2D (89.7% dosed QW) with mFU of 20.5 mo. Baseline characteristics were similar to previous reports, with the exception of a greater number of African American pts in the current analysis (n=32). ORRs ranged from 67–74% (≥VGPR, 55–59%) across cohorts. In the prior TCR cohort, ORR was 71.4% (40/56) and 57.7% (15/26) in pts with prior CAR-T and prior BsAb, respectively. ORRs were consistent across clinically relevant subgroups, except pts with EMD who had lower ORRs (48.5% [QW], 41.5% [Q2W], 44.0% [prior TCR]). DOR and PFS results suggest better durability in the Q2W vs QW cohort (12-mo DOR 60.6% vs 43.8% and 12-mo PFS 46.8% vs 34.9%, respectively). The safety profile was also consistent with previous results. Common AEs in the QW, Q2W, and prior TCR cohorts, respectively, included CRS (79.0%, 74.7%, 73.1%), taste-related AEs (72.0%, 71.4%, 75.6%), non-rash skin-related AEs (56.6%, 73.4%, 64.1%), nail-related AEs (55.2%, 53.2%, 59.0%), and rash-related AEs (39.9%, 29.9%, 32.1%); most were grade 1/2. Weight loss, assessed by vital signs (weight decrease ≥10% from baseline), occurred in 38.5% (QW), 34.4% (Q2W), and 38.5% (prior TCR) of pts. The most common grade 3/4 AEs were hematologic AEs, including anemia (31.5%, 25.3%, 26.9%) and neutropenia (30.8%, 21.4%, 47.4%). Infection rates were comparable to previous reports (any grade, 60.8%, 70.1%, 76.9%; grade 3/4, 22.4%, 20.1%, 25.6%). Dose reductions (15.4%, 9.7%, 11.5%) and discontinuations (4.9%, 9.7%, 5.1%) due to AEs remained low. There were no treatment-related deaths. **Conclusions:** With additional pts in the analysis, high ORRs were maintained across cohorts; with longer follow-up, pts continued to demonstrate durable responses, with longer DOR in Q2W vs QW dosing in pts naive to prior TCR. The safety profile was consistent with previous reports. These data support tal as a versatile treatment for pts with RRMM.

P-099

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 approved GPRC5D-targeting bispecific antibody for the treatment of patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) based on results from the MonumenTAL-1 study (NCT03399799/NCT04636552). The nationwide deidentified electronic health record-derived Flatiron Health MM cohort database study (Flatiron) evaluated real-world physician's choice of treatment (RWPC) in pts with TCE RRMM. A previous indirect comparison showed improved efficacy outcomes with tal vs RWPC in Flatiron; here, we report an updated adjusted comparison of tal vs RWPC 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 January 2024 data cut-off date; median follow-up was 29.8 and 23.4 months for the QW and Q2W cohorts, respectively. An external control arm was created from the Flatiron database as of July 2022 for pts who met key MonumenTAL-1 eligibility criteria (N=629 with 1169 eligible lines of therapy [LOT]). A base model adjusted for imbalances in baseline prognostic variables (refractory status, cytogenetic risk, ISS stage, time to disease progression on last LOT, number of prior LOT, time since diagnosis, age, and hemoglobin) using inverse probability of treatment weighting methodology. A full model also

adjusted for prior stem cell transplant, ECOG performance status, race, sex, and MM type. Balance after adjustment was assessed using standardized mean differences (SMD). Outcomes of interest were progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS). A weighted Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs, and a weighted Kaplan-Meier method was used to estimate median time-to-event outcomes. Sensitivity analyses evaluated the impact of alternative statistical methods and variable adjustment. **Results:** After reweighting, baseline characteristics were comparable across all pt cohorts, with SMD < 0.1. In the base model, pts who received tal QW had significantly improved PFS (HR 0.55 [95% CI] 0.45–0.68, P< 0.0001; median 7.5 vs 3.9 mo), TTNT (HR 0.59 [0.47–0.72], P< 0.0001; median 9.1 vs 5.1 mo), and OS (HR 0.58 [0.43–0.79], P< 0.0001; median 32.1 vs 16.5 mo) vs RWPC. Similarly, pts who received tal Q2W had significantly improved PFS (HR 0.45 [0.36–0.57], P< 0.0001; median 11.2 vs 4.0 mo), TTNT (HR 0.49 [0.39–0.61], P< 0.0001; median 11.7 vs 5.1 mo), and OS (HR 0.46 [0.33–0.64], P< 0.0001; median NR vs 15.8 mo) vs RWPC. Results were generally consistent across the full model and sensitivity analyses. **Conclusions:** With longer follow-up, tal at QW and Q2W dosing schedules continued to show superior effectiveness across all efficacy endpoints vs RWPC in pts with TCE RRMM.

P-100

Outcomes of R/R MM Patients with Renal Function Impairment Treated with Eque-cel in the Pivotal Phase 2 FUMANBA-1 Study

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Introduction: R/R MM and renal impairment(RI) tend to be more challenging to manage. Administration of anti-myeloma treatment is important to reduce the production of monoclonal FLC. Equecabtagene Autoleucel (Eque-cel) has demonstrated a favorable safety and efficacy profile in heavily pretreated RRMM patients. However, the impact of RI on the outcome of Eque-cel remains unknown. Especially when lymphodepletion (LD) is often adjusted in RI, and LD is also associated with the outcome. We evaluated outcomes of RRMM patients with RI treated with Eque-cel in FUMANBA-1 study (NCT05066646), including pharmacokinetics, efficacy, safety, and renal function changes. **Methods:** A retrospective analysis was conducted. Patients were divided into RI group and non-RI group, based on whether the creatinine clearance (CrCl) was ≤70 ml/min at the time of CAR-T therapy. Baseline characteristics were compared between the two groups. Pharmacokinetics, and efficacy endpoints, including ORR, CR, PFS, OS, MRD negativity and duration of MRD negativity, were evaluated. As for safety data, we mainly analyzed CRS and

Table 1 (abstract P-100) Baseline characteristics and efficacy.

	RI(N=28)	non-RI (N=63)
High-risk genetic factors	71%	70%
ISS stage III	18%	11%
EMD	18%	8%
ECOG 1	89%	68%
ORR	100%	98%
CR/sCR	79%	84%
D14 ORR	79%	64%
D14 MRD negativity	62%	57%
12-month MRD negativity maintaining	78%	83%
12-month PFS	77%	89%
12-month OS	86%	96%
PK	RI with LD adjustment (N=12)	RI without LD adjustment (N=16)
Tmax (days)	12	11
Median Cmax (copies/μg DNA)	120636	99603
Median AUC0-28 (day*copies/μg DNA)	1076206	986429
Median AUC0-last (day*copies/μg DNA)	1902160	1775274

ICANS, cytopenia. And changes of renal function were analyzed. **Results:** With a median follow up of 18.07months, 91 patients without prior CAR-T received eque-cel, of which 28 had RI with CrCl between 40 and 70ml/min and 63 belonged to non-RI group with CrCl >70ml/min. Most baseline characteristics in RI group were comparable to non-RI group.12 patients underwent LD adjustment in the RI group. The pharmacokinetics in the LD adjustment group was comparable to the standard LD group. RI group could also achieve response as rapid and deep as the non-RI group. The long-term efficacies for RI group were also not inferior. The specific data is shown in the table below. No significant CRS incidence difference was observed between the two groups. Only 1 grade 2 ICANS in the non-RI group, no ICANS occurred in RI group. A little higher prevalence of short-term severe cytopenia occurred in the RI group but recovered equally by day 60. 73.2% and 58.8% of all patients treated with eque-cel experienced improvement in CrCl compared to baseline at 14 days and 3 months post infusion. **Conclusions:** In the FUMANBA-1 study,RRMM patients with RI could also achieve similarly rapid, deep, and durable response with eque-cel treatment without compromising safety status. Renal function could also be improved due to the clearance of myeloma cells by eque-cel.Thanks to professor Lugui Qiu,the corresponding author of this paper.

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Burden of AL Amyloidosis and its Association with Cardiac Involvement: Initial Results from a Patient-Reported Outcome Survey

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Introduction: Amyloid light chain (AL) amyloidosis is a rare, progressive, and often fatal disease in which misfolded light chains form soluble, toxic aggregates and deposit as amyloid in organs; these deposits can lead to damage, dysfunction, and failure. Among patients with AL amyloidosis, those with cardiac involvement are at the highest risk for early death. This study examines the burden of AL amyloidosis in recently diagnosed cardiac and non-cardiac patients. **Methods:** Adults with AL amyloidosis diagnosed in the past 24 months were enrolled in a longitudinal, mixed-methods study. Patient-reported outcome (PRO) measures were used to assess disease burden, including the SF-36v2® Health Survey (SF-36v2), Kansas City Cardiomyopathy Questionnaire-12 Item Short Form (KCCQ-12), Work Productivity and Activity Impairment Questionnaire (WPAI), and a Patient Global Impression of Severity (PGI-S). Results are based on initial survey data collected in 2022-2023. Participants were grouped by cardiac involvement (yes/no) and number of organs involved (1, 2, ≥3). Differences in PRO scores were tested using parametric or nonparametric tests based on score distributions. **Results:** The analysis sample included 97 participants with a mean age of 59.4 years and greater proportions female (54.6%), White/Caucasian (86.6%), and based in the United States (74.2%). Mean time since diagnosis was 12.2 months and mean number of organs involved was 2 (range: 1-5). Almost all participants (92.8%) had received AL amyloidosis treatment prior to the initial survey. Cardiac involvement was reported by 57.7% of participants. SF-36v2 and KCCQ-12 scores indicated impacts on health-related quality of life (HRQoL), especially on physical health and social functioning. Mean SF-36v2 domain and summary scores were all below the general population normative score of 50, exceeding established thresholds for meaningful impairment for all domains except Mental Health. Participants with cardiac involvement had significantly ($p< 0.05$) worse mean SF-36v2 Physical Functioning scores (39.5 vs. 44.4, higher is better) and PGI-S scores (3.2 vs. 2.4, higher is worse) than those without cardiac involvement. Significant differences in the following scores were observed across groups defined by number of organs involved: SF-36v2 Physical Functioning, Role Physical, Social Functioning, and Physical Component Summary; KCCQ-12 Physical Limitations and Social Limitations; WPAI Activity Impairment; and PGI-S ($p< 0.05$). Participants with ≥3 organs involved experienced greater burden than those with fewer organs involved. **Conclusions:** In this sample of participants with recently diagnosed AL amyloidosis, significant disease burden related to symptom severity and HRQoL impacts was observed. Participants with cardiac involvement and a greater number of organs involved experienced additional burden in these areas. Results demonstrate the need for better therapeutic options in these key clinical subgroups.

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Ocular Complications Are Common in Patients With Multiple Myeloma Receiving Dexamethasone: Results of a Cross-Sectional Patient Survey

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Introduction: Treatments for multiple myeloma (MM) may predispose patients to ocular comorbidities such as cataracts and glaucoma from dexamethasone (dex), blepharitis from bortezomib, or keratopathy from belantamab mafodotin. Little is known about eye health in MM with regard to the prevalence of ocular comorbidities and eye health-related behaviors, e.g. periodic ocular exams as recommended for older adults by the American Academy of Ophthalmology. **Methods:** We conducted an IRB-approved survey of patients with MM through HealthTree Cure Hub for Multiple Myeloma. Patients answered questions about their demographics, MM history, ocular comorbidities, frequency of eye health visits, and interference with instrumental activities of daily living (IADLs; i.e., driving) due to ocular disorders. For cataracts and glaucoma, patients reported their most common typical weekly dex dose in milligrams (mg), which was grouped into high-dose (20-40 mg), low-dose (1-19 mg), no-therapy (no dex), and unsure. Responses were analyzed descriptively. **Results:** Of n=582 respondents, the mean age was 65.9

with 36% (n=211) aged 70+ at survey completion. Dex exposures were high-dose in 50% (n=290), low-dose in 12% (n=71), and no-therapy in 30% (n=177). The prevalence of cataracts was 63% for high-dose dex, 53% low-dose dex, and 51% no-therapy (p=0.025). Cataracts were asymptomatic in 43% (n=144), whereas 7% (n=23) of patients with cataracts reported resultant IADL limitations. The prevalence of glaucoma (7-11%, p=0.60) was comparable between the three dex groups, with 8% (n=4) of patients with glaucoma reporting IADL changes. Blepharitis or styes were reported by 23% (n=134), with 6% (n=8) of patients with blepharitis reporting resultant IADL limitations. Blepharitis was more common in bortezomib-exposed than bortezomib-unexposed patients (27% vs 20%, p=0.039). Other reported issues included dry eyes (39%, n=226), any type of orbital inflammation (2%, n=11), and retinal vascular occlusion (1%, n=6). With regard to eye health, 82% (n=476) reported seeing an optometrist or ophthalmologist at least once per year. Only 32% (n=170) recalled that an oncologist had recommended periodic eye exams. **Conclusions:** hile limited by recall bias and lack of longitudinal treatment exposure data, our cross-sectional study of over 500 patients living with MM illustrates the wide spectrum of ocular comorbidities and toxicities. Consistent with previous findings (Banerjee AJH 2024), higher dex doses are associated with greater rates of cataracts; however, dex dosing did not impact patient-reported rates of glaucoma. Blepharitis, often thought to be a rare toxicity of bortezomib, was reported by almost a quarter of patients even if bortezomib-unexposed. Interference with IADLs was fortunately infrequent. Our findings suggest that periodic eye exams, although inconsistently recommended by oncologists, are generally considered by patients living with MM to be a key component of supportive care.

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Real World Data on Efficacy and Safety of Low-Dose Direct Oral Anticoagulants (DOACs) for Venous Thromboembolism (VTE) Prophylaxis in Newly Diagnosed Multiple Myeloma

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Introduction: VTE risk is high in newly diagnosed multiple myeloma (NDMM) patients, especially within the first 6 months of treatment. SAVED and IMPEDE scores assess risk and NCCN guidelines recommend their use. Few studies explore thromboprophylaxis by risk category and induction regimen leading to varied treatments. We share our institutional experience using DOACs vs aspirin in NDMM patients and explore incidence of VTE, patient safety, and utility of SAVED and IMPEDE scores. **Methods:** NDMM patients aged 18+ from January 2018 to June 2022 were included. Those on anticoagulation for other indications or unable to safely take aspirin or DOACs were excluded. Primary outcome was VTE incidence in the first 6 months of therapy. Secondary outcomes were safety of low dose DOAC therapy, comparison of VTE scoring calculators (SAVED vs IMPEDE VTE), and patient and treatment factors. Fisher's exact test and Wilcoxon rank sum tests compared characteristics for 6-month VTE status. Subgroup analyses examined factors related to 6-month VTE incidence in patients that received daratumumab based induction, Carfilzomib, Lenalidomide, dexamethasone (KRD), all other induction regimens, and those with high risk cytogenetics. Major and minor bleeding were defined by the International Society on Thrombosis and Hemostasis (ISTH). **Results:** A total of 364 NDMM patients were included. Of these, 20% experienced VTE within 6 months. Of those who took aspirin, 20% had 6-month VTE. For DOACs, 21.2% had 6-month VTE. The overall cohort (P=0.96), subgroup analyses of patients who received daratumumab containing induction(P=0.82), KRD induction (P=0.51), all other induction (P=0.38), and those with high risk cytogenetics (P=0.70), showed no significant difference in 6-month VTE rate between aspirin or DOAC groups. Patients with SAVED score ≥2 or prior VTE history had significantly higher 6-month VTE rates in the overall cohort, those receiving regimens other than KRD or daratumumab containing induction, and those with high-risk cytogenetics (P< 0.01). Characteristics of age >80, sex, race, BMI >25, IMPEDE score, existing use of aspirin or low molecular weight heparin, or transplant status showed no significant difference in 6-month VTE in the overall cohort and in all subgroup analyses. There was a significant difference in minor bleeding with rates of 12.1% of the DOAC group and 2.5% of the aspirin group (P< 0.01). There was no significant difference in major bleeding events. **Conclusions:** This large review highlights real-world efficacy and safety of DOACs in NDMM. Choice of VTE prophylaxis didn't affect 6-month VTE rate, but DOAC use did cause more minor bleeding. Patients with SAVED score ≥2 and prior VTE history did have statistically significant increase in 6 month VTE rates overall and in all subgroups. Our study emphasizes that patient and treatment factors influenced 6-monthVTE incidence, while DOAC choice didn't. Trials evaluating risk-assigned thromboprophylaxis in patients with MM should build upon this data.

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Empowering Multiple Myeloma Patients: Impact of MMRF Education Programs and Results Of Patient Outcomes

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Introduction: Multiple myeloma is a rare, complex 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. **Methods:** The Multiple Myeloma Research Foundation (MMRF) focuses on accelerating novel therapies, driving personalized treatments, and empowering patients. To empower patients, the MMRF developed educational objectives within its programs. A longitudinal survey was created to measure positive behavioral changes based on the following objectives: Increasing understanding of standard treatments appropriate to disease stage. Enhancing understanding of and inquiry about research and clinical trials. Providing tools for self-advocacy and improved communication with care teams. In 2022 and 2023, 8,053 patients and caregivers participated in MMRF's educational programs, featuring myeloma specialists and covering topics from diagnosis to remission, presented in patient-friendly formats. **Results:** In 2022 and 2023, the MMRF distributed quarterly surveys to 7,232 patients and caregivers, yielding a response rate of 16.5% (n=1,200). 84% (n=1,005) reported taking actions towards their care including: Active Communication: 75% (n=753) pursued active communication with their healthcare team about treatment options and side effects. Confidence & Empowerment: 36% (n=361) felt more confident discussing treatment options with their doctor. Informed Decision-Making: 28% (n=289) accessed resources for informed decision-making. Engagement in Clinical Trials: 13% (n=129) communicated about, enrolled in, or participated in clinical trials. A survey limitation was multiple responses from the same individual. 166 respondents completed the survey in 2022 and 2023. **Conclusions:** Longitudinal and quarterly assessments are crucial for understanding multiple myeloma patients' needs. The MMRF's educational programs demonstrate impact, but research is needed to address gaps, including those hindered by barriers. Up to 15% (n=179) of respondents did not take further action due to distance to academic centers, access to a myeloma specialist, or support. Next steps for the MMRF include analyzing patient data to identify patterns across disease stages, attendance, and geography. A gap analysis will compare respondents who did not make positive changes. We also plan to expand support services for patients facing geographic barriers by leveraging our Patient Navigation Center, staffed by three oncology professionals. This center can provide support and knowledge sharing to assist patients in accessing services such as support groups, medical centers, and clinical trials. By conducting a comprehensive data analysis and enhancing services, we aim to empower more patients to take positive actions and ultimately improve their outcomes.

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PET/CT Has Prognostic Significance for CAR T Cell Therapy in Relapsed/Refractory Multiple Myeloma

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Introduction: Positron emission tomography–computed tomography (PET/CT) is pivotal in staging of multiple myeloma (MM), monitoring treatment response and detecting extramedullary disease (EMD). However, its prognostic role for heavily pretreated patients receiving CAR-T cell therapies is unclear. We retrospectively assessed PET/CT images of 53 patients who received commercially available CAR-T cell therapies at our center. **Methods:** Idecabtagene vicleucel (Ide-cel) was administered in 33 patients and Ciltacabtagene autoleucel (Cilta-cel) in 20 patients. PET/CTs were performed prior to lymphodepletion and retrospectively analyzed in joint sessions by 2 experts applying the four-eyes principle. Total metabolic tumor volume (MTV) was determined using a standardized uptake value (SUV) threshold adjusted to the degree of metabolic activity in order to precisely encompass the lesions. Response to CAR-T was assessed monthly according to IMWG guidelines. In 43 cases, follow-up (FU) PET/CT was available on day 30 (D30) after CAR-T re-infusion. **Results:** Fifty-nine percent of the patients prior to CAR-infusion showed focal FDG-avid lesions (FL). These patients were classified according to EMD status, with 23% of cases showing bone restricted osteolytic lesions, 11% had bone associated EMD defined as FL contiguous to bone but infiltrating stromal or soft tissue and 25% of cases with bone independent EMD defined as isolated extra-osseous FL. With a median FU of 11 [95%CI, 8-12] months, univariate COX-PH regression revealed that progression-free survival (PFS) was significantly affected by bone independent EMD (PFS: HR 3.8 [1.4-10.6], p=0.007), but not by bone restricted lesions (PFS: HR 1.3 [0.4-3.9], p=0.6), or bone associated EMD (PFS: HR 0.7 [0.1-2.8], p=0.7). Overall MTV ranged from 0 ml in PET-negative patients up to a value of 5313 ml. Optimal cut-point for was defined as 54,33 ml by ROC analysis (AUC=0.71). Patients with high MTV above this threshold had significantly worse PFS (log-rank test, p< 0.001). In multivariate analysis including the type of CAR-T as covariate, the negative prognostic value of bone independent EMD remained significant for PFS (p=0.01, OS: p=0.08). The proportion of initial responders defined as PR or better on D30 was equal amongst EMD groups (p=0.9). However, cases with bone independent EMD had a higher risk of relapse (OR=6, p=0.01). PET/CT on D30 revealed that 37.2% of patients were in complete metabolic remission (metCR), of which 69% were classified as CR, 25% as VGPR/PR and 6% as SD/PD by IMWG criteria. MetCR was associated with a trend towards improved PFS (log-rank test, p=0.06) and OS (p=0.12). **Conclusions:** PET/CT is of prognostic significance for risk stratification and response evaluation in MM patients treated with CAR-T cell therapy. PET/CT derived classification of EMD status shows that patients with bone independent EMD have

inferior outcomes to CAR-T cell therapy due to early relapses, which has important implications for future trial strategies.

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Assessment of Quality of Life, Frailty, Socioeconomic Status and Clinical Characteristics of Patients With Multiple Myeloma

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Introduction: Multiple Myeloma (MM) is more prevalent in the elderly population, with great morbidity and impact on patient's quality of life (QoL).The new advances in treatment shown recently do not benefit all patients, as socioeconomic inequality in access to diagnosis and treatment has been described, especially in countries like Brazil.At the same time, the elderly population has a higher rate of comorbidities and frailty, which can impact the choice of treatment, the intensity of adverse effects and the perception of QoL. **Methods:** This is a prospective study of patients over 18 years old with MM diagnosed since 03/01/2023 at Hospital Universitário Pedro Ernesto (HUPE).Clinical and sociodemographic data are collected from medical records. The International Myeloma Working Group (IMWG) Frailty Score for each patient is calculated.The EORTC QLQC30 generic quality of life questionnaire and the QLQ-MY20 multiple myeloma specific QoL module are applied at diagnosis, at the end of chemotherapy and after 100 days of hematopoietic stem cell transplantation.Responses to treatment are assessed according to the response assessment criteria suggested by the IMWG.The collected data is analyzed in SPSS 21. Descriptive analysis will be carried out and associations between QoL, socioeconomic status (SS), education, frailty, severity of presentation, clinical outcomes and QoL will be verified. **Results:** To date, data has been collected from 31 patients.60.7% are female, the median age at diagnosis is 65.5 years and the median time from onset of symptoms to diagnosis is 9.5 months.Approximately 74% were classified as social class C or lower, and 34.7% were classified as illiterate/incomplete elementary school. The distance between the patient's residence and the treatment site had a median of 30.5 (Km).Around 41% of patients were considered frail according to the IMWG frailty score.15 (53.5%) patients were treated with VCD protocol and 13 (46.5%) with VTD protocol. The overall response rate was 85.7%, 75% of which were Very Good Partial Response (VGPR) or higher. There have been 2 documented relapses.As of EORTC QLQC30, the median functionality score was 71.1 at diagnosis and 75.5 at the end of treatment (EOT). Patients also showed gains in QoL (median from 58.3 to 75). The scale of general symptoms had a median of 25.6 at diagnosis and 20.5 at EOT.Regarding the specific MM module, there was a reduction in the scale of symptoms related to the disease (median of 16.6 at diagnosis and 14.7 at EOT) as well as a gain in functionality (median of 58.3 at diagnosis and 66.6 at EOT). **Conclusions:** The results of the QoL scores seem to show a trend towards improved functionality, less symptom burden and better quality of life throughout treatment.Throughout the study, it is still expected to observe a correlation between frailty, SS and its relationship with the kinetics of QoL during treatment.

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Exploring the Role of the Combination of FDG PET Plus Whole Body MRI for Staging Newly Diagnosed and Relapsed/Refractory Multiple Myeloma: A Prospective Trial

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Introduction: The integration of FDG-PET/TC and WB-MRI in the diagnosis of MM may results in higher accuracy to detect bone lesion compared to them alone. This could be translated into better outcomes if early detection of myeloma defining events leads to earlier induction or re-induction treatments. **Methods:** In our Institution, from January 2021 to January 2023, we performed a prospective trial enrolling 73 consecutive newly diagnosed and relapsed/refractory MM (median age 63 years - range 85-35), according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET/CT. 31/73 (42%) had a newly diagnosed MM, 25/73 (34%) were in follow-up after autologous stem cell transplantation and 17/73 (23%) patients were affected by relapsed/refractory MM. Subsequently, in 2 cases WB-MRI were aborted and not diagnostic so patients were excluded from the final analysis. **Results:** In these 71 patients: 52/71 (73%) cases of concordance of WB-MRI and 18F PET-CT, 18/71 (25%) cases of discordance. In this group 15/18 (83%) cases FDG-PET/CT was negative and WB-MRI showed positive findings according to MYRADS criteria (5 micronodular pattern, 9 diffuse pattern e 1 focal pattern) (Figure 1 Newly diagnosed MM – diffuse pattern in WB-MRI, PET negativity), in 3/18 (17%) FDG-PET/CT was positive for focal lesions and WB-MRI was negative. IMWG criteria showed concordance with WB-MRI data in 16/18 (89 %), in 2/18 (11%) case of follow-up after autologous stem cell transplantation PET-CT showed a relapsed focal lesion while WB-MRI was negative. Accuracy of WB-MRI was 69/71 (97%), whilst PET-CT was 55/71 (77%). These results are in agreement with the literature data about the ability of WB-MRI to depict diffuse and micronodular pattern of bone marrow infiltration. **Conclusions:** Our preliminary results support a potential complementary role of WB-MRI and FDG PET/CT findings, on the management of patients with MM at both diagnosis and relapse. To date, there is no wide availability of WB-MRI because in concerning about costs and technical issues, but data are consistent with its possible future leading role in MM diagnostic work-up.

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Exploring the Role of the Combination of FDG-PET Plus Whole Body MRI for Staging Patients in High Risk Smoldering Myeloma: A Prospective Trial

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Introduction: According to IMWG criteria, Smoldering Multiple Myeloma (SMM) is an asymptomatic stage characterized by M-spike < 3 g/dl serum and/or bone marrow plasma cells infiltration between 10-59% in absence of myeloma-defining events and organ damage. In SMM setting, it is really important to differntiate high risk SMM (HR-SMM), in which treatment could be available thanks to clinical trials. 2016 IMWG criteria state that detection of bone lesions is mandatory for diagnosis of multiple myeloma and essential for diagnosis of SMM. It is really important to clarify in SMM the best imaging analysis in order to perform a correct diagnosis, and particularly it is necessary to define if the combination of FDG-PET/TC and WB-MRI could improve the assessment of lytic lesions and so the discrimination between high risk SMM and symptomatic MM. **Methods:** In our Institution we conducted a prospective trial, based on integrated new generation imaging, aiming to improve patients' stadiation and to define its prognostic implications. From January 2021 to January 2024, we performed a prospective trial enrolling 26 consecutive newly diagnosed high risk SMM, according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET-CT (median age 56; range 36-85). **Results:** Our comparison between WB-MRI and FDG PET-CT, showed a discordance between the two imaging modalities in 4/26 (15%) cases. In particular, in 3/26 (12%) cases WB-MRI showed bone lesions that have lead to symptomatic MM diagnosis according to IMWG criteria, while PET-CT was negative. In one case, PET-CT showed a diffuse uptake, not diagnostic for MM, while WB-MRI was negative. WB-MRI showed a 100% of accuracy in detecting SMM and MM. Therefore, WB-MRI has lead to a modification of the prognosis and treatment approach (observation in SMM vs treatment in symptomatic MM) in 3/26 patients (11%) (i.e. Figure 1, with DWI of C2 lesion). Furthermore, in 5/23 (22%) cases of confirmed SMM WB-MRI showed a slight diffuse alteration pattern of bone marrow without any overt lytic bone lesion, which could be a potential prognostic evidence. **Conclusions:** Our results support a fundamental role of WB-MRI in combination with FDG PET/CT in the stadiation of patients with newly diagnosed high risk SMM, which could modify prognosis and treatment, improving the differentiation with symptomatic MM. In particular, combination of WB-MRI plus FDG PET/CT could be more accurate in the detection of bone lesions than FDG PET/CT alone, being able to anticipate symptomatic MM diagnosis and consequently its treatment. Moreover, a diffuse pattern of marrow involvement could be detected in some HR-SMM patients without any overt lytic lesions: it is questionable if this group of patients is associated with a rapid progression in lytic lesions and so in symptomatic MM diagnosis. Prospective data on evolution of these patients are pending.

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Gastrointestinal Histoplasmosis in a Patient With Multiple Myeloma After Autologous Bone Marrow Transplantation: Oral Ulcer Differential Diagnosis. Case Report

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Introduction: Introduction/Background:Histoplasmosis is an opportunistic fungal disease caused by Histoplasma capsulate. In immunocompetent patients, it is generally asymptomatic. However, in immunocompromised host it can cause different clinical subtypes as pulmonary, disseminated, or gastrointestinal presentation. Immunocompromised patients, such as those with hematological malignancies, can be infected by Histoplasmosis and the prognostic is poor if several organs are affected. The incidence of histoplasmosis after HSCT is believed to be rare. There are few reports in the literature of histoplasmosis infection in Hematologic patients in patients who underwent autologous bone marrow transplantation (BMT) has been described. Mainly in non-endemic areas of the disease. The purpose of this case report is to highlight the importance of histoplasmosis in the differential diagnosis of those patients with a clinical history oral ulcers and non bacterial diarrhea. Outside endemic areas it might be under diagnosed even in immunocompromised patients so it could be a challenging diagnosis. The present case highlights the unusual, but possible, clinical scenario of Histoplasmosis gastrointestinal involvement after autologous stem cell transplant in a Myeloma patient. **Methods:** NA. **Results:** Case: P.H.D.S.M, male, 52 years old, with light chain (Kappa) multiple myeloma, ISS3 B treated with Daratumumab, Bortezomib, Lenalidomide and dexamethasone (DVD) 6 cycles and Autologous Stem cell transplant. On the 65th day after transplant he presented diarrhea, fever and multiple shallow oral mucosal ulcers, with a yellowish fibrinopurulent background with painless perilesional hyperemia. It was suspected to be Cytomegalovirus infection (CMV), despite negative quantitative PCR test. Oral and GI biopsy were performed and he was started on venous ganciclovir treatment. The oral biopsy result showed no viral inclusion but ulcered lesion infiltrated by neutrophils, lymphocytes and macrophages. The Macrophage cytoplasm showed many roundish structures compatible with Histoplasma Capsulatum. Gancyclovir was changed to Liposomal Amphotericin B. The patient improved diarrhea resolved and oral ulcers healed. **Conclusions:** Conclusion: We report a case of gastrointestinal histoplasmosis infection in a Myeloma patient after autologous stem cell transplant and DVD treatment. Thus, we recall the attention for

the importance of histoplasmosis suspicion as a differential diagnosis in patients undergoing stem cell transplant and possibly the impact of new immunotherapies for MM treatment.

P-110

Guillain-Barré Syndrome Following Autologous Stem Cell Transplantation for the Treatment of Multiple Myeloma: A Myth?

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Introduction: Guillain-Barré syndrome (GBS) is an acute autoimmune peripheral neuropathy characterized by inflammation of peripheral nerves, leading to progressive muscle weakness, paresthesia, and, in severe cases, paralysis that may require respiratory support. Although typically preceded by a viral or bacterial infection, a dysfunctional immune response triggers an inflammatory reaction directed against peripheral nerves. The exact mechanisms remain unclear, but are thought to involve a cross-reactive immune response to neural antigens shared between the exogenous agent and the nerves. Plasma cell disorders are frequently associated with neurological pathologies such as peripheral neuropathies. However, the occurrence of Guillain-Barré syndrome is rarely associated with multiple myeloma (MM), and even rarer after autologous hematopoietic stem cell transplantation. **Methods:** We present the case of a 65-year-old patient with a previous history of ischemic heart disease, treated for a lambda light chain ISS1 MM who achieved VGPR after 4 induction cycles of daratumumab-bortezomib-lenalidomide-dexamethasone, but who complained of bortezomib-induced sensory polyneuropathy. Autologous stem cell transplantation (ASCT) was complicated by Streptococcus agalactiae bacteremia, severe malnutrition, and muscle wasting, with recovery from aplasia by day 12. On Day 20 post-transplant, the patient experienced gait disturbances and peripheral paresthesia, initially attributed to peripheral amyotrophy and post-bortezomib polyneuropathy. By Day 26, gait disturbances worsened, with distal paresis of both lower limbs and absent deep tendon reflexes. The patient was admitted to the Neurology unit, where a thorough evaluation was conducted, resulting in the diagnosis of Guillain-Barré syndrome with no specific etiology identified. The infectious workup returned negative. The patient received immunoglobulins for 5 days and underwent intensive rehabilitation, resulting in partial neurological recovery. Three months after ASCT, he began maintenance therapy with daratumumab and lenalidomide without recurrence of the neurological condition. **Results:** The occurrence of GBS post-ASCT in MM consolidation treatment is very rare and poorly documented, though isolated cases in literature have noted its possible implication. The underlying mechanism may be mixed and related to immune reconstitution post-autograft. Pre-existing sensory polyneuropathy due to bortezomib poses both a risk and a confounding factor. While bacteremia with S. agalactiae is not commonly linked to GBS, it may have played a triggering role in conjunction with immune reconstitution post-ASCT. **Conclusions:** This case underscores a rare autoimmune neurological complication of stem cell transplantation, prompting inquiries into diagnosis, appropriate management, especially in highly immunocompromised patients, and presenting confounding factors.

P-111

An Orthopedic Consultation and Exercise Intervention in Patients With Multiple Myeloma During Induction Therapy: The Randomized Controlled GMMG-HD8-INDEX Trial

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Introduction: Osteolytic lesions are a hallmark of multiple myeloma (MM) and compromise stability of the skeletal system. Particularly during induction therapy, MM activity is still high with an increased risk of fractures. Thus, there are uncertainties whether and to which extent physical activity is possible. Our objective is to evaluate safety and feasibility of an exercise intervention during induction therapy, as well as effects on bone regeneration in a prospective, randomized controlled trial. The study is ongoing and first results will be presented. **Methods:** So far, 26 transplant-eligible patients with newly diagnosed MM, who underwent 18 weeks of induction therapy with isatuximab, lenalidomide, bortezomib and dexamethasone (Isa-RVd) were recruited. All patients received an orthopedic consultation on bone stability and activities of daily living. Patients were randomized 2:1 to exercise intervention or standard of care. The intervention group received an individualized exercise plan for whole body resistance training with particular emphasis on core and leg muscles. Patients were monitored weekly via an online training platform and orthopedic follow-up examination was performed at least once during every treatment cycle. Fracture rate was determined on CT- or PET-CT-scans at initial diagnosis (T1) and after induction therapy (T2). Serum and bone marrow samples were collected at both timepoints in order to evaluate effects of an early exercise intervention on bone regeneration. **Results:** At diagnosis, vertebral compression fractures were detected in 50% of patients. Spinal bracing was necessary in 12%, radiotherapy in 27% and kyphoplasty and/or surgical stabilization of the spine in 12% of patients. Concerning exercise feasibility, 71% of patients were able to perform at least 24 of 36 training sessions during

induction therapy. In the other patients, regular exercise was not possible, mainly due to infections and poor general condition. No injuries or other adverse events were reported in association with exercise. CT-scans at T2 showed new vertebral compression fractures in 3 patients. All of these patients were assigned to standard of care. No new fractures were detected in the intervention group. Immunohistological evaluation of bone marrow samples showed enhanced bone remodeling in patients who exercised regularly. **Conclusions:** Our first results indicate that an exercise intervention based on an orthopedic evaluation of bone stability is safe during induction therapy for patients with newly-diagnosed MM. However, patients need to be monitored closely and exercise plans should be adapted to individual clinical conditions.

P-112

Fall Risk Assessment and Fall Prevention in Patients With Multiple Myeloma: First Results of the MYFALL-Trial

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Introduction: The risk of falling is increased in elderly cancer patients and might lead to functional decline, loss of independence and hence quality of life. Several disease- and therapy-associated symptoms, for example sarcopenia, impaired mobility, peripheral neuropathy, and fatigue are linked to an increased fall incidence. Aim of the MYFALL-trial is to identify risk factors for falls and underlying causes of gait impairment in patients with multiple myeloma (MM) and includes an individualized exercise intervention for fall prevention. **Methods:** In the first part of the MYFALL-trial, a fall risk assessment was conducted. Patients with MM (n=82) who had undergone at least 6 months of systemic treatment were questioned about fall incidents, gait impairment and musculoskeletal pain. Questionnaires were used to assess peripheral neuropathy (EORTC-CIPN-20), fear of falling (FES-I), fatigue (MFI), and sarcopenia (SARC-F). Additionally, three mobility tests (timed-up and go (TUG), 30s chair rise and gait speed) were performed, as well as the MoCA-test to evaluate cognitive impairment. **Results:** Patients‘ median age was 68y and 63% were male. Overall, 55% of patients experienced gait impairment. Underlying causes were most often attributed to fear of falling (31%), balance/coordination problems (36%) and numbness of the feet (44%). In patients with gait impairment questionnaire-results in the following categories were significantly higher: age, peripheral neuropathy (sensory, motor and autonomic symptoms), fear of falling, and sarcopenia (all $p< 0.05$). Moreover, mobility (TUG) was reduced (mean 11.7s, $p< 0.05$) and the number of patients experiencing musculoskeletal pain was significantly higher (82%, $p< 0.05$). Among patients with gait impairment 33% reported falls in the last 12 months. In these patients tests for sarcopenia and mobility differed significantly, as was reflected by SARC-F score ≥4 and increased TUG (mean 15.3s). **Conclusions:** Gait impairment occurs frequently in myeloma patients and seems to be of multifactorial etiology. Advanced age, peripheral neuropathy, fear of falling, sarcopenia and reduced mobility are contributing factors. Of note, the incidence of musculoskeletal pain was particulary high in these patients, which is a known risk factor for falls. According to our results, further deterioration of muscle strength and decline in mobility are the decisive factors which eventually lead to fall incidents in patients with gait impairment. Part 2 of the MYFALL-trial will address these underlying issues by means of an exercise intervention consisting of resistance and balance training (including perturbation-based training) for fall prevention in myeloma patients.

P-113

An Artificial Intelligence-Based 3D-Segmentation Assessment of Sarcopenia Utilizing Whole-Body Computed Tomography in Patients With Multiple Myeloma

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Introduction: Sarcopenia is characterized by loss of muscle mass and strength, resulting in functional limitations and an increased risk of falls, injuries and fractures. Aim of this study was to obtain detailed information on skeletal muscle changes in patients with multiple myeloma (MM) during treatment. Therefore, an artificial intelligence-based 3D-segmentation method was established to assess entire muscle groups. **Methods:** Patients diagnosed with MM (n=51) who had undergone both initial (T1) and follow-up (T2) whole-body low-dose computed tomography acquisition prior to induction therapy and post autologous hematopoietic stem cell transplantation were examined retrospectively. Muscle volume (MV) and intramuscular adipose tissue volume (IMAT) of the autochthonous back muscles, the iliopsoas muscle and the gluteal muscles were evaluated. The tools TotalSegmentator and AutoMatiCA were combined with a separate python script. Subsequently, an artificial intelligence-network was trained in order to obtain a fully automated 3D-segmentation assessment. **Results:** Patients‘ median age was 58y, 38 were male and follow-up

CT-scans were performed after a mean of 11.8 months. Changes in MV and IMAT correlated significantly with body mass index (BMI, p< 0.0001). Patients (n=28) with a decrease of BMI (mean -2.2 kg/m2) during therapy lost MV (T1: 3419cm3, IQR 3176-4000cm3 vs. T2: 3226cm3, IQR 3014-3662cm3, p< 0.0001) whereas patients (n=20) with an increased BMI (mean +1.4 kg/m2) showed an increase of IMAT (T1: 122cm3, IQR 96.8-202.8cm3 vs. T2: 145.5cm3, IQR 115-248cm3, p=0.0002). Loss of MV varied between different muscle groups and was most prominent in the iliopsoas muscle(-9.8%) > gluteus maximus(-9.1%) > gluteus medius(-5.8%) > autochthonous back muscles(-4.3%) > gluteus minimus (-1.5%). Increase of IMAT in patients who gained weight was similar between muscle groups. **Conclusions:** The artificial intelligence-based 3D-segmentation process is a reliable and time-saving method to acquire in depth information on sarcopenia in MM patients. Loss of MV and increase of IMAT were reliably detectable and associated with changes in BMI. Loss of MV was highest in muscles with more type 2 muscle fibers (fast-twitch, high energy) whereas muscles with predominantly type 1 fibers (slow-twitch, postural control) were less affected. In order to acquire additional information on physical function and training effects, we are currently using this 3D-segmentation method in a randomized controlled trial on an exercise intervention during induction therapy.

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Multiple Myeloma Associated With Other Primary Malignant Neoplasms: Epidemiological Characteristics Over 20 Years of Hospital Cancer Registry

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Introduction: Multiple myeloma, a rare disease accounting for 1-2% of global neoplasms, is diagnosed through clinical examination and IMF criteria, with incidence increasing with age. Treatment includes medications and sometimes autologous bone marrow transplantation, significantly improving prognosis and survival rates. Advances in treatment have led to deeper, lasting responses, but also highlight the importance of studying other primary neoplasms influenced by patient, disease, and treatment factors. Descriptive epidemiological studies are essential to identify patterns and formulate analytical hypotheses in cancer. **Methods:** This study examines the sociodemographic, epidemiological, and clinical profiles of patients with myeloma and other primary malignant neoplasms treated at the AC Camargo Cancer Center between 2000 and 2021. It analyzes common neoplasms associated with myeloma, focusing on their topography, morphology, and diagnostic timing. Using ACCCC Registry data, the retrospective study excludes non-melanoma skin cancer and explores variables like sex, age, and types of neoplasms, along with their temporal relationship to myeloma diagnosis. **Results:** A total of 79 records were analyzed, with 69 deemed valid for epidemiological analysis of myeloma linked to other primary neoplasms. The median age at myeloma diagnosis was 69 years, ranging from 48 to 91 years. Prostate adenocarcinoma was the most common primary neoplasm at 25%, followed by breast neoplasms at 17% and colon adenocarcinoma at 16%. Non-Hodgkin lymphomas accounted for 12% of cases, making them the most prevalent neoplasms.Analysis revealed that 21.7% were diagnosed with myeloma before another neoplasm, 59.4% were diagnosed with a primary neoplasm before myeloma, and 18.8% were diagnosed simultaneously with both, underscoring the importance of ongoing monitoring for cancer patients due to the potential development of additional neoplasms. **Conclusions:** Conducting descriptive studies with an epidemiological profile is extremely important, especially in the field of cancer. This approach allows for a detailed survey of the population, identifying patterns that, in turn, enable the formulation of analytical hypotheses. In the specific context of multiple myeloma, where patient survival has increased due to current treatments and disease-related prospects, such studies gain significant relevance. This is due to the emerging occurrence of other primary neoplasms in this population, making it imperative to understand these phenomena to improve management and care strategies.

P-115

Safety of a Cannabis-based oil for patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation: protocol of a phase I/II study

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Introduction: Autologous stem cell transplantation is associated with symptoms that deeply impact quality of life of patients living with Multiple Myeloma (MM). Cannabis based products are used to mitigate adverse events related to cancer, yet safety data regarding its use among patients receiving high intensity chemotherapy is not available. Currently under Brazilian regulation, CBD-based products are allowed to be commercialized as long as THC concentrations don't exceed 0,2%. **Methods:** Study Design, Intervention and Sample Size: this is a phase I/II clinical trial of cannabis sativa stratum 160,3 mg/mL (Green Care ®, CBD 90 mg/mL, THC 2,3 mg/mL). During phase I, we will follow a classic 3+3 design to access the maximal dose. The target dose for each cohort will be 50 mg for cohort A, 100 mg for cohort B, 200 mg for cohort C and 300 mg for cohort D. The stratum will begin 7 days prior to HSCT admission and concluded 15 days after hospital discharge. At phase II, the maximum tolerated dose will be administered to 15 patients, in order to gauge the treatment's efficacy. Therefore the study will enroll up to 39 patients. Primary Outcome: dose limiting toxicities (hepatotoxicity, psychotropic effects or 'high', hallucinations or delirium, psychosis and paranoia, agitation, major depressive episode, mania or hypomania, incapacity to reach target dose). Secondary Outcomes: quality of life (accessed with EORTC QLQ-30 and EORTC MY-20 surveys), nutritional outcomes (body weight and albumin levels), dietary intake (% of calories and proteins prescribed

by a dietitian), highest grade mucositis, requirement of anti-emetics, requirement of painkillers, hospital discharge, neutrophilic engraftment, platelet engraftment, admissions to the ICU, febrile neutropenia and documented infections. Ethical Considerations: the study is currently approved by the institution's board review (IBR). **Results:** Current Status: the study will start accruing patients in June 2024. **Conclusions:** The current study aims to provide data on safety regarding the use of a CBD for symptom management for MM patients underfoing HSCT.

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Chemotherapy Related Nausea and Vomiting Prophylaxis With Aprepitant for Patients Receiving High Dose Melphalan Followed by HSCT: A Cost Utility Analysis (CUA)

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Introduction: patients that receive myeloablative doses of melphalan are considered to be at high risk for chemotherapy induced nauseas and vomiting (CINV). A combination of aprepitant, granisentron and dexamethasone is more efficacious than the combination of only anti 5-HT and corticosteroids. The objective of the present CUA is to define the cost-effectiveness of triplet anti-emetic regimen from a private health care provider perspective. **Methods:** A Markov model of 4 states (complete response and three states of nausea) was developed to compare a triplet (NK1, 5-HT, Corticosteroids) with a double (5-HT, Corticosteroids) for expected costs and outcomes. The transition probabilities were estimated from a prior randozimed controlled trial (Schmitt et al., J Clin Oncol, 2014). Model assumptions were that a patient would never 'come back' from a previous nausea estate, costs with medication were estimated with Brazilian currency according to maximum prices allowed by sanitary authorities. The comparator strategy of doublet did not include aprepitant as a rescue option. We also calculated the cost per additional patient on complete response at 7 days as well as the cost per patient-day in complete response. **Results:** Seven days after a single day infusion of melphalan, 63% patients receiving the a triplet prophylactic regimen remained in complete response (that is the absence of nausea or vomiting) as compared to 21% of patients receiving a doublet regimen. The use of aprepitant at a mean cost of R$ 351,00 resulted in an overall mean increment of 0,014 gain in quality of life adjusted year. The incremental cost effectiveness ratio was R$ 22.281,63/QALY. The cost per additional patient on complete response at 7 days was R$ 777,10 and the cost per patient day in complete response was R$ 144,39. **Conclusions:** The result of the present CUA suggest that aprepitant is cost-effective for the prevention of CINV given a commonly accepted willingness to pay threshold of R$ 100.000/QALY.

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How Do Patients Feel About How, When and Where They Get Their Treatments? A European Survey of Myeloma Patients

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Introduction: Myeloma patients may undergo many different types of treatment over the course of their cancer. There is already a high burden on patients due to the myeloma diagnosis, complications, and side-effects of treatments. We need evidence about how people feel, and what they prefer, about how treatments are administered (i.e. intravenous, subcutaneous, or oral routes of administration) and where (i.e. at home, in the community, or in a hospital). This survey aimed to explore perspectives of myeloma patients across Europe. **Methods:** Data was collected through an online survey disseminated by myeloma patient organisations in the Netherlands, Germany, Norway, Poland, Portugal, Ireland, France, and Israel and through a European network of myeloma patient organisations. The survey was available in 8 languages. Dissemination of the survey links occurred through social media, patient organisation distribution lists, newsletters, emails, flyers and face-to-face at support groups. Patients' attitudes to different treatment types were captured on a scale of 1 (entirely negative) to 10 (entirely positive). Perceived burden of treatments was assessed on a scale of 0 (no burden) to 10 (considerable burden) with items related to frequency, effort, physical, daily life, family life, and financial burden. **Results:** We received responses from 901 patients from 22 countries. Almost half (47%) of respondents had received 1 line of therapy, 26% had received 2 lines, 11% had 3, and 13% had 4 or more lines. Patients held the most positive attitudes towards oral treatments taken at home (mean 8.2, standard deviation 2.2). Patients were more positive about subcutaneous treatment as an out-patient (mean 7.0) than subcutaneous treatments at home whether delivered by a family member or friend (mean 5.8), by themselves (mean 6.0) or by health professionals (mean 6.8). Intravenous treatment had the highest reported overall burden (mean 30.1) and oral had the least (mean 18.7). The most burdensome aspect of intravenous treatment was reported to be the impact it had on daily activity and daily life. Patients reported the most important features of myeloma treatment to be the physical impact and the impact on day-to-day activities. **Conclusions:** This research provides insights into myeloma patients' attitudes towards, and the differential burden experienced from, different treatment modalities. Contrary to what might be expected, home was not always the most positively regarded location for treatment. The likely physical impact of treatment and the potential impact on daily life should be discussed up-front with patients during treatment decision-making.

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Real-Life Data on Patients With Multiple Myeloma (MM) and Initiative To Implement MM Oncology Navigation in the Macro-Region of Araçatuba-SP

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Introduction: Multiple Myeoloma (MM), an incurable malignant neoplasm, accounts for approximately 10% of hematological neoplasms, and according to records from the World Health Organization (WHO) it was responsible for more than 170,000 new cases and 66% of deaths overall. The National Navigation Program for People Diagnosed with Cancer was incorporated with Law No. 14,785 of December 2023 of the National Cancer Policy, its purpose is to offer continuous care to cancer patients, as well as their caregivers and family members, which will from the onset of symptoms to the follow-up of treatment, aiming to overcome barriers in the diagnosis and treatment of the disease. **Methods:** Objectives: Real-life data from patients with MM being monitored at Unacon da Santa Casa de Araçatuba (SCA) and identification of barriers in diagnosis from primary to tertiary care for future implementation in an unprecedented way in Brazil within the macro-region of Araçatuba-SP. Methods: The epidemiological profile, disease characteristics and treatment data were analyzed in 34 patients with MM followed in 2024 (January to April) within the SCA Unacon. The NICE (United Kingdom health system) cancer diagnosis and monitoring alarm system was adapted to the Brazilian reality of the Araçatuba-SP macro-region to begin the implementation of oncology navigation. **Results:** Of the total of 34 patients, there was a slight predominance of males (53 vs. 47%) and a median age of 69.5 years. The ISS was divided into I of 23.53%, II of 17.65%, III of 32.35% and undefined of 26.4% with 11.8% of extramedullary disease at diagnosis. Based on the APAC procedure code there were 67.6% of patients on 1L chemotherapy, 20.5% on 2L or more and 11.9% on palliative care with 11.76% receiving autologous consolidative HSCT. The most used induction protocol was CyBord and only one patient was on lenalidomide maintenance. In an attempt to reduce barriers to rapid diagnosis and treatment, we identified as a possible "red flag", the use of serum protein electrophoresis (SPE) in all patients in primary and/or secondary care who present non-deficiency anemia, a disease progressive and/or unexplained renal failure and persistent bone pain with or without suggestive radiological imaging. **Conclusions:** Real-life data from MM in the macro-region of Araçatuba-SP confirm those from GBRAM, especially in the SUS scenario, with advanced disease at diagnosis, very low percentage of consolidation HSCT and restricted access to effective treatments. Initial approach with SPE in suspected cases, followed by the implementation of oncology navigation in MM, using all SUS equipment; teaching/assistance partnership; regulation will bring a new reality to the care of patients with MM in the macro-region of Araçatuba-SP.

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Treatment Outcomes of Primary vs. Referred Patients with Multiple Myeloma Receiving Talquetamab or Teclistamab

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Introduction: Recent approval of bispecific t-cell engagers (BiTEs) provides novel treatment options with impressive response rates and durability in the relapsed/refractory multiple myeloma (MM) setting. These therapies require Risk Evaluation and Mitigation Strategies (REMS) training and requirements for monitoring and management of cytokine release syndrome (CRS) and neurotoxicity (NT) that may not be available to community providers. To overcome these barriers, we created partnerships allowing patients to receive initial step-up dosing at the University of Rochester Medical Center (URMC) along with ongoing telemedicine visits to help manage toxicities as patients returned to referring providers for continued therapy post step-up.We sought to understand the impact of these partnerships on outcomes of primary academic versus referral patients with a goal of reaching underserved populations and achieving similar outcomes for all patients. **Methods:** We identified patients using prescription data for teclistamab or talquetamab. Patient and disease characteristics were collected using manual chart extraction and included creatinine (Cr), hemoglobin (Hgb), disease state (free light chains and paraprotein levels), lines of prior therapy, time from diagnosis to first dose, race and age. Zip codes for the patient's primary address classified them as urban versus rural using the website Rural Health Information Hub (https://www.ruralhealthinfo.org). Rate and grade of CRS and NT, number of hospitalizations, progression free survival (PFS) and overall survival (OS) in patients receiving talquetamab or teclistamab from the time of FDA approval through December 31, 2024, were assessed through May 17, 2024. Referred patients who did not receive therapy were excluded, these patients were either too ill to receive therapy or chose not to receive therapy. Continuous variables were compared via the non-parametric Wilcoxon rank-sum test, categorical variables with Fisher's exact test and OS and PFS were compared using the log-rank test. **Results:** Data was collected on 43 patients. Rural zip codes were significantly higher in referred (N=20) than primary (N=23) patients (p=0.048). Hgb levels were significantly higher in primary patients (p=0.04) at therapy initiation. Referred patients tended to be older and with more advanced disease as found by higher Cr, FLC and paraprotein values, though there was insufficient evidence of a difference between the groups at an alpha=0.05 level. Secondary hospitalization rates between the groups were similar and no referral patients required a return to Rochester after discharge. There was insufficient evidence of a difference in the OS and PFS between the groups, these will be updated for longer follow-up. Updated hospitalizations will be collected for future analysis. **Conclusions:** Results suggest partnerships between academic and community providers can expand access of novel therapies to underserved, rural patients without increased toxicity or compromised patient outcomes.

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Diagnostic Value of Echocardiography in Multiple Myeloma Complicated with Cardiac Amyloidosis

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Introduction: A single-center, real-world retrospective study to investigate the clinical characteristics of multiple myeloma (MM) complicated with amyloidosis (AL), particularly cardiac amyloidosis (CA), and the diagnostic value of 2D-STI echocardiography to provide guidance for early screening and identification of MM complicated with CA were conducted in the first affiliated hospital of Soochow University from August 2017 to December 2023. **Methods:** This study enrolled 190 NDMM patients. According to histopathological results, the patients were divided into MM(125) and MM-AL(65) group, and MM-AL patients were divided into CA(20) and non-CA(45) subgroup based on the criteria for AL cardiac involvement. Comparative analysis of baseline clinical data was conducted to understand the clinical characteristics of MM-AL patients. Variables potentially predictive of CA diagnosis were selected from univariate analysis and tested the accuracy by calculating the AUC. Binary classification of each variable was conducted based on cutoff values, and a multivariate logistic regression model was established using these variables. **Results:** Comparative analysis revealed a lower proportion of bone pain as the presenting symptom in MM-AL patients (44.6% vs 68.8%, P=0.001), while the proportion of congestive heart failure was higher (10.8% vs 3.2%, P=0.048). MM-AL patients had a lower proportion of DS stage III (83.1% vs 95.2%, P=0.013), a higher proportion of frailty (44.6% vs 28.8%, P=0.029) and polyserositis (26.2% vs 4.8%, P< 0.001). Kappa light chain type predominated in MM patients (54.4%), and lambda type predominated in MM-AL patients (64.6%). Low QRS and infarct patterns were observed in MM-AL patients, but not in MM patients(0% vs 7.7%, P< 0.001). CA patients had elevated levels of NT-pro BNP and hs-TnT, relatively higher VEGF, and lower BM plasma cell proportion, and a higher incidence of low QRS(20.0% vs 2.7%, P=0.014), ST-T changes (50.0% vs 13.5%, P=0.002), and false infarction (20.0% vs 2.7%, P=0.014). CA patients increased in LA diameter, IVSd, LVPWd, RWT, E/e', PASP, and decreased in LVEF, GLS. There was a higher proportion of patients with hydropericardium(55.0% vs 10.8%, P< 0.001), NYHN grade III-VI(40.0% vs 6.7%, P=0.001), and major adverse cardiovascular events(30.0% vs 2.7%, P=0.013). In MM-AL patients, the model with LVEF, PASP, hydropericardium, and GLS as explanatory variables had the highest diagnostic accuracy for CA, with an AUC of 0.90 (95% CI: 0.81-1.00)(sensitivity: 95.6%, specificity: 80.0%, accuracy: 90.8%). **Conclusions:** The clinical characteristics of MM with CA patients differ from MM patients. The sensitivity and specificity of the multivariate logistic regression model proposed in this study are favorable, providing a tool for early clinical screening and identification of MM complicated with CA.

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Prevalence of Multiple Myeloma in Ecuadorian Hemodialysis Units. A SEN Study

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Introduction: More than half of MM patients suffer renal impairment, often presenting with acute injury due to cast nephropathy, light chain deposition, or amyloidosis. Though long-term hemodialysis is uncommon in MM patients, it greatly affects their quality of life and survival. The 2022 Ecuadorian Ministry of Public Health's "Information Bulletin: Patients in Renal Replacement Therapy (RRT)" lacks data on MM patients in hemodialysis units. Our survey addresses this by reporting the prevalence of MM patients on hemodialysis in Ecuador for the first time. **Methods:** This observational, cross-sectional study reports the prevalence of patients diagnosed with MM and end-stage kidney disease in hemodialysis in Ecuador. A survey was developed which was distributed to Ecuadorian nephrologists, and their respective institutions, through the support of the Sociedad Ecuatoriana de Nefrología (SEN). Data acquisition. The collected information included the total number of patients in hemodialysis units, the number diagnosed with MM, and the type and location of each unit.Statistics. Specific prevalence was calculated using the following equation: Prevalence = (Number of Patients with MM treated in the hemodialysis unit / Total number of patients treated in the hemodialysis unit by any cause [N]) x1000Additionally, we included 95% confidence intervals (95%CI) for prevalence. Sample. The sample to estimate the minimum number of patients required for this analysis (2744) was calculated based on the equation n=Nz2pq/(d2(N-1) + z2pq) where N was 21780 (Total Ecuadorian population in hemodialysis), using an acceptable error of d = 1%, z of 2.58, and an expected prevalence (p) of 5% based on a previous report. **Results:** In this study, conducted across ten Ecuadorian cities, 22 nephrologists from 21 institutions (Public 30%, military 10%, and private 60%) contributed data on a collective total of 2979 patients undergoing hemodialysis. Among these patients, 43 were diagnosed with myeloma. This corresponds to a relative frequency of 1.4%. and a prevalence rate of 14.4 cases per

1000 hemodialysis patients (95%CI 10.1 to 18.7). The prevalence of myeloma varied across cities. Sucúa had the highest rate at 4.44%, followed by Ambato at 3.81%. Guayaquil and Portoviejo had rates of 1.28% and 3.08%, respectively. Quito reported 0.76%, Manta 0.46%, and Ventanas, Ibarra, and Daule had rates around 1.11% to 1.31%. Riobamba recorded no cases. **Conclusions:** Our study provides the first prevalence data on MM patients undergoing hemodialysis in Ecuador, revealing significant regional variations. Sucua exhibited the highest prevalence, while Riobamba recorded no cases. This underscores the need for tailored healthcare strategies to address MM-associated renal complications across diverse regions. Future goals include expanding the survey, analyzing the clinical characteristics of this population, and extending this initiative to Latin American Hemodialysis Units.

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A Comprehensive Analysis of Jawbone Destruction in Multiple Myeloma: Tomographic Perspectives from a Series of Cases

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Introduction: Multiple myeloma (MM) is a hematologic neoplasm that affects bone metabolism and causes osteolytic lesions. Cone beam computed tomography (CBCT) demonstrates excellent performance in detecting and characterizing these lesions when involving the skull. It is a low-cost examination that emits low doses of radiation compared to other tomographic modalities. This study aimed to present the various patterns of maxillary bone destruction observed in CBCT images of 27 MM patients, acquired at different time points after diagnosis, and to establish correlations with clinical data. **Methods:** For the evaluation and characterization of lesions, multiplanar reconstructions were chosen, with the application of enhancement filters. Four distinct patterns of bone destruction were detected: diffuse, multilocular, unilocular, and perforated. **Results:** The study sample consisted of 48% female and 52% male patients, with a mean age of 56.5 years. The diffuse pattern predominated, affecting both maxillae. Multilocular and unilocular patterns were identified in 50% and 22.2% of cases, respectively, with the condyle being the most affected region. Perforated lesions were not observed in any case. Clinical data revealed that 37% of cases met the IIIA criteria and 37% met the IIIB Durie Salmon criteria. Bone lesions in more than 3 locations of the body or the presence of fractures were identified in 50% of cases. Osteonecrosis in the maxillae was reported in only 1 case. **Conclusions:** No significant relationship was observed between clinical characteristics and the identified tomographic patterns of bone destruction. The absence of perforated lesions may be attributed to three-dimensional visualization, revealing a diffuse pattern extending from cortical to trabecular bone structures.

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Patient Preferences for use of CAR-T therapy as an Early Line Treatment in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a generally incurable, heterogeneous disease affecting >35,000 patients annually in the United States (US). Chimeric antigen receptor T-cell (CAR-T) therapy, a novel treatment with demonstrated depth of response and durability, is now approved for patients as early as 2nd line (2L). Recent data from CARTITUDE-4 and KarMMa-3 show meaningful benefits in clinical and health-related quality of life metrics over current options for patients in earlier lines. However, patient preferences for the use of CAR-T in early lines remain unclear. Therefore, the objective of this study was to evaluate patient preferences for early-line CAR-T therapy use in MM. **Methods:** Patients with relapsed or refractory MM from the US, who had completed ≥1 line of treatment, were recruited via convenience sampling to participate in a cross-sectional survey between December 2023-March 2024. The survey included a Discrete Choice Experiment (DCE) comprised of a series of choice tasks in which patients chose between 2 hypothetical 2L treatment profiles. These profiles varied on 7 treatment attributes: median progression free survival (mPFS), median overall survival (mOS), treatment response, serious adverse events (SAEs), neurological events, cytokine release syndrome (CRS), and treatment administration (i.e., one-time infusion vs. various routes and schedules for agents). Attributes and levels were selected based on a targeted literature review, clinical data on standard 2L therapies in MM, including CAR-T, and insights gathered from patient focus groups. Patient characteristics were described, and attribute-level preference weights were estimated using hierarchical Bayesian modeling. **Results:** The sample comprised 127 patients with a mean age of 67 years. Most patients were female (54%), White (61%) and on active MM treatment (96%). The majority had received 2 lines of therapy (45%), mean time since MM diagnosis was 71 months, and nearly 10% received CAR-T. Patients' preferences were most influenced by extending mOS from 2 to 6 years, increasing mPFS from 7 months to 4 years, reducing CRS events from 95% to 0%, and decreasing SAEs from 73% to 28%. In contrast, attributes such as neurological events (decreasing risk from 9% to 0%), and treatment response (increasing response rate from 55% to 95%) had less influence.

While not the most influential factor, patients preferred a one-time infusion over other modes of administration (e.g., weekly or every other day injection). **Conclusions:** This study indicates that patients' treatment preferences were predominantly influenced by survival metrics in early lines of treatment for relapsed myeloma, suggesting a potential preference for CAR-T therapy given the demonstrated PFS benefit in as early as 2L+ patients in CARTITUDE-4. However, the safety profiles associated with more effective treatments like CAR-T should be clearly communicated, as the associated risks may influence preferences and treatment decisions.

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Trends in Survival and Causes of Death in Multiple Myeloma: A Single-Institution Experience

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Introduction: During the last few decades, treatment options for multiple myeloma (MM) have markedly progressed, and the overall survival (OS) has significantly improved. However, MM remains incurable, and patients are at risk of death from MM progression as well as complications and comorbidities. With the recent trends for prolonged survival and long-term treatment with novel agents, the cause of death may have changed over time. Understanding the recent trends in OS and causes of death is crucial for evaluating the efficacy of therapeutic strategies and patient prognosis in the era of novel agents. Thus, we investigated the trends in OS and causes of death in MM patients in a real-world setting. **Methods:** We examined the registry data for patients diagnosed with MM in our hospital between 2006 and 2022, and compared the incidence and causes of death between the periods of 2006–2014 and 2015–2022. **Results:** A total of 291 patients with MM were registered during the study period. The median age of the total patients was 74 years (range, 41–93 years), and 74 patients (25%) were aged ≥80 years. Regarding the two periods, 122 patients were registered in 2006–2014 (Period A), and 169 patients were registered in 2015–2022 (Period B). The population of patients aged ≥80 years was higher in Period B than in Period A (29% vs. 21%, p=0.104). There were no differences in other baseline characteristics, including sex, Ig subtype, performance status, and International Staging System stage, between the two groups. The median follow-up period was 23.5 months (range, 0.5–177.7 months). The median OS was 28.8 for Period A and not reached for Period B, with 107 and 50 deaths in Periods A and B, respectively. The OS at 2 years was significantly better in Period B than Period A (all patients: 74% vs. 52%, p< 0.001; younger group aged < 80 years: 79% vs. 57%, p< 0.001; older group aged ≥80 years: 58% vs. 31%, p=0.008). The main cause of death in both periods was disease progression, followed by infection, cardiovascular disease, renal failure, and second malignancy. The cumulative incidence of death from MM progression was higher in Period A in Period B (26% vs. 13%, p=0.011). The cumulative incidence of death from causes other than MM was also higher in Period A than in Period B (22% vs. 3.4%, p< 0.001). Similar trends were observed in patients aged ≥80 years. **Conclusions:** While MM-specific mortality has decreased over time, MM progression remains a threat to survival in MM patients. However, our findings show that not only disease control with novel agents but also improvements in complication control have contributed to the improved prognosis of MM patients. Clinicians should remain aware of the risks associated with MM treatments and underlying complications. Moreover, elderly patients exhibited similar trends in OS and causes of death, suggesting that they have also benefited from recent treatment advances with novel agents.

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Combination of Geriatric Assessment and Clinical Factors To Predict the Survival of Elderly Patients With Myeloma

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Introduction: Elderly patients with newly diagnosed multiple myeloma (NDMM) show heterogeneous outcomes due to their potential risk, and lack of the standard-of-care risk stratification model. In this study, we proposed the prognostic model by analyzing the additive value of geriatric assessment and clinical factors. **Methods:** The collected individual data from 131 elderly patients(≥65) with NDMM enrolled. An additive scoring system on the basis of top features predicting progression-free survival (PFS) and overall survival (OS) was developed. **Results:** At a median follow-up of 23.7 months, age, ADL, PLT, CRP, CPC had the highest impact on OS and were used to construct OS risk model. Likewise, age, ADL, PLT, CRP, CPC for PFS risk model. A value was assigned to each risk feature according to their OS impact (age >75 5 points, ADL >4 3 points, PLT< 100×109/L 4 points, elevated CRP 3 points, CPC≥0.105% 2 points). And for PFS risk model, age >75, CCI ≥2, β2≥3.5mg/L, PLT< 100×109/L and CPC≥0.105% were assigned 2, 2, 3, 2, 2 points repectively. Patients were stratified into three risk groups according to the total additive score. Median OS was not reached versus NR versus 54 versus 56 months, and median PFS was NR versus 47 versus 23 months, respectively. Nomogram was also constructed using the same variables. the AUC values obtained from our nomogram were 0.742, 0.773 and 0.807 for predicting the 1-, 2- and 3-year OS rates, respectively, which were higher than those of both the MRP model (0.692, 0.691, 0.683) and IMWG-GA model (0.649, 0.634, 0.659). Additionally, 1-, 2- and 3-year PFS in our cohort yield value of 0.775, 0.782,0.774, respectively, which also exhibited superior performance compared to both the MRP model(0.646, 0.607, and 0.602), and the IMWG-GA model(0.636, 0.506, and 0.576). **Conclusions:** Our simple prognostic staging system allowing a better stratification of patients with elderly NDMM. The additive geriatric metrics of this score fosters its future implementation with new prognostic variables.

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Characteristics and Outcomes of Patients With Multiple Myeloma Aged ≤ 40 Years – Experience From a Tertiary Care Cancer Centre in India

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Introduction: MM primarily being a disease of elderly, the data among young patients are limited. It is essential to describe the presenting features, characteristics and outcomes of MM patients ≤40 years. **Methods:** We analysed data of newly diagnosed Multiple Myeloma patients ≤40 years over 9 years from January 2013 to December 2021. **Results:** A total of 110 patients diagnosed with Multiple Myeloma were analysed out of the total 1980 patients screened (Incidence 5.5%). At the time of analysis 48 patients were alive, 15 patients were dead and 47 patients were lost to follow up. The median age of the cohort was 36 years with Male to female ratio of 3:1. Clinically significant anaemia, hypercalcemia, renal impairment and hypoalbumenia were seen in 42.7%, 11.9%, 17.3% and 41.8% of patients respectively. Extramedullary plasmacytoma was seen in 9% of patients. Multiple lytic lesions were seen in 88.9% and single lytic lesion was seen in 3.7% of patients. According to International Staging System 35.5%, 27.1% and 37.4% of patients were in stage I, II and III respectively and according to Revised International Staging System 24%, 69.8% and 6.3% of patients were in stage I, II and III respectively. According to mSMART 78.3% of patients were standard risk and 21.7% of patients were high risk. LCD was diagnosed in 21.6% of patients. 38.5% of patients received VRD and 55% of patients received VCD as first line induction chemotherapy. According to IMWG response assessment CR, VGPR, PR were seen in 11.8%, 60.2%, 25.8% of patients respectively. Among the 64 patients who received maintenance, proteasome inhibitors were given to 20.3% and IMiDs were given to 48.4% of patients. 27% of patients received ASCT. After a median follow up of 44.2 months mPFS was 45.9 months. 1 year, 3 year and 5 year overall survival rates were 93.9%, 91.1% and 81.2% respectively. 3 year OS rates of patients who received and did not receive maintenance therapy were 97.4% and 86.1% respectively (p 0.0052). 3 year PFS rate of patients who received and did not receive maintenance were 80.2% and 42.1% respectively (p < 0.0001). Among patients who received PI and IMiD, 3 year PFS rates were 83.9% and 78.7% respectively. 5 year PFS of patients who received ASCT were 58.5 and for those who did not receive ASCT were 27.8% (p 0.0043) and 5 year OS of patients who received and did not receive ASCT were 94.4% and 84.4% (p 0.031). **Conclusions:** Young patients accounted for 5.5% of all patients diagnosed with multiple myeloma. Younger patients presented with anaemia in approximately half and renal failure in about one fifth of patients. One fourth of patients had high risk cytogenetics. VCD and VRD are the commonly used first line regimens and ASCT was done in approximately one fourth of patients. Anaemia, Renal failure, poor performance status, HR cytogenetics, VCD compared to VRD, poor response to therapy, no maintenance therapy and no ASCT showed poor progression free survival.

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The Role of Spinal Bracing in the Management of Multiple Myeloma Spinal and Sternum Disease

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Introduction: Spinal involvement is the most common site of MM bone disease and is associated with inferior survival. Traditionally the management of MM spinal disease was with either minor or major surgical intervention for spinal stability. The role of spinal bracing(SB) for spinal instability and support is unclear. This study aimed to explore the impact of SB on the maintenance of spinal stability prevention of new fractures and deformity. **Methods:** We retrospectively evaluated the electronic records of multiple myeloma patients who were followed up in clinic between 2018-2023 and had SB. **Results:** Of the 905 MM patients, we identified 422 patients who had SB, 372(88%) at diagnosis and 50(12%) at relapse. 211(50%) patients had CTLSO brace, 208 (49%) TLSO and 3(1%) hard cervical collar. The indication for SB was spinal involvement 420(99%), spinal fractures 347(82%), spinal lesions 73(17%) and 4(1%) fractures and lesions. 135(32%) had sternum involvement; 94 (21%) had sternum lesions, 46(10%) sternum fracture and 5(1%) combination of both. The duration of SB was 3 months for 386(91%) patients. 91% of the patients received bisphosphonates. Systemic MM treatment included proteasome inhibitors and Immunomodulatory agents. At the time of SB 422(100%) experienced pain 78(18%) neurological signs or symptoms, 78(18%) had spinal plasmacytomas, 65(15%) spinal cord compression, 67(16%) received radiotherapy and 11(3%) had surgical interventions. Only 3 patients requiring SB at relapse, had previous surgery at the same spinal level. Most patients (96%) showed radiological signs of new bone formation and spinal stability on imaging and for 9(9%) imaging showed progressive deformity. The incidence of worsening of pre-existing fracture was 17.5% and occurred within the first 4.3(1-4.3) months. The incidence of subsequent fractures below SB was 16%. 28 patients showed radiological signs of worsening of preexisting fractures and 7 experienced new fractures below the level of SB: 32 at diagnosis and 3 at subsequent relapses. 18 had CTLCO and 17 TLSO brace and 29 required SB for 3 months. 33 had spinal and 10 sternum involvement. 9 also received radiotherapy (3 for spinal plasmacytomas, 4 for neurological symptoms, 2 for SCC). In this group of patients 1 showed progressive deformity and 8 showed signs of new bone formation. **Conclusions:** In this largest real world study patients with spinal and sternum disease were managed with SB. Early SB was a safe non-invasive method which played a major role in the prevention of spinal fractures and preservation of spinal alignment. A low risk of worsening of pre-existing fracture was observed mainly within the first 4 months. This is stressing the need for early intervention and repeating imaging if new or worsening pain. None of the patients from this cohort with spinal instability

required additional surgical interventions and the incidence of longer-term spinal deformity was low.

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68Ga-Pentixafor PET/CT-Based Response Assessment in Multiple Myeloma Patients and its Comparison with 18F-FDG PET/CT and IMWG Based Clinical Response

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Introduction: 18F-FDG PET/CT is the currently recommended modality for response evaluation in patients with multiple myeloma (MM). However, it ails from low sensitivity and also shows early normalisation to therapy in patients with myeloma. 68Ga-Pentixafor PET/CT; a CXCR4 targeted radiotracer has shown higher diagnostic accuracy compared to 18F-FDG PET/CT in MM, however, its utility in response assessment has not been evaluated. Our study evaluates the utility of 68Ga-Pentixafor PET/CT for response evaluation and survival outcomes in patients with MM. **Methods:** Forty (24M:16F; median age=56years; range=34-81years) treatment naive MM patients were recruited. 68Ga-Pentixafor and 18F-FDG PET/CT imaging was performed at baseline and at median time of 7.2 months of induction therapy. The clinical response (IMWG criteria) was classified as complete response (CR) that included sCR and VGPR, partial response (PR), stable disease (SD) and progressive disease (PD) respectively. The PET/CT imaging data was reconstructed and semi-quantitative parameters (SUVmax) along with image based response (CR, PR, SD and PD) were evaluated. Progression-free survival (PFS) and overall survival (OS) was assessed and survival differences between groups were compared using Kaplan-Meier survival curves. **Results:** Baseline 68Ga-Pentixafor PET/CT was positive in a significantly higher number of patients (39/40; 97.5%) as compared to 18F-FDG PET/CT (31/40; 77.5%) (p=0.021). 68Ga-Pentixafor PET/CT also showed significantly (p< 0.001) higher (by factor of 2.5) SUVmax values than 18F-FDG PET/CT (18.1±16.5 vs. 7.1±6.0). As per IMWG criteria, 34/40 (85.0%) patients showed CR, 5/40 (12.5%) PR and 1/40 (2.5%) showed PD. On 18F-FDG PET/CT based response evaluation, 21/31 (67.7%) patients showed CR, 7/31 (22.6%) PR and 3/31 (9.7%) showed PD. 68Ga-Pentixafor PET/CT evaluation showed CR in 13/39 (33.3%), PR in 23/39 (60.0%) and PD in 3/39 (7.7%) patients. All three response assessment criteria demonstrated significant difference (log rank test p< 0.05) in PFS among their respective categories. 68Ga-Pentixafor PET/CT identified 5/6 patients (83.3%) demonstrating poor response (PR, SD and PD group) whereas 18F-FDG PET/CT identified 4/6 (66.6%). 18F-FDG PET/CT and IMWG classified a higher proportion (67.7% & 85.0% respectively) of patients as CR, whereas 68Ga-Pentixafor PET/CT demonstrated 60.0% patients as PR. On sub-analysis, 68Ga-Pentixafor PET/CT further classified 34 patients with CR on IMWG into CR in 12/34, PR in 19/34 and PD in 2 patients (1-negative) which showed significant difference in PFS. Similarly, 21 patients with CR on 18F-FDG PET/CT were further classified into CR in 8 and PR in 12 patients (1-negative) which also showed significant difference in PFS. **Conclusions:** 68Ga-Pentixafor PET/CT showed excellent performance in PET-based response assessment and prediction of PFS in MM patients. Combining 68Ga-Pentixafor with 18F-FDG PET/CT may provide a comprehensive response assessment and survival analysis in these patients.

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Infections in Newly Diagnosed Multiple Myeloma: Incidence, Characteristics, and Outcome in a Tertiary Health Care Centre in India

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Introduction: Infections are a major cause of morbidity and mortality in patients with multiple myeloma (MM). It is largely due to their compromised immune systems from both the disease and its treatments. Infectious complications and outcomes also vary because of prevalence of multi drug resistant organisms (MDRO) and other background infections besides prophylaxis being used. In this analysis we study characteristics and risk factors for infections among newly diagnosed MM (NDMM) patients at a tertiary healthcare centre in India. **Methods:** A retrospective analysis was conducted using electronic medical records of 181 NDMM patients at a tertiary medical centre in India from July 1, 2022, to October 1, 2023. Data was then entered into an excel spreadsheet and Statistical analysis was performed using SPSS v29. We analysed the baseline disease characteristics, incidence and characteristic of infections, the treatment data, and outcomes. We planned to perform univariate analysis using chi-square test/ unpaired t-test followed by a multivariate analysis. **Results:** A total of 181 patients were analysed with a median age of 55 years (range : 30-85) and 121 (66.9%) being males. Comorbidities identified were hypertension (in 33.1% of patients) and diabetes (in 14.9% of patients). Regarding haematological abnormalities at presentation, 97 patients (53%) presented with anaemia, 42 patients (23.2%) had thrombocytopenia, and 18 (9.9%) had neutropenia. Disease characteristics revealed hypercalcemia in 24 patients (13.3%), hypoalbuminemia in 64 patients (35.4%), and raised LDH in 81 patients (44.8%). Renal damage was evident in 44 patients (24.3%) at presentation, while 154 patients (85.1%) had bony lesions. R-ISS stage I, II, III comprised 8.8%, 43.6%, 28.2% respectively. Infections were documented in 76 patients (42%). Among these 23 (30.2%) had bacterial infection, 15 (19.7%) had viral infection with only one patient (1.3%) having fungal infection. Sites of infection

were LRTI in 41 (53.9%) , 20 (26.3%) had URTI, 2 (2.63%) patients had UTI, 3 (3.94%) patients had soft tissue infection and tuberculosis infection in 3 (3.94%) patients. Out of the 76 patients 25 (32.9%) patients had microbiologically defined infection as a result of culture positivity. Number of episodes of infection were one in 43 (56.5%) patients, two episodes in 18 (23.6%) patients and more than two in 12 (15.7%) patients. Eight (10.5%) patients required admission to the ICU and 5 (6.5%) individuals died due to infections. On univariate analysis only absolute neutrophil count less than 2 x 10e9/L at baseline was found to be associated with increased risk of infection. **Conclusions:** The study reveals a high incidence of infection rate among NDMM patients in our cohort with a significant infection-related mortality rate of 6.5%. These findings highlight the importance of vigilant infection monitoring and management in this patient population and suggest caution while using intensive regimens.

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Diarrhea in Multiple Myeloma Autologous Stem Cell Transplant Recipients: Think Beyond Mucositis!!

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Introduction: Persistent diarrhea in Multiple myeloma patients undergoing Autologous transplant is related to conditioning regimen toxicity unless proven otherwise. However, we are observing an emerging rise in infectious complications in this setting and hence it is necessary to evaluate for the same to ensure better clinical outcomes. **Methods:** This is an ambispective study of 2 years duration (2021-2023) conducted at Department of Hematology and Bone marrow transplant at a tertiary care hospital in Northen India. A total of 106 multiple myeloma patients underwent autologous transplant during the study period, out of which 84 patients (79.24%) were newly diagnosed multiple myeloma who attained Partial response (PR) or better response after first line treatment, while 22 patients (20.37%) were relapsed refractory myeloma patients after multiple lines of therapy. Patients were stratified based on age, co-morbidities, disease status, prior treatment and dose of melphalan used during conditioning. All patients who had diarrhea (by standard definition) for more than 2 weeks post -transplant were evaluated for alternative etiology (other than mucositis) by using both conventional and molecular techniques along with colonoscopy (wherever needed). **Results:** Over the study period, out of the 106 patients included with median age of 62 years, 32 patients (30.19%) had persistent diarrhea. Twenty-nine of them (90.62%) had febrile neutropenia for which empiric/definitive antibiotics were given. Eight patients had Clostridium difficile toxins, 3 patients had Giardiasis, 1 patient had cryptosporidium oocysts detected on Stool routine analysis. Colonoscopy with biopsy and immunohistochemistry was performed in 18 out of the remaining 20 patients. CMV colitis was diagnosed in 6 patients, 2 patients had biopsy proven GVHD. Diarrhea in 12 patients was still attributable to mucositis after ruling out other etiologies. All the patients were treated as per standard treatment protocols including trial of steroids for the patients with GVHD. Successful resolution of diarrhea was achieved in 31 out of 32 patients. **Conclusions:** In the current treatment era, melphalan related mucositis is still the most common cause of debilitating diarrhea. However, with newer diagnostic modalities and a collaborative team approach, other infectious /non-infectious etiologies are being increasingly recognized in this subgroup of patients. A careful analysis of the causative agents could lead to more accurate management, early intervention and prevention of serious complications.

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Cyclosporine as a Rescue Therapy for Primary Graft Failure in Myeloma Autologous Transplant

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Introduction: Melphalan autograft is part of standard treatment protocol for newly diagnosed multiple myeloma.Graft failure is an extremely rare complication in Myeloma autotransplant.It has life threatening complications like infections and bleeding diathesis. Here we describe a rare case of Multiple myeloma who developed primary graft failure after Autologous stem cell transplant and how cyclosporine helped to effectively salvage this patient. **Methods:** In this retrospective study , we analysed BMT records of 170 patients who underwent autologous stem cell transplant for multiple myeloma between 2017 and 2024. Only one of our patients (0.59% incidence) had primary graft failure defined as abscence of neutrophil recovery by D28. We analysed the baseline characteristics of this patient and how cyclosporine was used as an effective salvage regimen for this patient. **Results:** 63 year old female patient, IgG Kappa Multiple Myeloma, R-ISS 2 with no high risk cytogenetic abnormalities on FISH test received 4 cycles of induction with VRd regimen. She achieved CR after 4 cycles and was planned for Autologous stem cell transplant. Her pre transplant evaluation was unremarkable.She did not develop any infections prior to transplant. She underwent autologous stem cell transplant with Melphalan 200mg/m2 as conditioning. Stem cell dose of 11million/kg was infused.She was started on G CSF from Day 2. Her neutrophil count did not recover till day 28. She developed probable fungal pneumonia on D25 which was managed with appropriate antifungals. She was started on Eltromopag 150 mg once daily and Cyclosporine (3 mg/kg in 2 divided doses with target tarough levels of 200-250) from Day 25 of transplant. Therapeutic level of Cyclosporine was attained after a week. Patients blood counts started improving one week after initiation of Cyclosporine and Eltromopag. Neutrophil engraftment was achieved by D43 and platelet engraftment by Day 60. Cyclosporine was tapered off by 60 days after count recovery. **Conclusions:** Pathogenic mechanism of primary graft failure in Multiple myeloma is largely unknown and T cell mediated supression of hematopoeisis could be a likely cause.We report our experience with successful use of empiric Cyclosporine in this case. Cyclosporine should be considered as a therapeutic option

in all cases of Myeloma with primary graft failure post autologous stem cell transplant.

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Daratumumab Treatment in the Patients' Own Home

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Introduction: Patients with multiple myeloma benefit from increasing overall survival. This is due to more effective and less toxic treatments that can be given for a long time. The success however strains the healthcare system and causes the patients to use substantial time on treatment. We tested if part of the treatment could be given outside the hospital, and if electronic Patient Reported Outcome (PRO) data could determine if patients needed to talk to a healthcare practitioner before each injection. **Methods:** From April 2022 to June 2023, 30 patient were included, mean age was 76; range 61-87. Eighteen patients already received daratumumab for ≥6 cycles and 12 patients were new on daratumumab. Patients already on treatment were followed for 7 cycles with two of three treatments given by a district nurse at home or in a local healthcare clinic, due to differences in the municipal healthcare. Patients new on treatment were followed for 6 cycles with every second treatment given outside the hospital. Prior to each treatment, patients reported their side effects electronically and an algorithm was developed to stratify patients as ready or not for planned treatment. For comparison, patients also had a telephone consultation with a specialized nurse. Patients registered any unplanned contact to the healthcare system between administrations. **Results:** In total, 255 of 269 planned administrations of daratumumab were given. All administrations were given safely, no unforeseen events occurred. Of 125 hospital-planned administrations, 122 (97.6%) were given and one was cancelled. Of 144 outsource administrations, 133 (92.4%) were given as planned, six were redirected and given at the hospital (two due to suspicion of infection and four for administrative reasons), and five administrations were cancelled. On average, patients saved 177 minutes per administration given at home compared to the hospital; 29 vs. 206. Even deducting transportation, time spent was reduced by a factor 3.5 (29 vs. 102). For patients treated at a local healthcare clinic, time was reduced by a factor 3.25 (63 vs. 205). There was no significant difference between numbers of unplanned health contacts between home and hospital administrations. 84% of the patients preferred to continue with home treatment. The PRO questionaries had a positive predictive value of 100%. In no cases did the algorithm recommend treatment when the nurse suggested further medical evaluation. In 171 of 223 questionnaires the algorithm recommended treatment. In 52 cases it recommended medical evaluation. Of these, 44 received planned treatment and 8 were cancelled/postponed. Only 40% preferred to receive calls from the nurse prior to each treatment afterwards. 52 % would like to continue reporting side effects via the app. **Conclusions:** Administration of daratumumab by a district nurse is safe, feasible, timesaving, and preferred by the patients. PRO data can effectively evaluate patients prior to treatment.

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Impact of Immune Paralysis on the Prognosis of Newly Diagnosed Multiple Myeloma Patients: A Retrospective Analysis

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Introduction: Multiple myeloma (MM) is a neoplastic disease characterized by the clonal proliferation of malignant plasma cells. Immune paralysis, defined as the suppression of the production of polyclonal immunoglobulins (Igs), is a significant complication in MM patients and may impact their clinical outcomes. This study aimed to evaluate the prevalence of immune paralysis in newly diagnosed MM (NDMM) patients and its association with clinical characteristics and prognosis. **Methods:** A retrospective analysis was conducted on 122 NDMM patients diagnosed between January 2018 and December 2022 at our hospital. Data were collected using statistical software to analyze the clinical features and prognostic significance of immunoparesis. The median follow-up period for the study cohort was 33 months (range, 12-63 months). Immunoparesis was assessed at diagnosis, and patients were stratified into groups based on the presence and severity of immunoparesis. Survival analysis was performed to compare PFS and OS between patients with and without immunoparesis, as well as between those with different durations of severe immunoparesis. **Results:** The study found that 80.5% of NDMM patients exhibited varying degrees of immune paralysis at initial diagnosis. Patients with severe immune paralysis tended to have a higher tumor burden and were more likely to suffer from anemia. While 32.6% of NDMM patients had concurrent infections at diagnosis. The progression-free survival (PFS) of patients with immune paralysis was significantly shorter than those without, with a median PFS of 28 months versus 43 months (P=0.006). Similarly, the overall survival (OS) of patients with immune paralysis was significantly shorter, with a median OS of 56 months vs. not reached (P=0.025). Notably, patients with severe immune paralysis had even shorter median PFS (21 months vs. 40 months, P< 0.001) and OS (35 months vs. 59 months, P=0.002) than those without severe immune paralysis. The duration of severe immune paralysis had a profound impact on both PFS and OS. Patients with severe immune paralysis lasting ≥3, ≥6, and ≥12 months showed significantly shorter median PFS and OS compared to those with non-severe or shorter duration of immune paralysis. Univariate COX analysis identified several poor prognostic factors for PFS and OS, including R-ISS stage III, a baseline plasma cell proportion of ≥70%, serum calcium concentration >2.65 mmol/L, and the presence of severe immune paralysis at diagnosis. However, concurrent infection at diagnosis was not a prognostic factor for PFS or OS. Multivariate analysis confirmed that severe immune paralysis lasting ≥12 months was an independent adverse prognostic factor for both PFS (P=0.004) and OS (P=0.015). **Conclusions:** The presence

and duration of severe immune paralysis at diagnosis are significantly associated with worse PFS and OS in NDMM patients.

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The Efficacy of Acupuncture in Alleviating Bortezomib-Associated Peripheral Neuropathy in Patients with Multiple Myeloma: A Comparative Study

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Introduction: Bortezomib, a proteasome inhibitor, is widely used in the treatment of multiple myeloma (MM) but is associated with a significant incidence of peripheral neuropathy, which can impair patients' quality of life and adherence to therapy. This study aimed to investigate the incidence and characteristics of bortezomib-induced peripheral neuropathy and to evaluate the therapeutic efficacy of acupuncture combined with pharmacological treatment. **Methods:** We retrospectively analyzed data from 120 MM patients treated with bortezomib between January 2017 and December 2022. The incidence and severity of peripheral neuropathy were assessed according to the NCI-CTC 5.0 grading system. Patients with different grades of neuropathy were treated with either acupuncture combined with medication or medication alone. The primary outcomes were the change in neuropathy scores and the comparison of treatment efficacy between the two groups. **Results:** Peripheral neuropathy developed in 53 of 120 patients (41.67%) during bortezomib treatment. Sensory neuropathy was universal among affected patients, with grade 1 in 18 patients (33.96%), grade 2 in 23 patients (43.39%), and grade 3 or higher in 12 patients (22.64%). Motor neuropathy and neuropathic pain were less common, occurring in 11.32% and 16.98% of patients, respectively. The most frequent manifestations were numbness in the limbs and radicular pain, with "stocking and glove" distribution of sensory abnormalities being a common presentation. Neurophysiological studies confirmed slowed nerve conduction velocities in the affected patients. In patients with grade 2 neuropathy, combined acupuncture and pharmacological treatment resulted in a significant improvement in symptoms compared to pharmacological treatment alone (pre-treatment score 21.50±3.32 vs. post-treatment score 17.25±2.22, $P< 0.05$). Similarly, for grade 3 neuropathy, the combined treatment showed superior efficacy over medication alone (pre-treatment score 25.17±1.47 vs. post-treatment score 20.67±1.21, $P< 0.05$). **Conclusions:** Bortezomib-induced peripheral neuropathy is a common complication in MM patients, with a high incidence of sensory neuropathy. The addition of acupuncture to standard pharmacological treatment significantly improved the symptoms of peripheral neuropathy in patients with grade 2 and grade 3 neuropathy. These findings suggest that acupuncture may be a valuable adjunctive therapy for managing bortezomib-induced peripheral neuropathy.

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Evaluating Racial Differences in the Systemic Impact of Monoclonal Protein in Multiple Myeloma Using Machine Learning

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells, leading to systemic effects on immune function, hematopoiesis, renal function, bone metabolism, and electrolyte homeostasis. While the clinical outcomes for MM have significantly improved with advancements in therapeutic strategies, the influence of race on disease biology and treatment response remains an intriguing and critical area of investigation. Racial disparities in healthcare outcomes have been well-documented, and understanding these disparities in the context of MM is essential for optimizing patient care and treatment strategies. This study aims to employ a machine learning approach to evaluate the systemic impact of monoclonal protein (M-protein) and explore potential racial differences between African American and Caucasian patients. **Methods:** The upper limit of observed M-spike was 3.5 g/dL. Forty-three clinical and laboratory variables were selected as predictors of M-spike values and were fed into a machine-learning model using the random forest algorithm. The model also included two lagged variables representing each subject's two preceding M-spike values. The dataset was randomly divided into a training set (80%) and a test set (20%). A regression tree was built using the training set and validated with the test set. Bootstrapping was employed to generate data sets (n=500) for model validation. The importance of each variable was assessed by excluding it from the model and evaluating the impact on the mean squared error (MSE). **Results:** The training set comprised 749 patient-based observations. The residual distribution of the random forest model indicated that nearly all M-spike values predicted using the 43 variables were distributed equally on either side of zero. The inclusion of race as a variable did not significantly change the residual plots. The weighted value of each of the 43 independent variables was determined by individually removing a variable from the model and measuring its effect on the MSE. Key variables, including the first lagged M-spike, serum total protein, second lagged M-spike, serum IgG, serum IgM, and serum IgA, had the greatest impact on the model. When race was added to the model, it had a low weighted value compared to other variables. The Pearson correlation coefficient between predicted and actual M-spike values was 0.96, and the Spearman correlation coefficient was 0.91. With the inclusion of race, these coefficients were 0.95 and 0.94, respectively, indicating no significant difference. **Conclusions:** Our machine learning analysis supports the hypothesis that there is no significant difference in the systemic impact of MM between African American and Caucasian patients, as measured by M-spike levels. These findings highlight the robustness of the model and suggest that racial differences may not play a major role in the systemic effects of MM.

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External Validation of a Machine Learning Model for Rapid Prediction of M-Spike Values in Multiple Myeloma Using the HealthTree Database

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Introduction: Multiple myeloma (MM), a malignant proliferation of plasma cells, often presents diagnostic challenges due to its complex clinical manifestations and variable patient outcomes. Despite advances in diagnostic methods, such as serum and urine protein electrophoresis to measure M-spike proteins, these techniques are often limited by delayed turnaround times which can postpone critical treatment decisions and lead to patient anxiety. Our previous study introduced a machine learning model utilizing a Random Forest algorithm to predict M-spike values rapidly and accurately using the same-day routine clinical and laboratory data from a single institute. Given the potential of this model, external validation is crucial to confirm its effectiveness and reliability across a broader, independent patient cohort. **Methods:** We conducted a retrospective analysis using an external dataset comprising 619 MM patients from HealthTree Foundation. This dataset was tabulated with comprehensive clinical and laboratory parameters like those used in our original model. We employed the same Random Forest model to this new dataset to predict M-spike values. The model's performance was evaluated based on its predictive accuracy, measured through the coefficient of determination (R^2) and mean squared error between the predicted and actual M-spike values. Statistical analyses were performed using the same software environment as in the initial study, ensuring consistency in evaluation metrics. **Results:** The median M-spike value was 0.16 (range 0.01-2.5 gr/dL). The residual distribution of the RF model indicated that nearly all M-spike values determined using the 43 variables distributed equally on either side of zero. The weighted value of each of the 43 independent variables was determined by individually removing a variable from the ML algorithm and measuring its effect on the mean squared error (MSE). The model demonstrated a strong predictive capability with an R^2 of 0.779 in the external validation, with Root Mean Square Error (RMSE) 0.2619 indicating substantial agreement between predicted and observed M-spike values. The scatter plot of predicted versus actual values highlighted the model's accuracy across the range of M-spike measurements. Feature analysis from the external validation aligned closely with our initial findings, with key predictors such as serum total protein and various lagged M-spike values maintaining high importance. This consistency supports the robustness of the model across different patient groups. **Conclusions:** The external validation of our Random Forest model confirms its potential as a reliable tool for rapid M-spike prediction in MM patients. This model can significantly enhance clinical decision-making by providing faster predictions than traditional methods. Future research should focus on continuous refinement of the model by integrating more diverse datasets and exploring real-time validation in clinical settings.

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Optimizing Feature Selection for Large Language Models in AI-Assisted Clinical Assessment of Multiple Myeloma

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Introduction: Large language models (LLMs) hold the potential to transform the healthcare industry by alleviating healthcare burdens, increasing accessibility in underserved areas, and providing multilingual support. Armed with extensive medical knowledge and natural language processing capabilities, these models require well-curated data inputs, or prompt engineering, for accurate diagnosis and personalized treatment planning. Multiple myeloma (MM), a complex hematological malignancy characterized by the proliferation of malignant plasma cells in the bone marrow, poses significant challenges due to its multisystemic impact. Implementing LLMs for MM clinical assessment necessitates identifying the most relevant features that reflect disease dynamics and patient status during each visit. This study utilizes a machine learning (ML) approach to select the most significant features for developing effective prompts for LLMs in the clinical assessment of MM patients. **Methods:** The study analyzed 1,472 clinical observations from patients with MM, focusing on 43 clinical and laboratory variables to predict same-day M-spike values. A Random Forest (RF) algorithm, known for its robustness in handling nonlinear relationships and high-dimensional data, was employed. The dataset was split into a training set (80%) and a test set (20%) to validate the model. Bootstrapping was used to generate 500 data sets, constructing an ensemble of regression trees whose results were aggregated. The importance of each variable was assessed by examining the impact of its inclusion or exclusion on the model's mean squared error (MSE). **Results:** The RF model demonstrated that nearly all M-spike values, determined using the 43 variables, were symmetrically distributed around zero residuals. Key variables identified as most influential included the first and second lagged M-spike values, serum total protein, serum IgG, serum IgM, and serum IgA. The RF model's predictions showed high correlation with laboratory-measured M-spike values, with Pearson and Spearman correlation coefficients of 0.96 and 0.91, respectively. Feature selection models were then compared to evaluate the minimal variable set required for accurate M-spike prediction. Five models (A-E) were developed, ranging from using all 43 variables to using only the most critical predictors. The Pearson correlation coefficients and root mean square error (RMSE) for these models were as follows: Model A (0.96, 0.21), Model B (0.96, 0.19), Model C (0.96, 0.19), Model D (0.95, 0.22), and Model E (0.95, 0.22). **Conclusions:** This study highlights the importance of accurate feature selection in developing prompts for LLMs to assess MM. By identifying a curated set of variables most correlated with

disease volume, we present potential list of parameters for prompt engineering to provide focused and comprehensive assessments. Future research should aim to refine these models further and explore their application in real-time clinical settings.

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Real World Single Centre Experience On The Use of Radiotherapy In The Treatment of Patients with Multiple Myeloma

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Introduction: Radiotherapy (RT) has traditionally played an important role in the management of patients with multiple myeloma (MM). Recent advances in treatment have led to a prolonged survival advantage. In this context, there is limited recently published data on the use of RT in MM. We analyse real-world patterns of RT use to evaluate the relevance of this treatment modality in the era of novel therapies. **Methods:** We identified patients with MM who received RT at our tertiary care centre between 2016 and 2023. Using electronic patient records we collected demographic, disease-related and RT-related data for individual patients. **Results:** 157 patients out of 905 who were reviewed in our outpatient clinic were treated with RT. Median age at diagnosis was 59 years, 62.4% of patients were male and 51% were white. 17.8% had high risk cytogenetic features and 12.7% had ISS stage III disease. Median number of treatment lines was 4 (range 1-9) with 90.7% of patients exposed to bortezomib, 84.1% lenalidomide, 47.7% pomalidomide, 34.4% daratumumab, 30.5% ixazomib, 20.5% carfilzomib, 13.2% isatuximab, 12.6% belantamab, and 2.6% CAR-T/bispecific antibodies (BsAbs). 76.8% of patients underwent at least 1 ASCT. We observed 331 episodes of RT within our patient cohort, with a median of 2 RT episodes per patient (range 1-9). 28% of the cohort received RT at the time of initial diagnosis. Type of tissue irradiated included bone (67.1%), bone/paramedullary (22.1%) and extramedullary soft tissue plasmacytomas (10.9%). The spine was the most irradiated site (39.6%) followed by the pelvis/sacrum (14.5), femur/tibia (8.2%) and skull/facial bones (8.2%). The mean dose of RT was 16.6Gy (range 6-45Gy), the median number of fractions was 5, and the most frequently used dosing schedule was 20Gy given over 5 fractions. Indications for RT included palliation of bone pain (66.2%), spinal cord compression (16.3%), post-operative consolidation (6.3%), prophylaxis/treatment of pathological fracture (5.4%), and extramedullary disease requiring 'debulking' (5.7%). 8.5% of RT episodes involved delivery of RT to a site which had previously been irradiated, due to later same-site relapse. RT did not affect haemopoietic stem cell (HSC) yield in those who underwent HSC collection; in patients without prior RT the mean HSC yield was 5.15x106 vs 4.30x106 in those who did require prior RT (t test, p=0.158). **Conclusions:** This single centre study involving patients on contemporary treatment protocols showed that RT was used mainly at subsequent therapy lines rather than at diagnosis and was predominantly used as a pain relief measure. An important observation was the low incidence of repeat irradiation at previous RT sites, suggesting the radiosensitive nature of MM. RT could continue to hold a role in patients who become refractory to systemic therapy as salvage bridging therapy especially in the era of CAR-T and BsAbs. More focussed studies on the timing of radiotherapy in the treatment pathway are warranted to maximise its use.

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Perceptions of Brazilian Hematologists in the Care of Patients with Multiple Myeloma in the Unified Health System: Brazil of Contrasts

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Introduction: Studies point to blood cancer, multiple myeloma (MM), as an emblematic example of discrepancies in access to pharmacological treatment, when we consider the realities of the public and private health sectors in Brazil. These contrasts impact the quality of life and survival of these patients. Until now, no national studies have highlighted these discrepancies from the point of view of Brazilian hematologists. This work is a segment of a larger project. **Methods:** Exploratory study based on narratives of a qualitative nature using thematic-categorical content analysis. Data was collected between November 2018 and May 2019 pre coronavirus 19 pandemic. The target population consists of Brazilian hematologist doctors who worked in the public health sector caring for patients with MM. The number of participants was determined a posteriori from the saturation of the answers, and the recruitment of experts was performed by the non-probabilistic technique Snowball. The data collection instrument was a semi-structured interview, the content analysis was based on the reading and rereading of the transcribed interviews, performed by the researchers. **Results:** A total of 15 interviewees, mean age of 46.8 years, 8 women, with representativeness in all Brazilian geographic regions, work relationship as a doctor or teacher, and the majority in federal public hospitals. As premises, exploring the perceptions of hematologists about the Unified Health System (UHS) was not possible without comparing it to the private sector, and the scope of UHS is restricted to the realm of tertiary care (hospital care). One of the categories identified is "Care for patients with MM: Brazil of contrasts". Topics: 1. Public sector, negative aspects, scarcity of resources limited access to new drugs, beds, and professionals leading to lower patient survival; positive aspects, rich field of professional experience and associated academic activity 2. Private sector, negative aspects, are isolated clinical practice and loss of autonomy; positive aspects, are greater access to treatment and resoluteness 3. Quality of patient care varies and depends on local factors such as the Federative State, discrepancies in UHS management, disease staging, and hospital resources 4. Cultural divergence of patients ranging from extreme resignation to great demands 5. Judicialization of health with divergent interpretations of the law. **Conclusions:** Overall, the interviewees are significantly impacted by the scarcity scenario and

state that the theoretical NHS differs from the real NHS, but they acknowledge the positive aspects of this clinical practice. The private sector has negative and positive characteristics that are opposite and complementary to the public sector and vice versa. The quality of care for patients with MM in the UHS is directly related to state/regional realities, hospital care structures, and the profile of patients, which impacts the judicialization of health.

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Risk and Incidence of Venous Thromboembolism in Newly Diagnosed Multiple Myeloma Patients

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Introduction: Venous thromboembolism(VTE) is a rare but major complication seen in patients with MM. Besides varied incidences across different races, different disease burdens and therapies impact the incidence of the same. There is scarcity of data in Indian patients. In this analysis, we evaluated the prevalence of baseline predisposition factors for VTE, risk scores and outcomes in a large cohort of newly diagnosed MM (NDMM). **Methods:** We retrospectively analyzed data from patients with NDMM between July 2022 to October 2023. Data was extracted from electronic health records, focusing on baseline risk factors for VTE, anti-myeloma therapy & VTE prophylaxis used and outcomes. VTE risk scores for each patient was calculated using the IMPEDE VTE and SAVED scores. Statistical analysis was done using SPSS V23. **Results:** The cohort was of 184 patients with sex ratio being 2.02(male/female) whose median age was 55 years(range 30-85). Hypertension was the most common comorbidity seen in 34.2 % of patients followed by diabetes mellitus in 15.2%. 20.7% patients were categorized as ISS stage I, 25% as stage II & 49.5% as ISS stage III. High risk cytogenetics were found in 19(10.3%) patients. VRd was the most commonly used induction regime (86.8%) of patients. Immunomodulators (e.g. lenalidomide, thalidomide, pomalidomide) were used in 76.7 % of patients out of which lenalidomide and thalidomide were given in 84.6 % & 3.2 % respectively. The dexamethasone used in these regimens was unanimously low dose defined as less than 160 mg per cycle(40 mg/dose). All patients received aspirin 75 mg as VTE prophylaxis. According to the IMPEDE-VTE score, 1 patient was high risk, 14 patients were intermediate risk and 164 patients were low risk. Similarly, 163 patients were stratified as low risk and 9 patients as high risk according to SAVED score. Overall the cohort was at Low risk according to both scores.Out of the 184 patients, only 3 patients - 1.63 % developed a single episode of VTE each during the duration of study. All the three patients had Lower Limb Deep Vein thrombosis episode within 6 months on initiation of treatment. No mortality was seen due to the thrombotic event. Among the patients who developed thrombotic events, 2 patients were having intermediate risk & one patient in low risk(0.61%) as per IMPEDE VTE score. Compared to data of the cohort which proposed this score, 15.2 % of patients had VTE episodes among high risk, 8.3 % in intermediate risk and 3.3% in low risk patients. In the sample for SAVED score, 1 high risk patient & 2 low risk patients developed a VTE episode. Opposed to this, 12% of high risk patients(n=686) and 7% of low risk(n=1711) developed VTE in the sample for SAVED score. **Conclusions:** In summary, our cohort had overall a low risk as well as low incidence for developing a VTE as compared to Western population. The risk scores had little utility given that most events occurred in low or intermediate risk rather than high risk score groups.

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Early Mortality in Newly Diagnosed Multiple Myeloma: Incidence and Risk Factors in an Indian Cohort

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Introduction: Recent advancements in treatments have led to improved survival rates for Newly diagnosed multiple myeloma (NDMM) patients. Despite these advancements, early mortality (EM) remains a significant challenge. Research has identified several risk factors for early mortality in MM patients, including advanced age, male gender, poor performance status, and comorbidities such as renal and cardiac conditions. Infections and treatment-related toxicities also play a significant role in early mortality, emphasizing the importance of timely interventions and effective infection control measures. This study addresses the lack of data on Indian populations by identifying the rate, the causes and risk factors of early mortality among NDMM patients in India. **Methods:** We conducted a retrospective analysis of 181 patients with NDMM at a tertiary medical center in India, from July 2022 to October 2023. Data were extracted from electronic medical records (EMR) covering patient demographics, clinical characteristics, treatment protocols, associated toxicities, and outcomes. Early mortality was defined as death within 180 days post-diagnosis. The data analysis was performed using SPSS v21. We started with a univariate analysis using the chi-square test for categorical variables and an unpaired t-test for continuous variables to explore significant risk factors, followed by multivariate logistic regression. **Results:** One hundred and eighty-one patients were analyzed of which 121 (66.9%) were

males. The median age for the cohort was 55 years (range: 30-85). The comorbidities were diabetes (27,14.9% of patients), hypertension (60, 33.1%), and ischemic heart disease (4, 2.2%). Based on disease characteristics, 53(29.3%) patients had an ECOG PS more than 2, 24 (13.3%) patients had hypercalcemia, 97 (53%) of the patients had anemia, 64 (35.4%) patients had hypoalbuminemia, LDH was raised in 81 (44.8%) patients.44 (24.3%) patients had renal damage, 154 (85.1%) patients had bony lesions, 60 (33.1%) patients had paramedullary lesions, and 12 (6.6%) patients had extraosseous disease. Early mortality was observed in 17 patients (9.4%). Causes of death were disease-related (5 patients, 29.4% patients), infections (5, 29.4%), disease progression (3,17.6% patients), other causes (2, 11.8%), and not available (1, 5.9%). Univariate analysis showed ECOG >2, hypercalcemia, hypoalbuminemia, presence of extraosseous disease, high R-ISS score, ISS score as the factors significantly associated with early mortality. Among these, extraosseous disease was found to be significant on multivariate analysis. **Conclusions:** Early mortality continues to pose a significant challenge in the treatment of NDMM. Our population showed similar EM rates to the rates reported in literature for other populations, with a significant proportion of patients dying from disease related causes, progression, and infections. This suggests need for more effective therapies and infection prevention measures to optimise early outcomes.

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Clinical – Epidemiologic Features and Disparities in Access to Diagnostic Tools and Novel Therapies for MM Patients in Public and Private Health Care – A Comparative Analysis of 2 Hospitals in Brazil

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Introduction: The diagnosis and treatment of Multiple Myeloma have rapidly advanced in recent years, resulting in increased survival rates and improved quality of life. However, inequities in access quality of care remain a known issue, especially amongst public and private healthcare services in Brazil, where more than 70% of the population depend on public healthcare system – Sistema Unico de Saude (SUS). This study aims to evaluate the discrepancies in diagnostic and therapeutic resources among patients treated at two different healthcare scenarios in São Paulo, Brazil between 2017 and 2023. **Methods:** This is a cross-sectional study of clinical, diagnostic, and therapeutic data from 247 patients with Multiple Myeloma, identified in eletronical records using the ICD-10 code C90. Data were collected from a private hospital (Hospital Israelita Albert Einstein - HIAE) and a public hospital (Hospital Municipal Vila Santa Catarina Dr. Gilson de C. Marques de Carvalho - HMVSC). The chi-square test was used for a univariate association between variables. **Results:** When divided between the private HIAE (185 patients) end the public hospital HMVSC (62 patients), the epidemiologic features showed an average age at diagnosis of 72 and 66 y/o respectively, with male predominance in both institutions (57% in HIAE and 58% in HMVSC). Only 9 patients (13%) at HMVSC had cytogenetic study results compared to 85% at HIAE, making it difficult to classify most of this population according to new prognostic scores as R-ISS and R2-ISS, reflecting the first challenge in adequate risk stratification in patients treated in public healthcare. Regarding ISS staging, there was no significant difference between patients from the two hospitals. Patients at HIAE had access to all approved novel therapies by Agencia Nacional de Vigilancia Sanitaria (ANVISA) whereas patients at HMVSC only had access to Bortezomib, Cyclophosphamide, Melphalan, Thalidomide, and Dexamethasone. The public service patients also had higher mortality rates compared to those in the private hospital (33% vs. 22%, respectively), not statistically significant (p= 0.3402). **Conclusions:** Previous studies have demonstrated differences in the quality of care for Multiple Myeloma patients due to socioeconomic disparities. Our study enlightens the inequity in access to diagnostic tests for better prognostic stratification and novel therapies between these 2 private and public hospitals, what reflects the macro scenario in Brazil, highlighting

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Enhancing Psychosocial Support for Multiple Myeloma Patients in Moi Teaching and Referral Hospital (MTRH) Kenya

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Introduction: Cancer represents a pervasive global health challenge and it exposes patients to a wide range of physical, psychological, social and financial problems. Although Multiple Myeloma is manageable yet incurable requiring ongoing care. The AMPATH Multiple Myeloma programme initiated support groups to address psychosocial concerns of these patients, aiming to enhance their quality of life. The objective of this support is to enhance overall well-being, reduce distress and improve coping strategies. **Methods:** This was a cross-sectional study design using semi structured questionnaires. This was conducted with patients who attended and participated in support group meetings held in March 2023 and November 2023. **Results:** Participants reflected on their experiences with cancer, noting the support received from their healthcare team during their hospital visits. However, upon returning home, they found themselves with feelings of isolation as they navigated their diagnosis alone. The persistence presence of worries, anxiety and stress stemmed from uncertainty about the future. To cope, they turned into support group meetings recognizing the importance of maintaining their treatment regimen while acknowledging the impact of the disease on their overall well-being. **Conclusions:** This support emphasizes on the importance of prioritizing the psycho-social well being of Multiple Myeloma patients, thereby, fostering patient-centered approach to support services that acknowledges and addresses patients' unique needs and experiences.

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Oral Symptom Assessment Using Patient Reported Outcomes (PRO) for Relapsed Multiple Myeloma Patients Treated with Talquetamab

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Introduction: Talquetamab (Tal), a GPRC5D bispecific antibody has significant clinical efficacy in relapsed refractory multiple myeloma (RRMM). However patients commonly report oral symptoms which may impact quality of life. These are not well characterised using standard CTCAE criteria or myeloma specific questionnaires. We therefore used validated oral health-specific questionnaires to better define symptoms. **Methods:** Triple class exposed RRMM patients received Tal 0.8mg/kg Q2W after a step-up phase. Oral health-specific questionnaires: NCI Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Event (NCI-PRO-CTCAE) (Q1-9), Xerostomia inventory and Scale of Subjective Total Taste Acuity (STTA) and EORTC-QLQ-C30 were performed at baseline, weekly for the step-up phase, every cycle through 1-5, every 3 cycles until end of treatment and at 1, 3, and 6 months post end of treatment. Supportive treatments included: saliva substitutes, dexamethasone mouthwash & nutritional supplements. **Results:** 11 patients (4 female, 7 male; median 60 y (range 51-71)), with a median of 5 prior lines (range 4-10) completed 107 questionnaires over a median follow-up of 9.1 months. Compliance for questionnaires was 91%. 9 of 11 (82%) patients responded (≥PR) and 3 are ongoing. At baseline, 7 patients reported dry mouth (median: occasional frequency/mild severity) and 3 reported up to moderate taste changes. At week 2, there were significant increases (p=< 0.05) in dry mouth frequency (median: frequent) & severity (median: moderate). Taste significantly worsened (p=< 0.05) by: severity (median:moderate), impact on daily life (median:sometimes). The STTA score deteriorated to 2 (moderate taste loss, sometimes inconvenient) and significant reductions (p< 0.05) occurred in appetite (median:moderate). The EORTC QLQ-C30 global health status score reduced by a median of 16.7 (p=0.031) and role functioning reduced by 33.3 (change by 10 = significant). All other scores remained stable. At week 3 there were further significant increases in difficulty swallowing (median:moderate, p=0.047), worsening of taste impact to frequent (range:not at all to always), difficulty eating dry foods (median:frequently). The median STTA score worsened to severe taste loss, frequently inconvenient. Additionally, there were further reductions in global health status (median 20.8) and role functioning (median 33.3). PROs detected taste changes earlier than clinician assessment (PRO:day 7, clinician:day 10). However by cycle 3, an improvement in global health status was observed and maintained. Oral symptoms persisted with individual variations. Patients stopping treatment showed improvements in taste, appetite loss and dry mouth at 3 months after last dose. **Conclusions:** Oral specific PROs demonstrated a significant worsening of oral symptoms, global health status with Tal by week 2 followed by an improvement in global health status. Oral symptoms improved by 3 months in those stopping.

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Innovative AI-Driven Decision Support Tool for Multiple Myeloma Using Retrieval Augmented Generation

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Introduction: Managing Multiple Myeloma (MM) requires precise and current treatment information, especially given the rapid advances in genomic research. Existing decision-support tools often lack the latest research and personalized insights. To address this, we developed an advanced Retrieval-Augmented Generation (RAG)-based chatbot uniquely designed for MM management. This tool uses RAG, which combines information retrieval with text generation, leveraging the largest multimodal literature repository and integrating proprietary data and databases like Semantic Scholar. **Methods:** Our chatbot utilizes the unstructr.io framework to systematically analyze and manage over 5 million MM-specific research papers dating from 1932 to 2024. A continuously updated large language model (LLM)-based web scraper populates our repository with the latest studies. The chatbot employs the DSPy framework to dynamically generate and optimize queries, using reasoning loops that reflect physician-like cognitive processes. The Reflexion framework enhances learning from interaction histories, improving response accuracy. The chatbot can address specific queries posed by oncologists, such as those related to rare genetic variants or complex treatment scenarios. **Results:** In a benchmark study comparing the RAG chatbot to existing medical AI platforms, including MedPalm by Google, our tool showed superior performance in several areas. It delivered precise medical recommendations within seconds, reducing average research time by 30% compared to other MM-specific applications. The chatbot achieved a high relevance score as evaluated by MM specialists, providing deep dives into patient-specific genomic data that influenced treatment decisions. It also exhibited a significantly faster adaptation to new MM research, integrating the latest findings and clinical trials into its recommendations. For complex queries involving patients with relapsed MM resistant to standard treatments and specific genetic mutations, the chatbot explored the implications of these genetic changes on standard therapies, suggested potential experimental treatments or clinical trials, and assessed the potential benefits and limitations of combining different targeted therapies. Unlike general models like ChatGPT, our chatbot continuously updates its repository with the latest research and clinical data while

implementing strategies to mitigate data misinterpretation, ensuring more accurate, context-specific, and reliable recommendations. **Conclusions:** Our chatbot offers clear advantages over generic LLMs and lays the groundwork for enhanced precision medicine. By tailoring responses to unique genetic and clinical profiles, it will improve clinical decision-making and patient care. Fine-tuning it on genomic and clinical data allows the chatbot to analyze patient data and prioritize findings based on the latest literature. Additionally, this system can serve as a foundation for tools that educate patients about their condition and treatment options.

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Measuring Symptom Improvement in Idiopathic Multicentric Castleman Disease: Protocol for a Novel Outcome Measure

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Introduction: Diagnostic criteria for idiopathic multicentric Castleman disease (iMCD) were first published in 2017.1 Symptoms are included in these criteria but there is no disease specific symptom scale to aid clinical care. Yet people with this rare lymphoproliferative disorder have a high symptom burden that impacts aspects of daily life, including work/education, social life, travel, mobility, personal relationships, and sexual functioning.2 A novel symptom burden scale for iMCD is timely and important as knowledge of the disease has evolved and a common metric for assessing progression and treatment outcomes would be beneficial. The aim of the study is to develop a patient reported outcome measure (PROM) to quantify symptom burden in iMCD, for use in clinical practice or clinical trials. **Methods:** A protocol for the development of a novel, standardized, PROM for assessing symptom burden in iMCD was developed and approved by a multi-stakeholder group (including patients, clinicians, industry representatives, and researchers). This international study has been registered with ClinicalTrials.gov - NCT05995834. A four-stage development process is proposed, that includes a patient advisory and wider multi-stakeholder advisory group. Stage one includes the development of draft PROM content from existing literature and expert opinion. Stage two explores the content validity of the draft PROM via online qualitative interviews with people living with iMCD. In stage three, the revised PROM will be administered quantitatively alongside existing scales to evaluate its psychometric performance and inform decisions on the final PROM. The PROM will be finalized based on the qualitative and quantitative evidence generated and in consultation with project advisors. Finally, in stage four, the PROM will be re-administered to observe change in symptom burden over time. This will be complemented with qualitative interviews in a mixed methods design to estimate a minimally clinically important difference for the measure. **Results:** Ethics approval for the project has been obtained from Australia, Canada, the United Kingdom, and the United States. The first stage of the project, which involved creating the draft content for the PROM, has been completed. Stage 2 had two parts: reviewing the PROM content and conducting 10 patient interviews, both of which have been finished. The project is now in the third stage, where it is expected that 100 patients will be surveyed using the agreed-upon symptoms identified as important during the consultation processes of stages 1 and 2. **Conclusions:** A new iMCD symptom burden PROM is being developed jointly by patients, academics, clinicians, and industry professionals. The measure is being developed in accordance with FDA regulatory guidelines, with necessary adjustments for rare diseases. The outcome of this research will be a new, validated symptom burden scale, intended for use in both routine clinical evaluation and clinical trials

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Central Nervous System Involvement in Multiple Myeloma Cases Reported at Instituto Nacional de Cancerología

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Introduction: Central nervous system (CNS) involvement in multiple myeloma represents an unusual presentation of extramedullary disease. Infiltration to the CNS in most cases appear as a sign of progression or relapse, representing less that 1% during the disease course. It is associated to a poor prognosis with a mean survival time of 4 to 7 months. **Methods:** A review was carried out from patients diagnosed with multiple myeloma with CNS involvement at the Instituto Nacional Cancerología in Mexico City, between April 2020 and April 2024. All patients had a confirmed diagnosis through imaging studies or cerebrospinal fluid analysis using flow cytometry or cytopathology. **Results:** Two hundred and twenty-eight patients were evaluated. We identified 8 patients with central nervous system involvement, 62.5% were women and the mean age of this group was of 52.25 years. The main clinical manifestations among our patients were amaurosis, headache, neuropathy, paresthesia and neurological deterioration. Other diagnostic methods used were flow cytometry and cytopathology of cerebrospinal fluid, demonstrating 62.5% (0.04%-80%) with CNS infiltration. On the other hand, imaging modalities included MRI or CT; findings revealed 25% cases of CNS infiltration in MRI and 50% in CT. The ISS was evaluated; 50% of the cases stage 1, 37.5% ISS 3 and 12.5% with an ISS of 2. One patient presented a relapse involving the central nervous system 6 months after autologous stem cell transplantation. The first-line therapy used included the combination of thalidomide, bortezomib, and dexamethasone. These medications were administered in half of the patients. Two of the cases were additionally prescribed with bortezomib and thalidomide because of tumor mutational burden. One patient due to functional status and comorbidities required simultaneously intrathecal chemotherapy with dexamethasone, methotrexate and

cytarabine. The overall survival was of 9.68 months (CI±3.41); despite the heterogeneity of regimens used and the implementation of anti-CD-38 therapies in 20% of the patients due to its availability. **Conclusions:** We found a 2.6% incidence of central nervous system involvement in patients with multiple myeloma. Progression of the disease occurred in 83% of the patients, consequently an evaluation for subsequent response to the chemotherapy regimens was not possible. Different types of treatment schemes were prescribed; mainly systemic chemotherapy, followed by intrathecal and in some cases radiotherapy. The median overall survival meets the range described in other populations from Latin America and the rest of the world. The limitations of this study are the low number of cases, due to the follow up time in which the study was carried out. This helps us to be aware that greater registration of this pathology is required not only at the national level, but also at the global level to achieve a strategy that improves the survival and quality of life of patients.

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Approach to Diagnosis and Management of Multiple Myeloma-Related Bone Disease in Latin America, a GELAMM Survey

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Introduction: Bone disease is present in up to 80% of multiple myeloma (MM) cases. These patients are at high risk of pathological fractures and need for radiotherapy or surgical interventions, which leads to impaired quality of life and high costs for health systems. The aim of this survey was to examine regular practices about diagnosis and management of multiple myeloma-related bone disease (MMBD) in Latin America (LA). **Methods:** An anonymous online survey was distributed to hematologists in LA who treat patients with MM via social media platforms and email contact list from the Latin American Myeloma study group (GELAMM) from April 29th to May 20th, 2024. This survey had 25 multiple choice questions, including type of center and clinician's approach to diagnosis and MMBD management. The results were descriptively analyzed. **Results:** 204 responses were recorded from 168 centers in 15 Latin American countries. 57% were from public centers. At diagnosis, 26% reported using PET-CT, 18% whole body low-dose CT, 17% X-ray, and 16% whole-spine MRI. About management, 2.5% responded they don't use any antiresorptive drugs (ARD) for MMBD. Within those who reported to use ARD, 69% employ them in all patients with MM at diagnosis, while the rest claimed using ARD only if patients have bone disease. 83% of physicians reported reinitiating ARD at relapse. 93% reported using zoledronic acid. Denosumab was accessible for 42% of participants, 60% for those in private practice and 25.5% for those in public systems. As for the duration of treatment, 73% claimed using ARD for 2 years, 14% for 1 year and 6% until progression. Regarding schedule, 50% reported using ARD monthly, 10% every 3 months, and 31% monthly the first year and then every 3 months. For patients with Creatinine clearance < 30 mL/min, 41% would employ denosumab (56% in private centers and 28% in public hospitals) and 40% wouldn't use any ARD. 88% executed prior dental examinations, and 58% claimed that this caused a delay for starting treatment. 20% of the participants reported not using Calcium and vitamin D supplementation, and 57% measure vitamin D plasma levels before starting treatment. **Conclusions:** To our knowledge, this is the largest survey about MMBD in LA. There are still centers that use x-ray examinations, an approach that, although no longer recommended, remains the only accessible method in some parts of the region. A large majority of physicians in LA use ARD, with zoledronic acid being the most frequent. Of importance, 31% reported using them only if patients have bone disease. The duration of treatment is usually two years, with very heterogeneous reported schedules. Physicians feel that dental examination delay initiation of ARD, a topic that should be further investigated. The use of calcium and vitamin D supplementation appear to be suboptimal, as well as vitamin D measurement. In conclusion, this information provides useful insights of how we approach MMBD in LA and allows us to identify areas for improvement.

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Whole Body Low Dose Ct (WBLDCT), As Initial Imaging Modality for Newly Diagnosed Multiple Myeloma Patients: Experience From a Tertiary Care Center in North India

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Introduction: For decades, the main imaging modality to detect bony lesions in multiple myeloma was whole body skeletal survey.1 Subsequently, CT, MRI and PET CT came to forefront with better sensitivity and specificity as well as detection of extramedullary soft tissue disease. The disadvantage with CT was the high radiation dose required; hence, low dose CT protocols were developed and has become one of the investigations of choice along with PET CT and MRI to detect bony lesions in multiple myeloma.2 We herein present Whole body low dose CT (WBLDCT) findings in patients of plasma cell dyscrasia presenting at our institute. **Methods:** We retrospectively collected the data from Hospital information system (HIS) & Radiology department for patients of plasma cell dyscrasia from Jan 2022 to Sept 2023. **Results:** The patients included were 73, out of which there were 58 cases of multiple myeloma, 10 cases of MGUS, 2 cases of smoldering myeloma, 1 case of non secretory myeloma, 1 case of plasmacytoma and 1 case of plasma cell leukemia. Lytic lesions were detected in 31 out of the 58 patients of multiple myeloma. The most commonly affected site was vertebra (31.5%)

followed by sacrum and pelvis (26%), ribs and sternum (20.5%), skull (20.5%) and long bones (20.5%). Extramedullary disease was present in 7 patients (9.6%). In 8 patients, bone lesions were the only CRAB feature present, which upgraded the diagnosis from SMM to multiple myeloma. We further analyzed the 13 patients (17.8%) who had 3 or more lytic lesions. Only 2 of these patients had hypercalcemia. On serum immunofixation, 7 of these patients were IgG kappa, 2 were kappa LC, 2 were lambda LC, 1 was IgA lambda and 1 was IgA kappa. 8 of these patients had normal cytogenetics while 5 had gain1q. 11 patients belonged to ISS Stage 3 while 2 patients belonged to II Stage 2. 9 patients had R ISS Stage 2 while 4 patients had R ISS Stage 3. **Conclusions:** This is one the first studies describing the spectrum of bony lesions in Whole body low dose CT in myeloma patients in Indian Scenario.

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Rapid Whole-Body PET/MRI With Fat-Suppressed T2-Weighted Imaging Is Superior to Whole-Body PET/MRI With Diffusion-Weighted Imaging (DWI) in Plasma Cell Disorders

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Introduction: Accurate diagnostic imaging is essential for the proper classification and management of plasma cell disorders (PCD), including multiple myeloma (MM). Whole-body (wb) imaging with low-dose CT and/or MRI with or without PET are widely considered to be the gold standard for imaging, with MRI showing superior sensitivity of early focal lesions, particularly when diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) are applied. However, DWI has limitations in wbMRI, including long scan times, image distortion, and incomplete fat suppression. T2-weighted fast-spin-echo imaging with uniform Dixon-based fat-suppression (T2-Dixon) is an alternative to DWI and may overcome some of these limitations. **Methods:** We retrospectively analyzed imaging and clinical decision making for all patients (pts) at our center with PCD who underwent wbMRI/PET between August 2019 and April 2022. 60 minutes after FDG administration, the following sequences were acquired: two-point Dixon for MR-based attenuation correction, 3D T1-weighted gradient-echo with Dixon, and T2-weighed fast spin-echo with Dixon. Once PET was completed from skull to feet, DWI was acquired. Two trained radiologists interpreted each scan independently and identified suspicious lesions and/or diffuse disease by T2-Dixon, followed by DWI and then PET. These results were then reviewed with a clinician trained in the management of PCD alongside clinical data to determine if the imaging findings would impact clinical management. **Results:** 34 PET/MRI scans were reviewed in this analysis. 25 scans (73.5%) were for pts with MM, 2 (5.9%) for MGUS, 3 (8.8%) for smoldering myeloma, and 4 (11.8%) for solitary plasmacytoma. Median age was 69 (range 31-84). DWI was not obtained in 3 pts who requested exam termination due to discomfort. Among cases with all available imaging modalities, 139 focal lesions were identified. T2-Dixon had a significantly higher sensitivity than DWI and PET, respectively 93%, 66% and 47% ($p< 0.001$). Adding DWI to T2-Dixon resulted in detection of 3 additional lesions, but none impacted clinical management. Adding PET to T2-Dixon and DWI detected 7 additional bone lesions and identified suspicious uptake in an otherwise normal-appearing lymph node. There were 5 false positive lesions for T2-Dixon, 9 for DWI, and 2 for PET. Among 11 cases with diffuse bone marrow disease, T2-Dixon identified all cases, DWI identified 10/11 (91%) and PET only detected 6/11 (55%) ($p=0.06$). **Conclusions:** Whole-body T2 with uniform Dixon fat-suppression detected more lesions than DWI in pts with PCD. Adding DWI to T2-Dixon did not impact disease stage or patient management. However, while PET demonstrated lower sensitivity than T2-Dixon in detection of focal and diffuse disease, it impacted management in one case by detecting extraosseous disease. Whole-body PET/MRI with T2-Dixon demonstrates promise as a rapid imaging modality in assessment of MM and PCD.

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Dietary Oleic Acid Influences the Myeloma Immune Microenvironment and Improves Clinical Outcomes

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Introduction: The impact of the microbiome and dietary interventions on cancer patient outcomes has garnered increased interest in recent years. In various cancer types, microbiome modulation has been linked to patient survival, exemplified by prolonged survival in metastatic melanoma patients following a high-fiber diet. Similar trends are observed in multiple myeloma (MM), where a plant-based diet has positively influenced minimal residual disease (MRD) status in patients treated with lenalidomide. However, further research is essential to fully understand the complex relationship between diet and MM. This study aims to provide evidence-based dietary recommendations to improve outcomes for MM patients. **Methods:** This study included 66 newly diagnosed MM (NDMM) patients between July 2021 and April 2023. NDMM patients reported their dietary habits (N=64) using standardized Food Frequency Questionnaires (FFQs). The FFQ data were analyzed with DGExpert, version 2.0, software. Serum (N=26) and bone marrow (N=27) samples were collected before therapy initiation and analyzed by targeted metabolomics. Bone marrow samples were analyzed by flow cytometry. All patients received Dara-VTD induction therapy, with responses evaluated after four cycles using IMWG criteria. To functionally validate dietary impacts on myeloma, BALB/c mice were engrafted with MOPC-315.BM myeloma cells. Mice were fed either a control diet or a diet supplemented with oleic acid. **Results:** Close correlations were observed between dietary intake and patient characteristics. Notably, high intake of monounsaturated fatty acids, particularly oleic acid (OA), was associated with a lower ISS stage and a higher rate of complete response (CR) to induction therapy in the patient cohort. Patients with OA intake above the median had a CR rate of 36%, compared to 20% in those with intake below the median. In a multivariate model, this effect was independent of age, ISS, cytogenetics, R-ISS, and BMI. Monounsaturated fatty acid intake was also associated with OA concentrations in serum samples, indicating the potential systemic benefits of OA. Additionally, OA intake correlated with a higher abundance of memory CD8+ T cells in the bone marrow. In a preclinical MM mouse model, feeding mice a diet rich in OA before and after tumor implantation prolonged overall survival (OS). **Conclusions:** Our clinical data suggest that a diet rich in plant-based unsaturated fatty acids, particularly OA, influences MM biology and the tumor immune microenvironment, positively affecting clinical outcomes. Notably, we supported our observations in human disease by a preclinical in vivo model of MM, demonstrating prolonged OS with a high OA diet.

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Correlation of the G8 Screening Exam With the Comprehensive Geriatric Assessment in Elderly Undergoing Autologous Hematopoetic Stem Cell Transplantation – Experience From a Single Center in Brazil

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Introduction: Older Adults patients are frequently becoming candidates for autologous hematopoietic cell transplantation (AHSCT) due to the aging population and the increase in incidence of hematological diseases in these population. Advancing age brings geriatric syndromes and vulnerabilities that affect the functional capacity of them. Comprehensive geriatric assessment (CGA) is a multidimensional tool used to identify older adults at increased risk of complications and assist in therapeutic decisions, but it is time-consuming and requires a multidisciplinary team. The G8 is a screening tool that could facilitate the identification of patients who benefited from CGA, but no analysis was done in the AHSCT setting to our knowledge. Furthermore, in the context of multiple myeloma (MM), there are other tools such as the R-MCI and the IMWG score to evaluate older adults patients. **Methods:** Retrospective, single-center study with analysis of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of G8 in relation to CGA. Consider CGA changed if ≥ 2 variables changed and G8 changed if ≤ 14 points. **Results:** 53 patients undergoing autologous HCT were able to be analyzed with all the variables: plasma cell dyscrasias (PCD) (37 patients) and lymphomas (16 patients). The median age was 67 years in both groups. In the group of PCD and lymphomas, the majority presented low risk according to HCT-CI, 67% and 62%, respectively. Cognitive function, emotional and nutritional status were predominantly normal in both groups. Most patients (60% of PCD and 67% of lymphomas) only showed changes in the functionality test (hand grip). Polypharmacy was common in 70% of patients in the PCD group and in 73% of patients in the lymphoma group. According to Fried's criteria, 46% of patients were defined as "fit" in the PCD group, while 50% of patients in the lymphoma group were classified as vulnerable. Regarding the CARG Toxicity scale, we observed that 54% in the PCD group were classified as low risk, while 67% of patients in the lymphoma group were intermediate risk. In our sample, in both groups the majority of patients presented altered results in the G8 test (62% in both groups). On the IMWG scale, the majority of patients, 75.7%, were classified as "Fit", in contrast to R-MCI, with intermediate/high risk predominating (62.2%). Progression-free survival was 55% in lymphomas and 70% in PCD, without statistical significance. The sensitivity of CGA in relation to G8 was 65%, specificity 60%, PPV 94% and NPV 15%. **Conclusions:** The older adults are at greater risk of developing geriatric syndromes and having poor outcomes in HCT. The study did not find that G8 a screening tool was sensitive and specific to replace the need of CGA, as weel, we were unable to correlate the IMWG and R-MCI scales with outcomes. However, CGA remains the best method for evaluating older adults transplant candidates, reflecting results similar to other studies.

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The Impact of Socioeconomic Status on Clinical Presentation in Multiple Myeloma

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Introduction: The association between socioeconomic status (SES) and its impact on cancer diagnosis, treatment, and outcomes

have been studied over several decades. In multiple myeloma (MM), data present some discrepancies. The aim of this study was to analyze the association between SES and clinical characteristics at MM presentation. **Methods:** Clinical and demographic data were retrospectively collected from medical records of all patients diagnosed with MM between January 2015 and February 2023, treated in two public hospitals (an university and a military one) and one private institution, in Rio de Janeiro, Brazil. To assess social class, it was administered the Brazilian Economic Classification Criteria (BECC) version 2021to patients, or to a family member in case of death. The information about the patient's educational level was collected during this interview or from medical records, and per capita income was estimated based on the neighborhood for patients living in Rio de Janeiro and on the municipality for those from other cities. To analyze the associations between SES and MM clinical presentation, patients were categorized as from higher or lower social class (AB x CDE), higher or lower educational level (≤ 9 x > 9 years of study), and with higher or lower income (according to median values found). **Results:** A total of 296 patients diagnosed between 2015 and 2023 from three institutions in Rio de Janeiro, Brazil, were included. For SES assessment, a social class questionnaire was administered to 231 patients or relatives; information about educational level was collected from 239 individuals and per capita income was estimated for 280 cases. Patients from higher social classes had a higher frequency of comorbidities, compared to those from lower classes. However, patients from lower social classes had a longer time from first symptom to the date of bone marrow evaluation, a higher proportion of Durie Salmon stage III and hemoglobin values < 8.5 g/dL, and also higher calcium values, when compared to patients from higher social classes. Among individuals who studied up to 9 years, there was a higher proportion of females, patients with performance status ≥ 2 and delayed diagnosis than those with more than 9 years of study. Individuals with higher estimated per capita income were older than those with lower income. Additionally, a higher proportion of patients with lower income presented with PS ≥ 2 and with symptoms at diagnosis. Among these individuals, the median hemoglobin value was lower, when compared to those with higher income. **Conclusions:** Lower SES was associated with delayed diagnosis, symptoms at presentation, advanced stage, poorer performance status, lower hemoglobin and higher calcium values. These findings underscore the importance of shaping health policies to promote greater equity in cancer diagnosis and treatment access.

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Multidisciplinary, Patient-Centric Bone Disease Management in Multiple Myeloma – a Single-Centre Experience

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Introduction: Bone disease is a prevalent issue affecting up to 80% of patients with multiple myeloma (MM) either at the time of diagnosis or during the disease progression. The frequency of detecting bone lesions varies depending on the imaging techniques employed, with more advanced cross-sectional methods like MRI or PET CT enabling earlier diagnosis. Managing the consequences of myeloma bone disease, such as bone pain, spinal cord compression, nerve root impingement from vertebral collapse, or fractures, necessitates a comprehensive, patient-centered approach. This approach involves a multidisciplinary team consisting of hematologists, radiation oncologists, orthopedic or spinal surgeons, interventional radiologists, nuclear medicine physicians, palliative care specialists, specialist nurses, and rehabilitation experts. We aim to share our experience in establishing a multidisciplinary team (MDT) for managing myeloma bone disease and the resulting outcomes for patients. **Methods:** Our approach begins with identifying patients with newly diagnosed or relapsed MM with symptomatic bone manifestations. These individuals are seen concurrently by a hematologist, palliative care and radiation oncologist, and specialist nurses to optimize pain management with steroids, chemotherapy, and analgesia. Subsequently, their cases are deliberated upon in an MDT tumor board, where their imaging scans are reviewed to determine if intervention by orthopedic surgeons or interventional radiologists can be offered for optimal pain control and functional recovery. Following stabilization of the bones and optimal pain control, patients requiring further rehabilitation undergo an assessment by our oncology rehabilitation specialists. They receive tailored rehabilitation programs, either as inpatients or outpatients, aimed at optimizing their functional abilities. **Results:** Between January 2023 and April 2024, a total of 23 patients, with a median age of 71 (range 26-82 years), were evaluated in this pathway. All patients received analgesia for pain management. Of these, 6 patients underwent open surgery for fracture fixation, 11 patients underwent kyphoplasty or vertebroplasty by interventional radiologists (IR), and 4 patients received radiation therapy in addition to surgical/IR interventions. Upon discharge, all patients showed improvement in ECOG performance status and pain scores, with the median Eastern Cooperative Oncology Group (ECOG) performance status score decreasing from 3 at the time of referral to 2 at discharge. Additionally, there was subjective reporting of reduced pain scores and high patient satisfaction. **Conclusions:** This pathway underscores the significance of personalized bone care, recognizing the unique nature of each bone manifestation and the need for a multifaceted approach. Future endeavors will focus on quantifying the benefits through quality of life assessments and examining the long-term outcomes of patients who underwent MDT care.

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Evaluation of Pseudo-CT MRI Sequences (Zero-Echo-Time (ZTE) and Back Bone (BB) Gradient-Echo) for the Detection of Lytic Bone Lesions in MM: Comparison with PET/CT

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Introduction: MRI is highly sensitive for assessing bone marrow involvement in multiple myeloma (MM), but does not allow assessment of mineral bone and detection of osteolysis. In this prospective study, we evaluated the diagnostic accuracy, repeatability, and reproducibility of two pseudo-CT MRI sequences (zero-echo-time (ZTE) and back bone (BB) gradient-echo) in detecting osteolytic lesions in MM, using whole-body CT (WB-CT) as the reference standard. **Methods:** Between June 2021 and December 2022, we prospectively enrolled consecutive patients with either a newly diagnosed (ND) MM or MGUS, or MM with progressive disease (PD) after therapy. All participants first underwent a clinically indicated 18F FDG-PET/CT, including an optimized WB-CT. They then underwent ZTE and BB sequences covering the lumbar spine, pelvis, and proximal femurs embedded in a 3.0T whole-body MRI (WB-MRI) examination at maximum one-month interval. Ten bone regions and two scores (categorical score: presence/absence of lytic lesion; semi-quantitative score: number of lesions) were evaluated by three radiologists on ZTE, BB, and WB-CT images. Accuracy (ACC), repeatability and reproducibility of MRI scores (from Gwet's agreement coefficients AC1/AC2) and agreement in semi-quantitative scoring were assessed per-sequence, per-region and per-patient. **Results:** A total of 47 participants were included (27 male, median age of 67 years (range 63-70), 21 NDMM, 26 PD, 5 biological progression, 21 progression under therapy with a median of 3 prior lines of therapy (range 1-8). In the per-patient analysis, ACCZTE and ACCBB were very high (=98%) for the 2 readers experienced in pseudo-CT reading, and high (≥ 0.85) for the external reader. In the per-region analysis, both ACCZTE and ACCBB were very high (at least ≥ 0.87) in the coxal bones and femurs; in the spine and sacrum, ACCBB remained high (≥ 0.91) while ACCZTE ranged from 0.74 to 0.89 due to false-negative observations. Regardless of sequences, per-region and per-patient analyses, repeatability was very good (all AC1 ≥ 0.87), while reproducibility was at least good (AC2 ≥ 0.63). Regardless of region, the semi-quantitative scores were higher with BB compared to ZTE. **Conclusions:** Both MRI-based pseudo-CT sequences had a high diagnostic accuracy in detecting osteolytic lesions in MM. The BB sequence had a higher accuracy than ZTE in the spine and a higher agreement with WB-CT. The inclusion of these sequences in WB-MRI may strengthen the value of the technique for the assessment of skeletal involvement in MM. Further studies are needed to assess the added value of these sequences in conjunction with conventional MRI sequences, and compare the diagnostic accuracy of WB-MRI supplemented with these sequences with that of FDG-PET.

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Cryotherapy Prevents Hair Loss in Multiple Myeloma Patients Undergoing Autologous Peripheral Blood Stem Cell Transplantation

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Introduction: The best outcomes for multiple myeloma include the use of high-dose melphalan and autologous peripheral blood stem cell (PBSC) transplantation. Melphalan given prior to the reinfusion of stem cells causes nearly complete hair loss in all patients at the doses used, (CTCAE v5 Grade 2). This outcome is widely expected and leads some patients to avoid doing an otherwise life sustaining procedure. In those that do proceed with the transplant, the alopecia can be emotionally traumatic.Cryotherapy is commonly used to reduce melphalan side effects in the GI tract during stem cell transplantation (Lilleby et.al. 2006). We, thus, initiated a trial to determine if scalp cooling done on both days of melphalan administration would minimize or even completely prevent hair loss. **Methods:** Thirty patients with multiple myeloma or AL amyloidosis undergoing an autologous PBSC transplantation had cryotherapy using the Penguin Cold Cap starting 60 minutes prior to each melphalan administration. All patients received either 70 or 100 mg/m2 of melphalan on 2 consecutive days. The cold caps were applied using manufacturer recommended guidelines (penguincoldcaps.com) and kept on for 5 hours after melphalan was started. Questionnaires were given to patients at Day 0 and 90 during the transplant process to determine tolerability and patient perceived benefit. Photographs were taken at Day -2, 7, 14, 30, 60 and 90 days after the transplant to grade hair loss using the CTCAE v5 guidelines. **Results:** To date, 22 of the 30 enrolled patients have reached the 90-day completion date. Hair loss was minimal to non-existent in all patients with no patients having Grade 1 or 2 hair loss. Photographs show minimal difference between pre- and post-transplant time points with essentially no hair loss noticed except at some areas where the scalp cooling device may not have touched the skin. The procedure was well tolerated with the main complaint being scalp discomfort due to cold. No skin reactions or toxicity was observed. Questionnaires document that most patients would do the procedure again. **Conclusions:** The Penguin Scalp cooling device can prevent nearly any detectable hair loss in patients with multiple myeloma undergoing high-dose chemotherapy and an autologous peripheral blood stem cell transplantation. This result was in marked contrast to the near universal Grade 2 hair loss in patients undergoing a transplant without this procedure. The process is simple, and the patients were overall very pleased with the results. The short 80-minute half-life of melphalan likely explains the better outcomes for multiple myeloma compared to breast cancer patients. This better cosmetic outcome should broaden the usage of high-dose chemotherapy and thus improve overall quality and quantity of life. Final results of the trial including photographs and questionnaire results will be available in time for the conference.

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Application of the IMWG Frailty Score in Newly Diagnosed Multiple Myeloma Patients in a Brazilian Cohort

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Introduction: Multiple myeloma (MM) predominantly affects older adults, presenting significant challenges in treatment management due to the heterogeneity in patient health status. Traditionally, chronological age has been a primary factor in determining treatment strategies. However, chronological age alone may not accurately reflect an individual's physiological condition and ability to tolerate and respond to therapy. Frailty scales, which assess a patient's overall health, functional status, and vulnerability to adverse outcomes, have emerged as critical tools in evaluating MM patients. The IMWG frailty score was designed to include four main domains: age, Activities of Daily Living (ADL), Lawton Instrumental Activities of Daily Living (IADL), and Charlson Comorbidity Index (CCI), and it has been validated in MM patients. The IMWG score categorizes patients into three subgroups: Fit, Unfit, and Frail. This study aims to apply the IMWG score to newly diagnosed MM patients and compare its utility against chronological age. **Methods:** A prospective cohort of newly diagnosed MM patients in a University Hospital was studied. The IMWG frailty score was calculated using the following criteria: age (< 75 years = 0; 75-80 years = 1; >80 years = 2 points), CCI (≤1 = 0; ≥2 = 1 point, with an additional point for each decade above 50 years), ADL (>4 = 0; ≤4 = 1 point), and IADL (>5 = 0; ≤5 = 1 point). Patients were categorized as Fit (0 points), Unfit (1 point), or Frail (2 points). **Results:** The cohort included 39 patients with a median age of 66 years (range 36-91). The ISS scores were distributed as follows: 31% scored 1, 31% scored 2, and 38% scored 3. Performance status by ECOG was 0-1 in 18%, 2 in 18%, 3 in 51%, and 4 in 15% of patients. Regarding the IMWG score, 18 (46%) patients had ADL scores >4, and 21 (54%) had ADL scores ≤4. IADL scores ≤5 was observed in 29 (74%) patients, and 90% (n=35) had a CCI ≥2. The IMWG frailty scores categorized patients as Fit (5%), Unfit (39%), and Frail (56%). The most prevalent comorbidities were renal failure (41%), diabetes (20%), and congestive heart failure (10%). Age, as a single parameter, categorizes patients as Frail and Unfit in 5% and 8% since most patients were aged less than 75 years. However, age, as an additional criterion in the ICC, contributed to point 79% of patients as ICC ≥2 (1 point in the final frailty score) and categorized patients as unfit independent of the comorbidities found. **Conclusions:** In this Brazilian cohort of newly diagnosed MM patients treated in a public institution, the IMWG frailty score classified more than half (56%) as frail and around 40% as ISS stage 3. Age is a double-weighted parameter in the score, contributing to the increase in the frail subgroup. The proportion of frail patients doubled the frequency reported from other reported cohorts. These findings indicate a delay in MM diagnosis and suggest a probable impact of socioeconomic status on health outcomes.

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Dengue Fever in Multiple Myeloma Patients: Clinical Characteristics and Outcomes

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Introduction: Dengue is the most widespread arboviral disease worldwide and is caused by the Dengue virus (DENV), transmitted through vectorial infection by Aedes aegypti, a common mosquito in South America. Common symptoms include fever, headache, joint pain, abdominal pain, rash, vomiting, and blood count alterations such as decreased platelet counts and lymphopenia. There is a lack of data regarding the diagnosis and management of Multiple Myeloma (MM) patients who present with dengue and some presentations may overlap with toxicity of myeloma drugs. Here, we present 11 cases treated during the current epidemic in Brazil, including one case treated with a bispecific antibody (BsAb). **Methods:** We collected clinical data of patients with MM and Dengue being treated at an Oncology Center (AC Camargo Cancer Center) in São Paulo during the first semester of 2024. We described the population based on epidemiology, MM related data and dengue related data. Dengue was graded as per Brazilian Ministry of Health recommendations on a scale of A to D. **Results:** Eleven patients were identified. The mean age was 66 years old [CI: 63-84], and the majority were male (70%), with IgG/Lambda (45.4%) and cardiovascular comorbidities (72.7%). All patients were IMID exposed (100%); most were anti-CD38 (54.5%) and proteasome inhibitor exposed (90.9%). Most patients were currently on treatment (90.9%), in the first line of therapy [CI: 1-4], and the most common regimen was lenalidomide maintenance (27%). Most cases were classified per severity as Dengue C (54.5%) and presented with normal hematocrit [mean 39.4%, CI: 28.4-43.9], lymphopenia [mean 286 cells/µl, CI: 209-1115], and thrombocytopenia [mean 79,000/µl, CI: 23,000-253,000]. Thrombocytopenia worsened during the disease course for most patients [median 16,000/µl, CI: 6,000-203,000], and two patients required platelet transfusions. Hematocrit levels lowered with treatment [mean 32.7%, CI: 28.9-37.2]. Fever was the most common symptom (90.9%) and did not occur in the only patient using teclistamab. Hypogammaglobulinemia was uncommon (27.2%), and intravenous immunoglobulin was used only for the BsAb patient. Grade 1 bleeding (petechiae) occurred in four patients. All patients received support treatment with intravenous fluids, antipyretics and withhold of MM treatment. All patients were admitted for in-hospital stay and were discharged after resolution of symptoms and an increase in platelets. The mean duration of the hospital stay was 8 days [CI: 3-15]. Only one patient needed intensive care. The mortality rate at 30 days was 0%, excluding the five patients who have not reached this mark yet. **Conclusions:** We report here the first cohort of patients with concurrent Multiple Myeloma and Dengue infection. The diagnosis and management are challenging and needs high suspicion in cases without classical symptoms such as fever. Support treatment still seems to offer good outcomes. More data is required for definitive conclusions.

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Patient Experiences in Clinical Trials and Expectations from Future Treatments of Multiple Myeloma: Online Survey and Qualitative Interviews in China

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Introduction: Understanding patient perspectives is crucial to optimize clinical trial (CT) design and accelerate the development of novel treatments. Although the number of CTs in China has increased, CT experiences of patients and expectations from novel treatments have not been well studied. This research aimed to understand these factors in Chinese patients with relapsed/refractory multiple myeloma (RRMM). **Methods:** Data were collected between December 2023 to January 2024 through online surveys (N = 50) and interviews (N = 15) from patients with RRMM or caregivers in China. Quantitative data were analyzed using descriptive statistics, while thematic analysis was used for qualitative data. **Results:** Overall (N = 65), average age of patients was 57 years and 66% of them were male. Most of the patients (69%) were diagnosed with RRMM for >3 years and 97% of patients had participated in CTs by physicians' recommendation. In the survey, 46% of patients expressed difficulty in understanding the information provided by physicians and 94% of them reported shared treatment decision-making with physician. For patients in the survey, the main reason to participate in CTs was access to new drugs and better treatment outcomes (64%). Overall, 88% of patients in survey reported that they complied very well or perfectly to physicians' requirements during the trial. The main reasons for not completing the CT procedure or treatment were uncontrollable factors, poor health, and unclear requirements. In the survey, 96% of patients reported improvement in their disease or physical condition by participating in CTs. Majority of patients (80%) in survey reported having good experiences, while 20% never had a good experience participating in CTs. Conversely, 32% of patients in survey shared bad experiences in terms of more blood collection, frequent hospital visits, and more bone marrow collection, while 68% of patients never had a bad experience. Nearly all patients (96%) in survey showed willingness to participate in future CTs. For future treatments, patients in the interviews preferred oral administration (80%) or treatment at home (53%) and lesser treatment frequency (53%); expected more convenient treatment procedures (53%), and better efficacy and safety (93%). Patients preferred efficacy over safety when choosing new therapies in both survey (58%) and interviews (73%). However, 56% and 57% of patients aged ≥ 60 years preferred safety over efficacy in survey and interviews, respectively. **Conclusions:** Although physician provided sufficient disease information, about half of the patients expressed difficulty in understanding the information, suggesting an urgent need for patient-friendly medical communications. Patients preferred oral treatment, expected more convenient procedures, and preferred efficacy over safety when choosing new therapies. These results would be helpful to improve design of CT for patients with MM and overcome barriers to CT participation.

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Investigation of the Radiological Techniques To Detect Osteolytic Lesions, Fractures, and Osteoporosis in Multiple Myeloma Patients

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Introduction: Multiple myeloma is a malignancy of clonal plasmacytes.Osteolytic lesions represent a criterion for smptomatic myeloma and are associated with bone lose, pathological fractures, and osteoporosis. Skeletal surveys with other sophisticated techniques and dual energy x-ray absorptiometry (DEXA) are used to screen lytic lesions and bone mineral loss, respectively. Here, we aimed to investigate the rates of detection regarding osteolytic lesions and bone mineral loss by several imaging techniques. **Methods:** The Study was carried out in Adnan Menderes University Hospital /Turkey between the years 2004-2022. Three hundred and ten symptomatic myeloma patients were creened retrospectively. The results of radiological techniques were recorded. The detection rate of osteolytic lesions, fractures, and plasmacytomas by imaging techniques, as well as bone mineral loss with DEXA was recorded. Also, associations with gender, myelomatype, lytic lesions, and osteoporosis were investigated. **Results:** Skeletal survey ant PET- CT detected lytic lesions in 71,3% and 81,2 % of patients, respectively. PET-CT had a sensitivity of 96,1% and specificity 90,6% to detect lytic lesions. MRI was only used for patients eith suspicious fractures and detected them for all patients who underwent MRI. The osteoporosis rate was 83,1 % for 113 patients who underwent DEXA. Any association between lytic lesions and gender/myeloma ytpe was not detected. **Conclusions:** Our study demonstrated that osteolytic lesions are not correlated with gender or myeloma type. PET-CT is a sensitive and specific method for detecting osteolytic lesions. Although DEXA is sensitive, its specificity is limited to detect osteoporosis in patients with lytic lesions.

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Gut Microbiota Differences Among Transplant Ineligible Patients With Newly-Diagnosed Multiple Myeloma Treated With dara-len-dex

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Introduction: Emerging studies in MM have shown the association of gut microbiota in MM disease progression, disease response, and treatment toxicity. However, all of the previously conducted work has been done in younger patients with either a precursor condition of MM or those undergoing autologous stem cell transplant. There are no studies of gut microbiota in older transplant ineligible MM patients, which form the majority of patients with MM. The role of gut microbiome may be even more important in older adults with MM, who may have increased gut permeability leading to systemic inflammation and immune dysregulation, altering the gut microbiome and ultimately contributing to poor health outcomes seen in this patient population. The objective of our study was to characterize the gut microbiome among older adults with MM initiating treatment with dara-len-dex. Our hypothesis was that gut microbiome would be different among frail versus fit older adults initiating treatment. **Methods:** Patients with MM who started dara-len-dex were enrolled between January 2023-January 2024. Baseline demographics including frailty status (both IMWG and simplified frailty indices) and disease characteristics were collected in addition to feces samples. DNA was extracted from 23 fecal samples and subjected to 16S rRNA v3-v4 sequencing. We assessed taxonomic diversity through the Shannon and Simpson diversity indices and evaluated beta-diversity using Bray-Curtis dissimilarity. To examine the influence of baseline demographics and disease characteristics on the gut microbiome, we employed Multiple Factor Analysis (MFA), a multivariate method integrating structured groups of variables. This analysis encompassed 20,148 quantitative and qualitative variables organized into 21 variable groups. Multidimensional distance calculations between samples were performed, incorporating taxonomic data, diversity indices, frailty status, disease information, sex, antibiotic and dexamethasone usage, circulating cytokine levels, and various blood markers. **Results:** Results revealed no difference in alpha or beta diversity of the gut microbiome based on sex, frailty status ,antibiotic or dexamethasone usage; however, samples clustering based on frailty status (both IMWG and simplified) and dexamethasone use. Frailty status had the largest impact on community composition, with fit and frail patients forming two distinct clusters. The presence of these clear clusters highlight the significant impact of frailty status and dexamethasone usage on the gut microbiome of patients and their associated variables. No differences were detected based on sex and disease cytogenetics at diagnostics. **Conclusions:** The results of this study suggests that the gut microbiome of patients with MM initiating treatment with dara-len-dex is notably influenced by the frailty status of the patients. Further follow up is ongoing to understand the impact of this frailty-microbiome association on both toxicity and disease progression in MM.

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Cell-free DNA Whole Genome Sequencing for Non-Invasive MRD Detection in Multiple Myeloma

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Introduction: Accurate detection of minimal residual disease (MRD) is crucial for evaluating treatment efficacy in multiple myeloma (MM), yet current methods are invasive and often limited by bone marrow (BM) sample quality. We therefore compared standard MRD methods with whole-genome sequencing (WGS) of cell-free DNA (cfDNA) for less invasive monitoring. **Methods:** The MM Molecular Monitoring (M4) prospective cohort study included 45 newly diagnosed transplant-eligible MM patients (pts) uniformly treated with standard-of-care frontline therapy at 8 Canadian sites. MRD testing was performed at 100 days post-autologous stem cell transplant (ASCT) (n=39) and/or after one year of lenalidomide (len) maintenance (n=33). We analyzed 43 pts by multiparameter flow cytometry (MFC) (71 samples, CytoQuest Technologies), 39 by EasyM (57 samples, Rapid Novor), 28 by clonoSEQ (Adaptive Technologies), and by 18 PET/CT imaging. We performed 30-40X WGS on CD138+ selected BM cells pre-treatment initiation to inform of somatic mutations (n=11) and tracked them by 30-40X WGS in longitudinal peripheral blood cfDNA samples (cfWGS, n=12). **Results:** MRD-negative rates at 100 days post-ACST were 0% for EasyM (n=30), 20% for cfWGS (n=5), 45% for clonoSEQ (n=11), and 49% for MFC (n=39). After 1-year of len maintenance, MRD-negative rates were 22% for EasyM (n=27), 29% for cfWGS (n=7), 41% for clonoSEQ (n=17), 59% for MFC (n=32), and 83% for PET (n=18). Among EasyM-positive samples at 100 days post-transplant, only 21/27 remained positive after one year of maintenance therapy, likely due to delayed M-protein clearance. By May 2024, 12/45 pts had relapsed, with an average time to relapse of 714 days (SD=375) after initiating len. At post-ASCT, all relapsed pts were positive by EasyM (n=6) and clonoSEQ (n=2), 67% (n=6/9) by MFC (mean proportion aberrant cells 0.006%, limit of detection (LOD) range 0.00038%-3.4%) and 50% (n=1/2) by cfWGS. One year post maintenance, all relapse samples were positive by EasyM (n=8), 67% by clonoSEQ (n=4/6), 78% by MFC (n=7/9, LOD 0.00035%-0.38%), 100% by cfWGS (n=3), and 17% by PET (n=1/6). All negative MFC and cfWGS relapse cases were positive below LOD. No EasyM-negative pts relapsed within 2 years (n=6). Relapse within 2 years occurred in 17% of

clonoSEQ-negative (n=2/12), 5% of MFC-negative (n=2/38), 33% of cfWGS-negative (n=1/3), and 33% of PET-negative (n=5/15) samples. cfWGS showed 82% concordance to EasyM (n=11), 67% to PET (n=6), 50% to MFC (n=12), and 25% to clonoSEQ (n=8). The lower concordance to MFC and clonoSEQ was mainly due to cfWGS positives missed by these methods but identified by EasyM. However, 2 clonoSEQ-positive pts were below LOD by cfWGS. **Conclusions:** cfWGS is a promising MRD alternative which is less invasive than MFC and clonoSEQ. It benefits non-secretory and some light chain only patients where EasyM is not currently feasible and uniquely informs of clonal dynamics at progression. Future work will aim to improve sensitivity and validate findings in a larger cohort.

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Study of Cellular Senescence in the Bone Marrow of Multiple Myeloma Patients During Disease Progression

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Introduction: Multiple myeloma (MM) is preceded by monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (sMM), which are characterized by significantly heterogeneous biological and clinical features. MM cells accumulate in the bone marrow (BM) during myelomagenesis, where they interact with various cell subsets, which support their growth and proliferation. Nevertheless, the exact mechanisms leading to overt disease remain unknown. We evaluated potential changes in the BM niche during progression from MGUS to sMM and MM, focusing on the levels of cellular senescence, reported to play an active role in tumor development and cancer cell proliferation. **Methods:** GLF-16, a fluorescent analogue of the dye Sudan Black B which binds to the characteristic senescence biomarker lipofuscin, was used to detect senescent cells both with flow cytometry and fluorescence microscopy. The NCI-H929 and L-363 MM cell lines were driven to senescence with various concentrations (6.25-100 μM) of hydrogen peroxide (H2O2) for 24, 48 and 72 h. Primary BM samples of patients with MGUS, sMM and MM were analysed with the next-generation flow (NGF) cytometry panels together with GLF-16, to evaluate the levels of senescence in normal and clonal plasma cells and in distinct BM cell subsets. **Results:** Exposure of both MM cell lines to H2O2 increased the levels of GLF-16 positive (+) cells in a dose- and time-dependent manner. The optimal H2O2 concentration for inducing maximum cellular senescence and minimum cell apoptosis was 25 μM, leading to 8.5%, 15% and 30% GLF-16+ cells at 24, 48 and 72 h after H2O2 treatment, respectively. Fluorescence microscopy verified the changes in GLF-16+ cell size and the percentages of senescent cells. Primary BM MM cells stained with GLF-16 showed increased expression of the dye compared with BM T cells, mature B cells, NK cells, monocytes and neutrophils, all of which had similar levels of GLF-16+ cells and were used as internal baseline controls. Of note, B cell precursors in all BM samples analyzed, marginally expressed GLF-16 and thus, were used as an internal negative control. Aberrant plasma cells showed a relevant 1.4-1.6-fold increase in the mean fluorescent intensity (MFI) of GLF-16 compared with their normal plasma cell counterparts for all samples tested. No differences were observed in the levels of senescent aberrant plasma cells between MGUS, sMM and MM, although more samples need to be analyzed to highlight alterations between the three groups. **Conclusions:** Senescence has been associated with cancer development, therefore its study and possible implication in MM progression is of great interest. The dye GLF-16 stains senescent clonal plasma cells with high specificity and our preliminary results show that primary BM clonal cells from patients with MM display increased senescence, an observation which can be eventually of clinical significance.

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Establishing MRD Benchmark for Deployment of T-cell Redirection as Post Induction Therapy in Newly Diagnosed Multiple Myeloma

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Introduction: Autologous stem cell transplantation (ASCT) has been the prime post-induction consolidative strategy to increase the depth and duration of response in newly diagnosed multiple myeloma (NDMM). The use of highly efficacious triplet and quadruplet induction regimens offering long term disease control have paved the way for minimal residual disease (MRD) as an important early response endpoint for accelerated drug approval correlating with clinically meaningful outcomes. Novel T cell redirecting therapies (TCRT) produce high response and MRD negativity rates in patients with relapsed MM, and numerous trials are underway to test their efficacy in early line treatment, including in NDMM as alternative to ASCT. Towards this end, it is critical to understand the historical impact of ASCT on MRD burden and generate a benchmark for evaluation of TCRT as consolidation. **Methods:** We collected MRD status by next generation sequencing

(NGS; clonoSEQ®) irrespective of IMWG response post triplet (PI+IMiD+dex) and quadruplet (triplet + anti-CD38 mAb) induction and 60-100 days after ASCT in consecutive patients at one large volume myeloma program along with participants of two single arm phase 2 trials with quadruplet induction followed by ASCT (NCT03224507, NCT04991103). We assessed MRD at 10-5 and 10-6 thresholds. We report the effect of ASCT on MRD negativity rates and quantitative disease burden according to type of induction therapy and in different cytogenetic subsets. **Results:** We obtained post-induction and post-ASCT MRD in 330 patients, 124 (38%) were clinical trial participants, 279 (85%) had received quadruplet induction, 106 (33%) had 1 high-risk chromosome abnormality [HRCA, gain/amp(1q), del(17p), t(4;14), t(14;16), t(14;20)] and 44 (14%) had 2+ HRCA. For patients receiving triplet induction, MRD≤10-5 post-induction was 16% (MRD≤10-6 4%) increasing to 41% post-ASCT (MRD≤10-6 24%). Among patients with MRD≥10-5 post-induction, ASCT lowered the MRD burden≥1 log for 56% patients. For patients receiving quadruplet induction, MRD≤10-5 post-induction was 29% (MRD≤10-6 15%) increasing to 59% post-ASCT (MRD≤10-6 45%). When evaluating based on cytogenetic risk group among patients who received quadruplet induction, MRD< 10-5 post induction was 19%, 31% and 28% (MRD≤10-6 17%, 14%, 10%) which improved to 53%, 66% and 65% respectively, post-ASCT (MRD≤10-6 41%, 50%, 48%) of patients with 0, 1 and 2+ HRCA, respectively. Among patients with MRD≥10-5 post-induction, ASCT lowered the MRD burden≥1 log for 69% patients (60%, 72% and 81% of patients with 0, 1 and 2+ HRCA, respectively). **Conclusions:** This dataset provides granular data to delineate the impact of ASCT on MRD as legacy consolidative strategy in NDMM and provides an important benchmark for evaluation of efficacy of TCRT as experimental consolidative strategy. This information can guide effect size calculation in the design of ongoing and future TCRT trials.

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Advanced circulating tumor DNA (ctDNA) Profiling: Enhancing Non-Invasive Detection and Characterization of Measurable Residual Disease (MRD) in Multiple Myeloma (MM)

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Introduction: MRD assessment in bone marrow (BM-MRD) is a crucial prognostic indicator in MM. Despite MRD testing is well-established in MM clinical trials, it is not yet common in routine practice. Implementing less invasive methods to monitor MRD in peripheral blood (PB) could enhance its adoption in standard clinical settings. **Methods:** This study involved 243 patients undergoing monitoring during MRD assessment in PETHEMA/GEM clinical trials, with BM-MRD processed using next-generation flow (NGF) cytometry. PB-MRD was analyzed in 83 of these patients using ctDNA with CloneSight, a highly sensitive (>10-4) next-generation sequencing (NGS) method based on patient-specific multiplexed amplicon mini-panels targeting somatic mutations identified at diagnosis. Additionally, two cases employed PhasED-Seq, which uses multiple somatic mutations within individual DNA fragments and 67 new BM-MRD positive samples have been included to enhance ctDNA detection sensitivity. In all cases, PB-MRD was then evaluated using BloodFlow, another high-sensitive method (10-7) that combines immunomagnetic enrichment with NGF. **Results:** CloneSight was performed in a total of 83 patients, of whom 9 could not be studied due to the absence of suitable somatic mutations for PB-MRD tracking (88% applicability). A total of 194 longitudinal samples were studied, of which 12 (6%) were PB-MRD positive, from 9 of the 74 (12%) patients. In 166 of the 194 samples, BM- MRD was simultaneously analyzed using NGF. The concordance between PB-MRD using CloneSight and BM-MRD using NGF was 67% (62% double negative and 5% double positive MRD results). The frequency of CloneSight-/NGF+ and CloneSight+/NGF- discordant assessments was 31% and 2%, respectively. Of note, only 3 of the 74 (4%) MRD negative patients relapsed thus far. Upon analyzing PB-MRD with both methods described above, another 4/74 patients were CloneSight- /BloodFlow+, of whom 1 progressed. Of note, the only case (1/74) being CloneSight+/BloodFlow- relapsed. The negative predictive value (NPV) of double negative MRD detection in PB using BloodFlow was about 80%. CloneSight also offered a high positive predictive value (PPV) of 100%. The landmark median PFS of patients with negative vs positive PB-MRD using CloneSight was NR vs 14 months, respectively (HR:11.7, P< .001). **Conclusions:** Our inquiry revealed that CloneSight and BloodFlow effectively detect PB-MRD with high sensitivity detecting ctDNA and circulating tumor cells (CTCs), respectively. In addition, the presence of mutations and CTCs was consistently related to inferior progression-free survival (PFS). These methods also demonstrated a high PPV, suggesting that the identification of such events in the group of BM-MRD-positive patients could stratify those at immediate risk of relapse.NB, AMM, YRH, ML, LN and CG contributed equally to this work as co-authors. JML, BP and NP contributed equally to this work as senior co-authors.

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Characteristics of Immune-Genes Rearrangements in Chinese Multiple Myeloma Patients

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Introduction: Immune genes may play effective roles in malignant hematological diseases. In multiple myeloma (MM), the study of immune genes landscape was rare. MRD monitoring is the most important application of immune genes in MM, providing a strong prognostic measurement for treatment efficiency. Though microenvironment could be crucial in MM, related research was limited. **Methods:** BM and PB samples from patients and health donor (HD) were collected. Using CD138 beads to sort malignant plasma cells in BM, and extracting gDNA from CD138+ plasma cells and T cells from BM and PB to construct libraries for NGS. **Results:** NGS of Ig repertoire (IR) was used to identify tumor clonotypes and build the Ig genes landscape. Based on 269 dominant clonotypes, IGH V3-74 is the most biased gene to use in patients with 1q21 duplication while IGH V1-69 presented higher usage frequency in patients with 13q14 deletion. NGS of IR had higher sensitivity than MFC in MRD detection. There were 22 MFC-negative patients tested positive in NGS of IR in our study, breaking the susceptive MRD-negative situation and also the temporary CR in early therapy. Results of NGS-MRD were highly relative to therapy response, we classified patients into PD, VGPR and CR group that PD group had the highest MRD value, followed the VGPR group, CR group had the lowest value. Then, we performed bulk TCR-seq in BM and PB. Interestingly, the consistency between PB and BM in Shannon diversity and Clonality were great well. However, the clonotypes' uniformity in PB and BM was poor. After that, we build the receiver operating characteristics (ROC) curve of TCR diversity. Compared to HD, TCR Shannon diversity and clonotypes were lower in MM patients while the clonality was higher. The AUC values of TCR diversity were over 0.7 which were reliable. TCR diversity results correlated great well with clinical diagnosis that the ISS-1 group presented the highest TCR diversity index included Shannon index and clonotypes, and the lowest clonality, followed ISS-2 group and then ISS-3 group. According to the clinical responses which were classified into PR-PD group and CR group, TCR diversity index presented great indications, especially Shannon diversity and clonotypes. Most of patients could reach the CR status temporarily during the early therapy, and the CR group showed higher diversity and more clonotypes than the VGPR group. Overall, the above results suggested the huge potency of TCR diversity index to be biomarkers of indicating the clinical responses and prognosis of NDMM. **Conclusions:** In this study, we established the immune-genes rearrangements landscape in Chinese MM patients under different genetic backgrounds, presented a sensitive method in MRD monitoring and uncovered the potency of TCR diversity index to be regarded as biomarkers for MM prognosis.

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Urine Bence Jones Proteins as a Novel Source for De Novo Light Chain Sequencing

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Introduction: Multiple Myeloma (MM) is a type of cancer of the bone marrow characterized by an anormal growth of the number of plasma cells, which produce a monoclonal antibody (M-protein). Blood-based mass spectrometric minimal residual disease (MRD) monitoring of clonotypic M-protein peptides requires M-protein sequence information. De Novo protein sequencing is not always possible, for example because serum samples might not be available, or sequences obtained from serum have low coverage due to interferences coming from polyclonal background in sera with low baseline concentration of M-protein which is often the case in light chain (LC) only multiple myeloma (MM). Bence Jones proteins secreted in urine might be an ideal source to retrieve the light chain sequence as urine is a cleaner matrix and is easy to collect. The aim of this study is to analyze whether M-protein sequence can be retrieved from urine samples obtained from MM patients. **Methods:** Paired serum/urine samples from 23 MM patients with low M-protein concentrations were prepped using in-solution protein digestion and ran on an Eclipwse mass spectrometer (Thermofisher). De Novo Protein sequence analysis and selection of peptides were performed using a several bioinformatics software and the paired urine/serum light chain sequences were aligned using an ad-hoc online tool (https://en.vectorbuilder.com/tool/sequence-alignment.html). Peptides obtained from these sequences were selected for quantitation of M-protein in serum follow-up samples of eight patients using targeted-MS analysis and Skyline software. **Results:** LC sequences were obtained in 19 out of 23 urine samples. 9 of those sequences showed more than 90% similarity with the sequences obtained from serum, including 1 sequence with 100% similarity. 4 sequences showed between 80 and 90% similarity and the remaining showed a similarity lower than 80%. Of this challenging cohort with low M-protein concentrations, we were able to identify clonotypic peptides from all 19 LC sequences. 8/23 patients had follow up serum samples that were used to monitor the clonotypic peptide found in urine and quantify the LC. The clonotypic peptides of 4 of these patients were only obtained from the urine samples. **Conclusions:** Urine provides a suitable alternative to serum for free light chain M-protein de novo sequencing. Good quality peptides that allow the quantitation of M-protein and MRD-monitoring in serum may be extracted from sequences obtained from urine samples; even in cases where no good candidates are obtained from the serum samples.

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Serum BLYS and Soluble (sBCMA) Levels in Multiple Myeloma (MM) Patients

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Introduction: B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS), is important in B-cell differentiation and has three receptors, one of which is BCMA (B-cell maturation antigen). BCMA can be cleaved from the B-cell and circulate as its soluble factor (sBCMA). Although, serum BLyS levels have been investigated for their predictive importance, its prognostic significance remains controversial. sBCMA has an enormous interest at present due to the drugs that work against it. Thus, the objective of this research was to examine the prognostic importance of both, serum BLyS and sBCMA, in patients with MM as well as the possible correlations of these two soluble molecules with different therapies. **Methods:** We studied 64 MM patients from diagnosis until last follow up or death; Medical records were reviewed after patients' informed consent was obtained. Median age of patients was 66 years (57% men, 43% women). Ig type was IgG in 66%, IgA in 22%, light chain in 11% and IgD or biclonal in 1%. Thirty percent of patients were ISS 1, 25% ISS 2 and 45% ISS 3. Serum BLyS and sBCMA was measured at diagnosis. All patients were symptomatic and received treatment immediately. Furthermore, a subset of patients who received (Proteasome Inhibitor, N = 19, Immunomodulatory Drugs, N=16 and Daratumumab, N=22) were evaluated for serum BLyS and sBCMA before therapy. In addition, 4 patients were examined before receiving anti-BCMA treatment. serum BLyS and sBCMA were measured by commercially available ELISA kit (DuoSet® Development Systems), according to the manufacturer's instructions. Frozen sera from 15 healthy individuals were also measured. Median was used as a cut-off point in survival analysis. Statistical analysis was performed using the SPSS v29.0. software. **Results:** Median serum BLyS levels at diagnosis were 121,6 pg/ml (range,14-24785) in patients and 81 pg/ml (range, 14-995) in HI and sBCMA levels were 560 pg/ml (range, 141-50964) in patients and 160 pg/ml (range, 70-1030) in HI. Overall survival was improved in patients with increased sBCMA/BLyS ratio (p=0.029). The levels of sBCMA were preserved increased all over the course of the disease. For all three treatment types, serum BLyS and sBCMA levels were statistically significant lower before treatment (p=0.042 and p=0.027, respectively) and increased at best response. As expected the ratio of BCMA/Blys was decreased at best response compared to treatment initiation. In addition, patients with decreased sBCMA/BLyS ratio showed longer duration of response. (p=0.011). Serum BLyS levels below median before treatment correlated with a response VgPR or better (p=0.04). **Conclusions:** This preliminary results show that serum sBCMA/BLyS ratio is of prognostic significance for overall survival and duration of response. Levels of sBCMA levels remained increased all over the course of the disease. Indeed, we can not say if the levels were increased or decreased, since BCMA is cleaved from the cell surface.

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Tumor Associated Macrophages' cytokines; CD163, CCL4 and CCL2, as Possible New Biomarkers for Overall Survival and Transformation in Smoldering Multiple Myeloma

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Introduction: Tumor associated macrophages (TAM) constitute a major part of the bone marrow microenvironment and play a pivotal role in growth of various hematologic malignancies, such as Multiple Myeloma (MM). Cytokines secreted by TAM, such as hemoglobin scavenger receptor CD163, Monocyte Chemoattractant Protein-1 (MCP1/CCL2), and Macrophage Inflammatory Protein (MIP/CCL4) can be detected in their soluble forms and reflect the TAM burden and function. Interactions between these cytokines and their levels correlate with disease progression and metastases risk, mainly in solid tumors. In our study, we aimed to investigate the clinical utility of those in patients with Smoldering Multiple Myeloma. **Methods:** One hundred and sixty (160) patients were included in the study and clinical and laboratory characteristics were reviewed, after patients' informed consent. Serum sCD163, CCL4 and CCL2 were tested in frozen sera collected at patients' diagnosis in 19, 62 and 62 patients respectively, and in healthy individuals (HI). Measurements were performed by ELISA (Duo-Set R&D Quantiquine) according to the manufacturer's instructions. Their median age was 69 yrs (range, 34-86), 59% were women and 41% men. Median value of variables was used as the cut off point, except for CCL4, for which "detected" or "not-detected" was used. Median time to evolution (TTE) was 103 months (range,4-291), with a total of 13 patients (20%) evolving to symptomatic MM. Median overall survival (OS) was 108 months (range, 11-291). Statistical analysis was performed with the SPSS v.26 software. **Results:** Median sCD163 was 26826 pg/ml (11831- 97286) in HI and 26443 pg/ml (18266 - 39088) in patients with SMM. Median CCL2 was 147.5 pg/ml (22-187) in HI and 176,5 pg/ml (17-9911) in patients. CCL4 was not detected in HI and was detected in 32% of the patients (0-9641pg/mL). Shorter time to treatment was observed in patients with a ratio of CD163/CCL4 above the median (p =0,053) (Figure 1) and a ratio of CCL2/CCL4 above the median (p=0,041) (Figure 2). Patients with a ratio of CCL2/CCL4 values above the median had a statistically significant decreased OS (p=0,051) (Figure 3). **Conclusions:** Our findings reveal that cytokines related to TAMs burden could predict TTE in SMM, and seem to be indicators of OS, supporting that cells of the monocyte-macrophage lineage may play a role in disease

pathophysiology and progression. sCD163, CCL2 and CCL4 could eventually prove to be significant biomarkers in SMM.

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Perspectives of Single-Center Community Hematologists/Oncologists on Minimal Residual Disease Testing Among Patients With Multiple Myeloma

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Introduction: Minimal residual disease (MRD) testing in multiple myeloma (MM) is an important tool for monitoring remission status and relapse. MRD negativity is an independent prognostic factor for progression-free survival (PFS) and overall survival (OS) in MM. However, optimal use of MRD testing remains unclear for healthcare professionals (HCPs). This survey explored hematologist/oncologist (hem-onc) perspectives on MRD testing, barriers to testing, and use of test results for clinical decision-making. **Methods:** This was a prospective survey of hem-oncs practicing in a single community oncology practice with multiple locations throughout Florida, USA. To be eligible, hem-oncs must have been treating patients with MM and have used MRD testing for MM in their clinical practice. The survey questions captured hem-onc perspectives on drivers and barriers for MRD testing, patterns of MRD testing, and the use of MRD testing in treatment decision-making. **Results:** A total of 22 hem-oncs were included in this study, with a median of 2.5 MRD tests ordered per provider between September 2019-October 2023; 86% had >5 years' experience treating MM patients and 73% stated they were comfortable/very comfortable with MRD testing. The 3 most highly ranked reasons for conducting MRD testing were: to monitor patient remission status (91%), to detect recurrence of myeloma (59%), and to aid in treatment decision-making (50%). The 4 most frequently perceived barriers by hem-oncs for MRD testing were: logistics of sending samples to MRD testing facilities (96%), lack of insurance coverage (73%), lack of local testing facilities (68%), and unfamiliarity on next steps based on the results (32%). Most hem-oncs (82%) stated that they only conduct MRD testing if covered by insurance. Most hem-oncs considered MRD testing as essential for patients with high-risk cytogenetics (59%) or transplant eligible patients (55%), while 27% stated that all patients should receive MRD testing, regardless of disease characteristics. Hem-onc perspectives on next steps following a MRD negative test varied: 46% reported that they would not discontinue treatment, with most hem-oncs (86%) reducing the intensity of the regimen to a maintenance regimen. Following a MRD negative test, 36% of hem-oncs reported that they would discontinue treatment, with the most frequent (92%) reason being to give patients a treatment break. Most (77%) hem-oncs considered MRD negativity as an acceptable endpoint in clinical trials, while 18% and 5% preferred the use of OS and PFS, respectively. **Conclusions:** Among hem-oncs who use MRD testing for MM, most were comfortable with MRD testing and used results to monitor disease and aid treatment decision-making. However, opinion on how MRD results should be used to inform clinical decisions was variable. Thus, there remains an opportunity to generate data on the clinical outcome of MRD negative results to inform the use of MRD testing by hem-oncs and guide them in clinical decision-making.

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Daratumumab As Consolidation Therapy in Multiple Myeloma Patients in >VGPR/MRD Positive After First Line Therapy: Final Analysis of the Multicentric Phase 2 Study DART4MM

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Introduction: Although multiple myeloma patients experienced progresses in survivals the disease is still incurable. Novel drugs give deeper responses respect to the past, CR is not sufficient to testify durable response. MRD status measured both by NGF or NGS is a consolidated prognostic parameter in MM trials. A consolidation therapy after ASCT has been reported to increase the level of MRD responses. Daratumumab, IgG/k monoclonal antibody anti-CD38, is now the standard of care therapy. However, trials are ongoing to show Daratumumab efficacy as consolidation/maintanance therapy after a first line of therapy and MM eradication potential as means of MRD negativity, especially if used in a very good responder group of patients after ASCT. **Methods:** Bone marrow aspirates from MM patients, achieving >VGPR after a fixed first line of therapy were collected from 5 centers for MRD positivity. NGF was centralized at the Hematology University of Siena, measured according to Euro Flow guidelines with 2 height colors tubes. MRD detection was set at 10-6 in all samples analyzed. Clinical and biological data as well as molecular cytogenetics information was collected. PET/CT at screening and every 6 months; ISS status and presence of high-risk features by FISH. Daratumumab was given according to monotherapy schedule weekly for 8 times and then every two weeks for 8 times. Primary endpoint was set at 6 months: MRD neg patients stopped the drug,MRD pos patients continued once a month until 24 months. MRD was measured at 2, 6, 12, 18, 24 months (MRD2, 6,12,18,24). PFS and OS were measured and analyzed related to MRD status, FISH risk, ISS. **Results:** Between December 2018 and March 2022 , 110 MM patients were screened and 50 were enrolled.

Median age was 61 (range 40-77); ISS 3 was present in 16% of the patients. High risk cytogenetics in 9/50(18%) patients. 45 patients received an ASCT(1 ASCT 34; 2 ASCT 11) and 5 patients after VMP treatment. Seventeen (34%) patients were judged in CR and 33 (66%) in VGPR at the enrollment. At the primary endpoint 15/50 (30%) patients were MRD negative. Interestingly other 8 patients became MRD negative for the first time after 6 months and during darat therapy between month 6 and 24 and 2 patients had a MRD neg detection at month 2 but unsustained later. Totally 27/50 (54%) MM patients had at least one MRD neg detection. At a median follow up of 41 months (range, 26-65), 23 (46%) patients relapsed (15 before 24 months). Median PFS and OS are not reached. In particular achieving at least one MRD negativity is statistically significant vs not reaching MRD negativity (NR vs 24 months, p=0,001). Particularly, MRD6 negativity is not significant (44 vs 39 months, p=0,44) but MRD12 it is (NR vs 49 months, p=o,0001). **Conclusions:** Dara is efficacious as consolidation/ eradication therapy given 6 to 24 months in multiple myeloma patients already achieving >VGPR but MRD pos by NGF. About a third of patients do achieve long term MRD neg status.

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Evaluating Ethnicity-Specific Risk Stratification Models of Multiple Myeloma With Global Risk Stratification Models in Real Life Scenario

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Introduction: Ethnicity-related biological diversity affects treatment outcomes, yet global risk stratification models for multiple myeloma (MM) often overlook this factor. Previously, we introduced ethnicity-specific risk stratification models: the Consensus-based Risk-Stratification System (CRSS) and Modified Risk Staging (MRS), both incorporating high-risk cytogenetic aberrations (HRCA). This study compares these models in Indian MM patients against global risk stratification models. **Methods:** Patients with MM (n = 244) were stratified as per the ISS, R-ISS, MRS, CRSS, and R2-ISS models. In addition, patients were labelled as high-risk (HR) based on the presence of IgH translocations [t(4::14, t(14::16, t(14::20)] with either 1pdel and/or 1q gain or 17pdel and/or TP53 mutation and compared with those not having HR features. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier survival curves and Cox proportional hazard models. The risk stratification models were compared, and a higher Harrel's C-index and a lower Akaike Information Criterion (AIC) indicated the superiority of a model. **Results:** Out of 244 patients with MM, 163 were treated with a triplet regimen (VRD=86, VCD=59, VTD=11, VPD=7), 67 with a doublet regimen (VD=20, RD=37, DT=10), while 9 and 5 patients, respectively, received melphalan and cyclophosphamide-based regimens as their initial therapy.The ISS and MRS models do not consider HRCA, and the ethnicity-specific model, namely MRS, demonstrated better performance with a superior C-index for both PFS and OS compared to the ISS. Among the models incorporating HRCA, the CRSS, which includes ethnicity-specific information, yielded the highest C-index and the lowest AIC (Table 1). **Conclusions:** The current study highlights the improved efficacy of risk stratification models that utilize ethnicity-specific thresholds for prognostic biomarkers in MM. The CRSS and MRS models include extra biomarkers, i.e., serum calcium, hemoglobin, age, and eGFR, along with modified thresholds for albumin and beta2 microglobulin. Consideration of the unique biology of specific populations and incorporating additional parameters can help improve the performance of risk stratification models.

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Novel Drug Induction Followed With Autologous Hematopoietic Stem Cell Transplantation Plus Maintenance Therapy Improves Survival of Myeloma Patients Harboring 1p32 and Overcomes Its Adverse Prognosis

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Introduction: The prognostic significance of 1p32 deletion in newly diagnosed multiple myeloma (NDMM) remains a subject of

Table 1 (abstract P-172) Performance indices of various risk stratification models for progression-free survival (PFS) and overall survival (OS).

	PFS				OS			
Model	HR	95% CI of HR	C-Index	AIC	HR	HR - 95% CI	C-Index	AIC
ISS	1.888	1.421-2.510	0.6154	1259.84	1.538	1.179-2.0	0.5609	1438.7
MRS	1.902	1.462-2.47	0.6273	1259.8	1.865	1.443-2.411	0.6134	1427
R-ISS	2.304	1.715-3.059	0.6359	1251.97	1.781	1.347-2.356	0.5886	1433.65
CRSS	2.484	1.889-3.265	0.6678	1240.2	2.034	1.59-2.60	0.6244	1417.8
RISS2	1.995	1.517-2.624	0.62	1254.37	1.95	1.479-2.571	0.6089	1423.87
HR-MM	2.008	1.288-3.130	0.5456	1275.01	2.296	1.555-3.390	0.5716	1435.35

debate. Although identified as a high-risk cytogenetic abnormality, studies have produced conflicting results regarding its impact, and it is currently not recognized by the International Myeloma Working Group (IMWG) in the risk stratification for MM. This study evaluated the prognostic influence of 1p32 deletion and assessed the response to treatment in NDMM patients harboring this deletion. **Methods:** In the retrospective cohort of 298 NDMM patients, 172 underwent autologous stem cell transplantation (ASCT), while 126 received non-transplant therapy. We compared the clinical characteristics and survival outcomes between patients with and without the del(1p32) mutation to elucidate its prognostic relevance. **Results:** Of the 298 NDMM patients, 24 (8.05%) exhibited del(1p32). Median progression-free survival (PFS) was 49.0 months for del(1p32) positive patients versus 57 months for those without the deletion (p = 0.019). Median overall survival (OS) was 59.0 months versus not reached (p = 0.001), respectively. Multivariate analysis confirmed del(1p32) as an independent prognostic factor, significantly associated with a higher risk of disease progression (HR = 1.290, p = 0.041) and mortality (HR = 2.347, p = 0.022). In the non-transplant cohort, median PFS was 24.0 months for del(1p32) positive patients compared to 40.0 months for negative patients (p = 0.019), with median OS at 54 months and not reached (p = 0.014), respectively. ASCT patients showed no significant difference in median PFS and OS when stratified by del(1p32) status. However, the median PFS for del(1p32) positive patients increased from 24 months in the non-transplant group to 71 months post-ASCT (P = 0.006), with median OS improving from 54 to 86 months (p = 0.120). **Conclusions:** Del(1p32) is an independent adverse prognostic marker in NDMM. Treatment strategies incorporating novel drugs followed by ASCT and maintenance therapy appear to ameliorate the negative impact of 1p32 deletion, suggesting a potential pathway to improve outcomes for this high-risk group.

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Outcomes of Patients with Newly Diagnosed Myeloma Cast Nephropathy in the Modern Era- A Retrospective Cohort Study

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Introduction: Myeloma cast nephropathy (MCN), caused by the precipitation of immunoglobulin light chain in renal tubules, is a negative prognostic biomarker in newly diagnosed multiple myeloma (NDMM). Trials often exclude patients with moderate-severe renal failure and do not uniformly report International Myeloma Working Group (IMWG) criteria-based renal response. Thus, the outcomes of MCN patients are not well-defined in the modern era, especially in those receiving anti-CD38 monoclonal antibody (anti-CD38mAb)-based frontline therapies. We retrospectively studied the MCN outcomes in the anti-CD38mAb era. **Methods:** 274 consecutive NDMM patients were treated at CUIMC 11/15/18 to 4/01/24. MCN was defined as: no other causes of acute renal failure AND (a) evidence of light chain casts on renal biopsy; OR (b) serum creatinine of >2mg/dL, or 2021 CKD-EPI eGFR of < 40mL/min/1.73m2; ≥1g/d proteinuria; and involved FLC ≥50mg/dL. We used IMWG criteria to define renal response. **Results:** 48 of 274 patients had MCN; 226 were contemporary controls. Median time from diagnosis to treatment in MCN patients was 6 days (IQR: 1-11.5 days). 36/48 MCN patients (75.0%) received upfront anti-CD38mAb-based regimens versus 121/226 (53.5%) controls.178/274 patients (65.0%) had an R2-ISS of at least 3 and 105/274 (38.3%) underwent autologous stem cell transplantation, without significant difference between MCN and controls. Baseline median eGFR (75.3 vs 18.5mL/min/1.73m2) and urine protein (0.336 vs 3.218g/d) were significantly increased in MCN patients vs controls (p< 0.001 for both). 68.2% of patients achieved at least a very good partial response by 6 months without significant difference between MCN and controls (p=0.344). Of 7 MCN patients who required hemodialysis (HD) at diagnosis and survived 6 months, 3 (42.9%) became HD-independent at 6 months, and the remainder were HD-dependent. 6-month renal overall response rate was 72.9%, rate of partial response (PR) or better was 41.7%, and complete response (CR) rate was 37.5%. MCN patients receiving upfront anti-CD38mAb-based regimens had a numerically higher rate of renal PR or better versus those who did not (46.9% vs 37.5%, p=0.425). Median follow-up time was 31.0 months (range 0.8-133.2 months) for controls and 29.4 months (range 4.2-78.1 months) for MCN patients. Overall survival (OS) at 1 and 3 years was 94.4% (87.3-100%) and 73.3% (53.4-100%), respectively, in MCN patients receiving upfront anti-CD38 mAb; and 95.4% (92.2-98.8%) and 84.9% (77.8-92.7%), respectively, in controls (p=0.500). MCN patients receiving upfront anti-CD38 mAb had mean OS within 5 months of control OS (p=0.035). **Conclusions:** MCN outcomes have improved in the modern era: >50% achieved renal response by 6 months and >33% achieved renal CR. There was no significant difference in early mortality between patients with or without MCN at diagnosis. Long-term follow-up is needed to determine if modern therapies can eliminate the negative prognostic impact of MCN.

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Real-World Minimal Residual Disease Testing Patterns: Findings From the Connect® MM Registry

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Introduction: Treatment advances in multiple myeloma (MM) are helping patients (pts) achieve deep remission. As such, the traditional criteria for assessing complete remission may no longer be adequate. Minimal residual disease (MRD) status post treatment is a strong and independent prognostic factor in MM (Szalat R, et al. Haematologica 2024; doi:10.3324/haematol.2023.284662) that was recently recognized as a viable endpoint in clinical trials by the FDA's Oncologic Drugs Advisory Committee (Apr 12, 2024; www.fda.gov/advisory-committees). However, the timing and method of testing are not yet standardized. This analysis assessed MRD testing patterns and explored prognostic signals associated with MRD status in a real-world cohort of pts with MM. **Methods:** The Connect® MM Registry (NCT01081028) is a large, prospective, US observational cohort study of newly diagnosed pts with MM enrolled from Sep 2009 to Apr 2016. Pts with evidence of at least one MRD test from Sep 28, 2009 to Feb 7, 2024 were included in this analysis. Data collected included MRD date, method, and sensitivity; baseline demographics; clinical characteristics; and treatment patterns. All were analyzed descriptively. Time to next treatment (TTNT) from the first MRD test was estimated using the Kaplan-Meier method with start of a new line of therapy as the event and death, study discontinuation, or Feb 7, 2024 as censoring events. **Results:** Among the Connect MM cohort, comprising approximately 3011 pts, 82 (2.7%) had undergone MRD testing. The median age of pts undergoing MRD testing was 61.5 years, and most (61.0%) had Eastern Cooperative Oncology Group performance status score of 0–1 at Registry enrollment. Among these 82 pts, a total of 119 MRD tests had been carried out. Around half (49.6%) of all tests were MRD negative, 41.2% of tests were MRD positive, and 9.2% had an unknown result. The most frequently recorded test sensitivity was 10-6 (22.7%) and the majority of tests were carried out using flow cytometry (81.5%). Around 1 in 4 (26.1%) tests were carried out in pts enrolled in a clinical trial. Most commonly, the MRD tests were carried out during the first line of therapy (41.2%), with lenalidomide, bortezomib plus dexamethasone (RVd) being the most common regimen (16.0%) received by pts in the line where the MRD test was conducted. Median TTNT was longer in pts who were MRD negative (51.2 months) versus MRD positive (4.1 months) at the first MRD test. Around 50.0% of MRD-positive pts initiated a new regimen within 3 months of the first MRD test, compared with only ~ 6.0% of MRD-negative pts. **Conclusions:** This analysis of pts in the Connect MM Registry provides the largest dataset of real-world MRD testing patterns available to date, with enrollment from 2009–2016. MRD testing was uncommon, except as part of a clinical trial. MRD status assessment was not considered standard of care in real-world settings. As such, only a small proportion of pts with MM underwent MRD testing in clinical practice.

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Predictors of Unsustained Measurable Residual Disease Negativity in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma

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Introduction: Most transplant eligible NDMM patients can achieve bone marrow MRD negativity after standardized treatment, but how to maintain long-term MRD-negative status after achieving MRD negativity is a current challenge. The aim of this study was to identify predictive factors for the reappearance of MRD in transplant-eligible patients with NDMM who had achieved bone marrow MRD negativity. **Methods:** We retrospectively analyzed data from transplant-eligible NDMM patients who had been detected as MRD-negative by two-time multiparametric flow cytometry tests. Regular and dynamic bone marrow MRD monitoring was performed at our center, and patients were monitored at the end of induction and every 3 to 12 months after transplantation. **Results:** Out of 390 enrolled patients, 261 (66.9%) achieved MRD negativity. The median age was 55 years, with 70.1% of patients being R-ISS stage II-III. The median time to MRD-negative was 10.3 months. After a median follow-up of 27 months, 37.2% of patients lost MRD-negative status. Among these patients, 28.9% had maintained 3 years of persistent MRD negativity. Additionally, 47.4% of patients had a positive MRD test result before biochemical or clinical progression. The median time from MRD positivity to a progression survival event (progressive disease or death) was 11.4 months.HRCA ≥1, PLT < 100*10^9/L, and reaching first MRD negativity after the start of maintenance were significant predictors of failure to maintain MRD negativity. Maintenance therapy, such as lenalidomide, bortezomib + dexamethasone, and daratumumab, reduced the risk of MRD reappearance compared with thalidomide/interferon administration. **Conclusions:** This study highlights the factors that contribute to the reappearance of MRD in transplant-eligible NDMM patients and emphasizes the importance of early attainment of MRD-negative status and maintenance therapy options to maintain long-term MRD negativity.

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PDCD6 Expression as a Prognostic Indicator in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a clinically heterogeneous malignant hematological disorder with a variable prognosis. The programmed cell death protein 6 (PDCD6) has been linked to the progression of various cancers and is known to be associated with poor clinical outcomes. The objective of this study was to investigate the expression levels of PDCD6 in MM and to explore its correlation with prognostic parameters. **Methods:** We conducted a comprehensive analysis of PDCD6 expression in a cohort consisting

of 8 healthy controls, 11 patients with monoclonal gammopathy of undetermined significance (MGUS), 5 with smoldering multiple myeloma (SMM), 92 with newly diagnosed MM, and 5 with plasma cell leukemia (PCL). PDCD6 expression levels were quantified using quantitative PCR (qPCR). Kaplan-Meier survival analysis and Cox regression analysis were employed to assess the relationship between PDCD6 expression and progression-free survival (PFS) and overall survival (OS). **Results:** PDCD6 expression levels were found to increase progressively with disease advancement when compared to healthy controls. Specifically, PDCD6 expression was higher in patients with MGUS, SMM, newly diagnosed MM, and PCL in ascending order. The optimal cutoff value for PDCD6 expression, as determined by X-tile analysis, was significantly associated with prognostic outcomes in newly diagnosed MM patients. Patients were categorized into high and low PDCD6 expression groups based on this threshold. The Kaplan-Meier survival analysis revealed that high PDCD6 expression was significantly associated with poor prognosis. The median overall survival (OS) for patients with high PDCD6 expression was 29 months, whereas the median OS for patients with low PDCD6 expression had not been reached ($p< 0.001$). Similarly, the median progression-free survival (PFS) for high PDCD6 expression patients was 19 months compared to 41 months for low PDCD6 expression patients ($p< 0.001$). Clinical correlation analysis indicated that high PDCD6 expression was significantly associated with older age, advanced ISS stage, and deletion of chromosome 17p in MM patients. The Cox regression analysis demonstrated that high PDCD6 expression, along with older age, advanced ISS stage, and chromosome 17p deletion, were independent adverse prognostic factors for both PFS and OS. Notably, PDCD6 overexpression was identified as an independent prognostic factor, suggesting its potential utility in prognostic stratification of MM patients. **Conclusions:** Our study underscores the importance of PDCD6 in the prognosis of multiple myeloma and provides a foundation for further research into its clinical applications. The identification of PDCD6 as an independent prognostic factor offers valuable insights for the development of targeted therapies, ultimately aiming to enhance patient management and outcomes in multiple myelom

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Leveraging AI for Modeling MRD and Survival Outcomes in Multiple Myeloma Based on Comprehensive and Up-to-Date Clinical Evidence

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Introduction: Minimal residual disease (MRD) has been recently accepted by FDA as an endpoint for accelerated approval in multiple myeloma. Aggregate analysis on the correlation between MRD and survival outcomes requires extensive manual literature review. By leveraging AI with expert-in-the-loop, we are able to generate reliable evidence from a comprehensive list of clinical studies with up-to-date outcomes. **Methods:** This study presents an AI-assisted framework that identifies relevant studies and filters critical information to analyze clinical data. The associations between MRD and various survival endpoints across different patient populations were modeled using weighted least squares. The strength of these associations was measured by the coefficients of determination (R^2) with their 95% confidence intervals. **Results:** The AI searched for eligible studies reporting progression-free survival (PFS), overall survival (OS), overall response rates (ORR), and MRD data with more than 50 patients per treatment arm, using next-generation flow cytometry or sequencing methods with a minimum sensitivity of 10^-5 from January 1, 2010, to May 29, 2024. This enabled us to extend the list of studies from 15 to 26 trials. The analysis results reported R^2 of 0.75 (0.58 - 0.92) for PFS hazard ratio (HR) versus MRD negativity odds ratio (MRD- OR); 0.44 (0.14 - 0.75) for OS HR versus MRD- OR; and 0.54 (0.27 - 0.80) for ORR OR versus MRD- OR. Subpopulation analysis yielded R^2 of 0.64 (0.38 - 0.90), 0.85 (0.73 - 0.97), and 0.75 (0.56 - 0.94) for PFS HR versus MRD OR in newly diagnosed transplant-eligible, newly diagnosed transplant-ineligible, and relapsed or refractory MM patients, respectively. **Conclusions:** This research introduces a novel way to conduct automatic, contemporary analyses of the association between MRD and different survival endpoints. Furthermore, the analysis results corroborate the validity of using MRD as an endpoint for accelerated approval.

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Rates of Successful Diagnostic Clonal Identification (ID) With Adaptive clonoSEQ®

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Introduction: The FDA's Oncologic Drugs Advisory Committee (ODAC) voted 12 to 0 supporting the use of minimal residual disease (MRD) as a regulatory end point for accelerated approval of new treatments for patients with multiple myeloma. In this context, the most used MRD testing in the United States is clonoSEQ® that leverages next generation sequencing (NGS) and polymerase chain reaction (PCR) to identify and quantify rearranged and translocated receptor gene sequences, a trackable marker of myeloma MRD burden at any given time. First, a successful diagnostic clonal identification (ID) is needed for any future MRD tracking of the identified clones. We have evaluated the rates of successful clonal ID at our institution. **Methods:** We have established an institutional practice at Emory Winship Cancer Institute to send samples for clonoSEQ® identification (ID) and MRD testing. We have identified 3553 myeloma patient samples sent to Adaptive clonoSEQ® ID (N=1164) and MRD (N=2389) assessments between 01/2018 and 03/2024. We have evaluated testing by era to identify rates of detection of clonal ID: era 1 from 01/2018-12/2021 and era 2 from 01/2022-03/2024. SPSS version 29.0, Chicago was used for statistical analysis. **Results:** Among the 1164 samples sent for clonal ID, the median time from the sample collection at diagnosis to ID testing was 94.71

weeks (0.14-1001.29). Median time from sample collection to ID testing differed by era of testing: era 1 vs era 2 - 121.71 weeks (0.14-1001.29) vs 47.14 weeks (0.29-804.9), p< 0.001. Median time from testing to reporting ID results is 1.43 weeks (0.71-216 weeks), which did not differ by the era 1 vs 2 - 1.29 (0.71-216 weeks) vs 1.71 (0.71-188 weeks). Diagnostic clonal identification occurred in 82.8% of patients. Failed testing (10%) and polyclonality (7.2%) were the most common reasons to prevent clonal identification. In the more recent years, after 01/2022, successful clonal identification occurred in higher number of patients. Compared from era 1 to era 2, successful clonal ID was higher (91% vs. 79%, respectively, p< 0.001), failed testing was improved (2.1% vs 13.1%, respectively, p< 0.001) while the rates of polyclonality did not differ (7.3% vs 6.9%, respectively, p=NS). **Conclusions:** In aggregate, diagnostic clonal identification for assessment of future MRD testing occurred in 82.8% of patients. In the more recent years (after 01/2022), successful clonal identification by clonoSEQ® occurred in 91% of patients with a significant decline in failed testing (2.1%). This likely represents an effect of the denatured DNA samples captured from era 1. Polyclonality continues to be a major deterrent for successful clonal identification in 7% of patients. Our data informs the industry sponsors and the investigators to accurately plan for sample size estimations for future clinical trials using MRD as an endpoint.

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MRD Tracking in Blood Using a De Novo Sequencing From SPEP Gel of M-Protein in Multiple Myeloma Patients

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Introduction: Multiple Myeloma (MM) is considered as a rare blood disease, characterized by the uncontrolled growth of malignant plasma cells in the bone marrow, leading to the secretion of monoclonal immunoglobulin (M-protein). Current routine techniques like serum protein electrophoresis (SPEP) and immunofixation (IF) offer reliable detection, but their sensitivity is limited for complete response assessment. Sebia's M-inSight assay emerged as a novel, ultra-sensitive, and non-invasive liquid biopsy tool for monitoring Minimal Residual Disease (MRD) in MM patients. M-inSight utilizes cutting-edge mass spectrometry (MS) to accurately identify and quantify unique clonotypic peptides. Unlike traditional MS techniques analyzing intact M-proteins, M-inSight bypasses interference from the polyclonal background by targeting these unique clonotypic peptides. Identifying the best clonotypic peptides, typically done with a baseline serum sample, is required for patient signature. This study proposes a combined approach utilizing the high sensitivity of M-inSight with the specificity of HYDRAGEL SPE for M-protein sequencing. This combination aims to provide an addition to the M-inSight workflow proving a powerful tool for longitudinal monitoring of MRD in MM patients. **Methods:** Samples from 15 newly diagnosed non eligible for transplantation MM patients from a Sanofi clinical trial (NCT02513186) were chosen to assess the de novo sequencing in gel of the M-protein. All patients were selected from VRDI Part B cohort (bortezomib, lenalidomide, dexamethasone) consisting of evaluating the preliminary efficacy (complete response [CR] rate) of isatuximab administered at the selected dose in combination with bortezomib based regimen. Serum samples were separated through electrophoresis gel on Hydrasys 2 (Sebia). The M-protein bands were excised and directly digested with specific enzymes for the de novo sequencing using mass spectrometry. Same serum samples were sequenced using Melon gel enrichment to allow a direct comparison of the 2 sequences obtained with both preparations. **Results:** Sequences were obtained for the light and heavy chains using both preparations. Each M-protein sequence had a coverage of at least 95% with a confidence of 98%. The sequences obtained with both techniques showed a similarity ranging from 90 to 100%. Identical clonotypic peptides were found for all patients when comparing both methods, allowing a quantitative monitoring of a total of 302 serum samples. M-insight was able to monitor the disease on 5 patients who had a stable disease with a low level of M-protein. All 4 patients that developed PD had an increase of M-protein of at least 2-fold at 2 consecutive timepoints. The lowest M-protein concentration level measured by M-InSight was 0.01 mg/dL. **Conclusions:** Identical M-protein sequenced from the gel and directly from serum demonstrates the specificity and robustness of M-inSight in serum. The separation in gel allows an alternative sample preparation for M-protein sequencing.

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Implementation of a Stepwise Systematic FISH Strategy in Identifying Clinically Relevant Cytogenetic Abnormalities in Plasma Cell Neoplasms in Resource Constraint Settings

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Introduction: Pre-treatment cytogenetic characterization is an integral part of modern treatment protocols in Plasma cell neoplasms (PCN) and is essential for risk stratified therapy. Genetic characterization is routinely performed by Fluorescent in situ hybridization (FISH) analysis on CD138 positive enriched plasma cells to identify IgH gene rearrangements, trisomies, 1p deletion/1q amplification and 17p deletion. A comprehensive characterization involves testing for multiple partners of the IgH gene a systematic testing strategy is essential to judiciously use resources and the limited number of CD138 enriched plasma cells. We present a systematic cytogenetic strategy performed in a stepwise manner to judiciously use enriched plasma cells and also save resources. **Methods:** 629 PCN patients were diagnosed at our center from January 2017-December 2022. Interphase FISH was performed on positively selected CD138 plasma cells in a stepwise manner.

The first step included FISH analysis using TP53 deletion probe and IgH break-apart probe. Patient samples that tested positive for IgH rearrangement were reflex tested using specific fusion probes to identify the partners. Testing for t(11;14) and t(6;14) was done first to rule out the standard risk IgH rearrangements followed by identifying high risk IgH rearrangements i.e. t(4;14),t(14;16), t(14;20). The extended panel included testing for hyperdiploidy (gains of 5, 9 and 15) and 1p deletion/1q amplification. FISH analysis for CMYC was performed in a subset of patients. **Results:** Cytogenetic abnormalities were identified in 435 patients (69.15%). IgH gene rearrangements were seen in 20.8% (129/629) of patients with t(4;14) been the most frequent (8.7%,55/629) followed by t(11;14) (5.08 % 32/629). No IgH partner could be identified in 30 IgH rearranged patients. 17p deletion was observed in 10.49% (66/629) of patients and hyperdiploidy in 19.2% (121/629). Chromosome 1 related abnormalities were detected in 36.8% (232/629) of patients with 1p deletion in 6.04% and 1q gain in 30.84% patients. cMYC gene rearrangement was seen in 1.58% (10/629) cases, all of which were associated with 1q amplification and plasmablastic morphology. **Conclusions:** A systematic stepwise FISH analysis on enriched CD138 positive plasma cells is an effective efficient strategy to identify the cytogenetic abnormalities that are essential for risk stratified therapy in modern treatment protocols. We report a relatively higher frequency of TP53 in comparison to the western literature. The frequency of cMYC rearrangements is less in our cohort as the analysis was done in a subset of patients subject to availability of plasma cells.

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Impact of Minimal Residual Disease in Apheresis Product (aMRD) Assessed by Multiparametric Flow Cytometry (MFC) in Transplant-Eligible Multiple Myeloma (MM) Patients

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Introduction: The assessment of MRD by MFC in bone marrow (BM) is one of the strongest prognostic factors for predicting progression-free survival (PFS) in MM. Although the presence of aMRD hampers the outcome of patients who underwent autologous stem cell transplantation (ASCT), its value is not completely understood. The aims of the study were to evaluate the prognosis factor associated to aMRD detection and its correlation with response and PFS. **Methods:** A retrospective observational study was designed including patients who received ASCT between 2005 and 2023 at the University Hospital of Salamanca. The aMRD evaluation was performed by MFC. **Results:** Forty-three (10.4%) of the 414 patients who received ASCT had aMRD +ve. The median age at ASCT was 60 years, 64% were men, 27% ISS-3 and 18% had high risk cytogenetic (HR). No differences were observed between aMRD +ve and -ve patients according to the baseline characteristics. Ninety percent of the cohort received ASCT in 1st line, and both aMRD +ve and -ve groups were treated with similar induction schemes, and a similar number of patients received subsequent consolidation and/or maintenance therapy. No differences in aMRD detection were observed based on induction schemes or number of cycles prior to stem cell harvest. Patients with aMRD +ve achieved poorer responses than those with aMRD -ve before the stem cells harvest (very good partial response or better: 26% vs 68%, P< 0.001). In addition, the presence of aMRD +ve identified patients with poorer responses than those with aMRD -ve: at ASCT (MRD -ve in BM: 0% vs 22%), after ASCT (MRD -ve in BM: 14% vs 51%) and during follow-up (MRD -ve in BM: 23% vs 62%) (all P< 0.001). With a median follow-up of 56 months, patients with aMRD +ve had significantly lower PFS than those with aMRD -ve (31 vs 58 months, P=0.002). In HR patients, the aMRD -ve did not overcome their poor prognosis and the median PFS was comparable to those patients with aMRD +ve (both 33 months; P=0.679). By contrast, patients with ISS-3 and aMRD +ve experienced shorter median PFS than those with aMRD -ve (18 vs 42 months; P=0.009). Three prognostic groups of patients were established according to aMRD and MRD in BM status before ASCT: aMRD plus MRD +ve in BM (31 months), aMRD -ve plus MRD +ve in BM (49 months, P=0.007) and aMRD plus MRD -ve in BM (72 months, < 0.001). Likewise, the aMRD plus MRD in BM +ve group presented higher probability of early relapse after ASCT (PFS ≤24 months) than the remaining groups: 46% vs 37% vs 35% (both P=0.046). **Conclusions:** The response achieved before stem cell harvest was the only prognostic factor associated with the aMRD detection in our series. The presence of aMRD was associated with inferior responses and PFS in patients undergoing ASCT, with a half of them experiencing early relapse. The impact of aMRD according to the different sensitivity reached with MFC, as well as an external comparison with a transplant center that does not perform aMRD, will be presented at the meeting.

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Monoclonal Gammopathy of Uncertain Significance (MGUS) Like Profile in Transplant-Eligible Multiple Myeloma (MM) Patients: Clinic-Biological Characteristics and Prognosis Significance

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Introduction: The MGUS-like model allows to identify three groups of MM patients with different progression-free survival (PFS) by quantification of plasma cells (PCs) and clonal PCs in bone marrow (BM): MGUS-like, intermediate, and MM-like groups. However, the characteristics of these groups and their effect on response were not evaluated, furthermore, the model has not been validated in real-world patients. **Methods:** A retrospective observational study was conducted including patients who received autologous stem cell transplantation (ASCT) between 2005-2023. The MGUS-like profile was determined at diagnosis using the calculator available in http://www.mgus-like.com/. **Results:** The model was applied in 402 patients: 38 were MGUS-like (10%), 182 were intermediate and 182 were MM-like profiles (both 45%). MGUS-like patients had less anemia (Hb ≤10 g/dL: 7%), renal failure (CrCl ≥2 mg/dL, 0%), BM infiltration assessed by cytology (≤10% of PCs: 71%), and less secretory disease, but more presence of lytic lesions (87%) and paraskeletal plasmacytomas (70%), compared to the intermediate and MM-like profiles (all P< 0.05). No MGUS-like patients were ISS/R-ISS 3, whereas these patients enriched the intermediate (23%/13%) and MM-like groups (36%/20%) (P< 0.05). MGUS-like patients had fewer high-risk cytogenetic abnormalities than intermediate and MM-like patients: t(4;14) (4% vs 8% vs 11%), t(14;16) (0% vs 2% vs 2%) and gan1q (0% vs 25% vs 31%) (all P< 0.05). No differences were observed in del1p. However, del17p was more frequent in the MGUS-like than the intermediate (9%) and MM-like groups (22% vs 9 vs 6%; P< 0.05). The median age at ASCT was 60 years, and 90% of patients received ASCT in 1st line. No differences were observed among groups in induction, consolidation, and maintenance schemes. More patients with MGUS-like profile achieved complete response with minimal residual disease (MRD) negative (75%) compared to the intermediate (57%) and the MM-like profiles (53%) (both P< 0.05). With a median of follow-up of 56 months, the median PFS of MGUS-like group was not reached and was significantly prolonged compared to the remaining groups: intermediate (63 months) and MM-like (42 months) (both P< 0.05). Notably, no differences were observed in PFS of MGUS-like patients according to del17p status (both not reached). Also, in those patients with ≥8 years of follow-up, MGUS-like patients had excellent outcome, with an 8-year PFS of 80%, compared with 53% in the intermediate (P=0.06) and 41% in the MM-like groups (P< 0.05). **Conclusions:** The MGUS-like profile identified transplant-eligible patients with less aggressive disease and with fewer high-risk abnormalities but with more lytic lesions and plasmacytomas. The MGUS-like profile was a predictor factor for MRD negativity. The prognostic model was validated in our series and the MGUS-like group presented longer PFS and could be a prognostic tool to predict the long-term efficacy of ASCT.

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The Utility of Mass Spectrometry in Defining Minimal Residual Disease in Treated Multiple Myeloma Patients

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Introduction: In multiple myeloma (MM), minimal residual disease (MRD) negativity following therapy correlates with longer progression-free survival (PFS). The FDA has recently approved the use of MRD in complete response (MRD in CR) as an accelerated approval endpoint in MM trials. Compared with gold standard bone marrow (BM) MRD techniques, a minimally invasive blood-based MRD test would be ideal due to ease of collection and ability to take longitudinal measurements. Mass spectrometry (MS) techniques provide a highly sensitive method to detect and monitor patient specific M-proteins. This study aimed to compare the sensitivity and prognostic utility of MS with BM next generation flow cytometry (NGF) at MRD time points and with IMWG CR criteria at best response and MRD timepoints within a UK hospital setting. **Methods:** MS analysis was performed within a UK hospital laboratory using a MALDI-TOF MS system (EXENT, The Binding Site, UK). Transplant eligible and non-transplant eligible patients were recruited at varying stages of disease. Median follow up was 18 months. A total of 240 serum samples from 137 individual patients were tested for the presence of M-protein by conventional methods (serum electrophoresis (SPEP), immunofixation (IFE), free light chain (FLC)) and MS. BM NGF was performed to a sensitivity between 10 -5 and 10-6 at pre- and 100 days post-transplant for a subset of patients. **Results:** When compared to conventional techniques MS showed increased sensitivity over an algorithm of SPEP, IFE and FLC. Comparing MS against NGF results, agreement at pre-transplant was 88%. At post-transplant agreement

was 56%, with 4 NGF negative samples being MS negative and 4 NGF negative samples being MS positive.Evaluating PFS at post-transplant showed that a negative NGF MRD status approached significance (p=0.051). At this same time point the IMWG response status (CR vs non-CR) did not have a significant association with PFS (p=0.44). However, MS positivity post-transplant was significantly associated with an inferior PFS outcome (p=0.02). When evaluating patients at best response, 80% of samples classified as CR were MS positive. Across all response groups MS negativity showed a significant PFS advantage and this was also seen when analysing those in CR only (p=0.002). This suggests that MS can be used to define deeper response groups, including refinement of "MRD in CR". **Conclusions:** This study aimed to evaluate the viability of using MS to identify M-proteins and define MRD in treated MM patients in a hospital laboratory setting. We found MS outcompeted the algorithm of SPEP/IFE/FLC in detecting the presence of M-protein. Our data suggest that MS negativity carried comparable prognostic performance to BM MRD negativity at the 10-5 to 10-6 threshold. We propose that MS is a powerful MRD tool that can be complementary to BM MRD techniques and be used to guide BM sampling. The use of a blood-based assay will improve the patient experience of MRD testing.

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Single Tube Twelve Color Flow Cytometric Myeloma MRD Assay- A Single-Center Experience From Eastern India

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Introduction: Advances in diagnosis, risk-stratification and treatment modalities have led to attainment of deeper responses in multiple myeloma (MM). Minimal/measurable residual disease (MRD) is an important prognostic factor evaluating the depth of response post-therapy. MRD analysis by conventional multiparameter flow cytometry (MFC) has a low sensitivity, identifying up to 1 myeloma cell in 10,000 cells. To reach a higher sensitivity international myeloma working group (IMWG) recommends EuroFlow group developed 2-tube 8-color next-generation flow cytometry (NGF) for myeloma MRD evaluation. To incorporate the NGF-MRD in myeloma we developed a single tube 12-color high-sensitivity myeloma MRD panel. In this study, we present the data obtained from NGF-MRD from our laboratory. **Methods:** A total of 70 samples from 46 myeloma patients were studied post-bortezomib based therapy at different time points. Five post-autologous stem cell transplant (ASCT) samples were also included. NGF-MRD was performed on a single tube 12-color antibody panel (CD38, CD138, CD45, CD19, CD20, CD81, CD27, CD56, CD117, CD229, kappa and lambda). All the samples were processed following a bulk lyse-stain-wash protocol. To reach adequate sensitivity acquisition of five million events were acquired whenever possible. A total of 20 events and 50 events were considered for the lower limit of detection (LOD) and lower limit of quantification (LOQ) respectively. Simultaneous evaluation of bone marrow morphology, serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE) and serum free light chain assay (sFLC) were also performed. **Results:** The overall MRD positivity was 57.1% (40/70 samples, MRD range 0.0005%-8.04%). Except one sample (MRD, 0.0005%), LOQ criteria was achieved in all positive MRD samples. Five million cells could be acquired in 65.7% samples (46/70 samples). Significant hemodilution was present in 19 samples (based on mast cell%). A light chain restriction could be demonstrated in 100% of MRD positive samples. CD19, CD45 and CD56 were able to identify abnormal plasma cells in 95%, 92.5% and 92.5% MRD positive samples respectively. 12 samples had MRD level below 0.01%. 30% (12 samples) of all MRD positive cases were in stringent complete response (sCR) at the time of MRD evaluation. 36.6% of MRD negative samples were showing residual monoclonal protein on biochemical evaluation. **Conclusions:** In this study we demonstrated a single tube 12-color myeloma MRD assay which is highly sensitive and could achieve the desired sensitivity recommended by IMWG response assessment guidelines. A significant proportion of patient with sCR with MRD positivity could be identified. A proportion of patients with biochemical evidence of disease and MFC-MRD negativity were noted in this study as described in the literature.

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Identifying a New Risk-Stratification Strategy by Including Single-Cell Biomarkers in Multiple Myeloma

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Introduction: Despite advances in new therapies, a subset of multiple myeloma (MM) patients still faces poor prognosis. Identifying these ultra-high-risk patients is of paramount importance. Existing staging methods, such as R-ISS and R2-ISS, do not incorporate gene expression information of tumor cells. Our aim is to develop a novel staging method for MM that integrates traditional staging factors, cytogenetics, and gene expression information. **Methods:** To accurately identify novel biomarkers associated with patient prognosis, we performed single-cell sequencing on bone marrow aspirates from four ultra-high-risk patients (OS < 24 months) and eight non-high-risk patients (OS > 24 months) undergoing VRD treatment. We utilized multivariate COX regression analysis to evaluate new gene markers and traditional staging factors, and developed a new staging strategy by employing a weighted scoring method. **Results:** Firstly, we classified Ig light chain-restricted MM cells into 10 cellular subclusters by unsupervised clustering. Besides

subcluster 4, the other subclusters of MM cells group together. We found that subcluster 4 was significantly increased in patients with overall survival less than 24 month. Of note, compared to other MM cells, subcluster 4 displayed higher proliferation and drug resistance scores. We further identified seven genes significantly increasing in subcluster 4 and constructed a seven-gene score to represent the characteristics of subcluster 4. Using the dataset of CoMMpass study of newly diagnosed MM patients, multivariate COX regression analysis revealed the seven-gene score is an independent prognostic factor. The seven-gene score more effectively identified ultra-high-risk patients compared to UAMS70 and SKY92. Based on the hazard ratios from the multivariate regression, we assigned weighted scores to the independent prognostic factors, including ISS stage, del(17p), 1q+, t(4;14), and the seven-gene score, and established a new staging model, MR-ISS. Compared to the ISS, R-ISS, and R2-ISS staging systems, the MR-ISS established in this study more evenly risk stratified patients (Low 16%, Intermediate 34%, High 38% and Ultra-high 11%), and better identified ultra-high-risk patients (OS < 24 months). We further validated the performance of MR-ISS using the GSE136337 dataset and an internal dataset. Additionally, we quantitatively assessed the 7-gene score in 139 newly diagnosed patients using both single-color and multi-color ddPCR, confirming its superior performance of the MR-ISS staging system and providing the possibility in clinical routine assay. **Conclusions:** Our study identified an aggressive characteristic with seven genes highly expressed in ultra-high-risk patients by single-cell RNA-sequencing. A further risk stratification system (MR-ISS) incorporates ISS stage, del(17p), 1q+, t(4;14), and the seven-gene score was developed. Our study provides a more effective and convenient risk-stratify model in clinical practice to identify the ultra-high-risk group patient.

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Prognostic Implication of JAM-A Expressing Circulating Tumor Plasma Cells in Multiple Myeloma

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Introduction: Junction adhesion molecule A (JAM-A), is a protein expressed in various cell types, including endothelial cells, leukocytes, and plasma cells (PCs). The interactions between JAM-A expressing endothelial cells and malignant PCs influence tumor growth and dissemination in multiple myeloma (MM). Previous reports have demonstrated that high JAM-A expression on bone marrow (BM) tumor PCs in newly diagnosed MM patients correlates with patient outcomes, suggesting JAM-A as a potential target and biomarker in MM. However, studies on JAM-A expression in circulating tumor cells (CTCs) remain lacking, which is crucial for a comprehensive understanding of the dynamics and interactions between malignant PCs and the tumor microenvironment, as well as the mechanisms underlying disease dissemination. In this study, we examined the dynamics of JAM-A expression on CTCs in MM and explored its association with cytogenetics and disease prognosis. **Methods:** Sample processing protocols were performed after adapting Euroflow guidelines. NDMM patients were classified as JAM-Ahigh/low based on the median value of fluorescence intensity on CTCs by FACS. Statistical analyses were performed using GraphPad software. The study was conducted in conformity to the Good Clinical Practice Guidelines (study n° 7411, prot. n° 0073322). All enrolled patients provided their informed consent. **Results:** In this study, we investigated the expression of JAM-A on BM-PCs and CTCs in different disease settings. In BM, a group of 135 patients showed heterogeneous levels of JAM-A+ malignant PCs at diagnosis, followed by a decrease on JAM-A levels after therapy and an increase on JAM-A at relapse. JAM-A levels in the BM do not seem to be associated to high-risk (HR) cytogenetic abnormalities while in peripheral blood, high JAM-A expressing CTCs (n = 144 NDMM: 24 1q gain/amp, 22 other HR factors and 98 standard risk subjects) correlated with high-risk cytogenetics, showing statistically significant differences between the 1q gain/amp group, compared to patients with other HR abnormalities and with no cytogenetic abnormalities. Patients with low JAM-A on CTCs at diagnosis showed superior survival compared with patients with high JAM-A expressing CTCs (n = 67). Therefore, we analyzed the expression and distribution of JAM-A on CTCs, evaluating the relationship between JAM-A levels and progression free survival (PFS): The median PFS in NDMM with higher JAM-A expression levels was 19 months and differed significantly from the median PFS in patients with the lower JAM-A which was 23 months. These results demonstrate that JAM-A expressing CTC frequencies are associated with cytogenetic risk factors and disease outcome. **Conclusions:** These results underscore the potential clinical utility of JAM-A as both a prognostic biomarker and a therapeutic target in MM, suggesting that JAM-A levels on CTCs could help stratify patients according to risk and guide more personalized treatment approaches.

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Quantitation of Immunoglobulin Free Light Chains is Impacted by Glycosylated Monoclonal Proteins

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Introduction: The glycosylation of immunoglobulin light chains (LC) in patients with monoclonal gammopathies was

described using MALDI-TOF mass spectrometry. This post-translational modification is a risk factor for development of AL amyloidosis or cold agglutinin disease. We hypothesized that free light chain (FLC) measurement by turbidimetry could be impacted by the presence of glyco groups on the surface of the light chains. **Methods:** A retrospective analysis of 91,498 samples with MASS-FIX mass spectrometry testing clinically ordered for any reason between 2018 and 2023 was conducted. Serum FLC determination was performed by turbidimetry (Optilite, Binding Site, USA). Significant differences between groups were determined using the Wilcoxon test or chi-square test, with statistical significance set at $p < 0.05$. Statistical analysis was performed using R Statistical Software (version 4.2.2). **Results:** From the 91,498 samples tested, only one measurement per patient was used (n=50,772). Out of those, 81% were not analyzed, as the samples were negative (n=35,078), had multiple small clones (n=2,542), more than one monoclonal protein (MP) or heavy chain disease (n=1,028), contained a therapeutic monoclonal antibody (n=1,059) or had no FLC data (n=1,414). The remainder of the samples (n=9,651) were positive for a single MP and included. 561 showed LC glycosylation (5.8%) and 9,090 did not. A higher percentage of glycosylation was observed in κ-associated MP for all isotypes, with κ FLC (10.7%) showing the highest prevalence of glycosylation. FLC concentrations were higher in glycosylated MP compared to non-glycosylated MPs. Significant differences were found between glycosylated and non-glycosylated MPs in IgGκ (median κ FLC 4.86 mg/dL vs 2.89 mg/dL, $p < 0.001$), IgGʎ (median λ FLC 5.12 mg/dL vs 2.26 mg/dL, $p< 0.001$), and IgMʎ (median λ FLC 7.84 mg/dL vs 2.64 mg/dL, $p< 0.001$). In contrast, IgAκ and IgAʎ isotypes showed similar FLC concentrations in glycosylated MPs compared to non-glycosylated IgAs (IgAκ, 3.17 mg/dL vs 3.60 mg/dL, p=0.54 and IgAλ, 2.17 mg/dL vs 2.88 mg/dL p=0.65). Among those with a κ-involved isotype, the FLC ratio was elevated (>1.65) in 62.5% of all non-glycos and 71.6% in glyco MPs ($p< 0.001$). When separating by isotype, the difference was significant for IgGκ only, with a median FLC ratio of 3.58 in glycos vs. 1.89 for non-glycos ($p< 0.001$). Among those with λ-involved isotypes, FLC ratio was below the reference interval (< 0.26) in 25.6% of non-glycos compared to 43.8% in glycos ($p< 0.001$), and the isotype with significant differences was only IgGʎ ($p< 0.001$). In IgAκ and ʎ isotypes, abnormal FLC ratio outside reference intervals was similar in glyco and non-glyco MPs. **Conclusions:** We show that LC glycosylation has an impact in FLC measurement, when compared to non-glycosylated MPs. The effect can be summarized as higher FLC quantitation in IgG glycosylated MPs. Further characterization of this phenomenon is encouraged.

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Microbiome Analysis in Bone Marrow Reveals Distinct Bacterial Profiles Across Multiple Myeloma Stages

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Introduction: Multiple myeloma (MM) is a malignant plasma cell tumor characterized by clonal proliferation within the bone marrow, leading to symptoms such as bone degradation, anemia, and renal dysfunction. Recent studies suggest that imbalances in microbial communities might contribute to immune dysregulation and tumor progression. However, the role of the bone marrow microbiome in MM remains underexplored. **Methods:** Multiple myeloma (MM) is a malignant plasma cell tumor characterized by clonal proliferation within the bone marrow, leading to symptoms such as bone degradation, anemia, and renal dysfunction. Recent studies suggest that imbalances in microbial communities might contribute to immune dysregulation and tumor progression. However, the role of the bone marrow microbiome in MM remains underexplored. **Results:** No significant differences were observed in alpha diversity (Chao1 and Shannon indices) between MM patients and healthy controls, or in beta diversity among the groups. Nevertheless, distinct microbial compositions were noted at different disease stages. Wilcoxon tests showed significant microbial variations at various taxonomic levels, although Proteobacteria was the most abundant phylum without statistical differences across groups. Signature species in the RRMM group, such as Pediococcus acidilactici, Faecalibacterium, and Roseburia faecis, are known for producing short-chain fatty acids. Pathways including Enterobacterial Common Antigen Biosynthesis, L-rhamnose Degradation II, Sulfoglycolysis, and the Superpathway of L-Tryptophan Biosynthesis were found upregulated in disease states. **Conclusions:** The study reveals significant microbial and functional changes in the bone marrow microbiome at different MM stages, suggesting that the microbiome may impact MM progression and treatment responses through metabolic interactions. This research provides new insights into the potential diagnostic and therapeutic targets related to the bone marrow microbiome in MM.

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Planning Ahead: Leveraging Machine Learning Algorithms to Predict Short-Term Treatment Response in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a heterogeneous hematologic malignancy with variable prognosis and treatment responses. Current prognostic models such as the International Staging System (ISS) and Revised ISS (R-ISS) are based on baseline characteristics at diagnosis and do not incorporate any alterations that may occur throughout the course of treatment. This study aims to develop a dynamic short-term treatment response prediction model for MM using machine learning algorithms. **Methods:** We evaluated 662 newly diagnosed MM patients treated at Zhongshan Hospital Fudan University between 2017 and 2021. By integrating lymphocyte subsets in peripheral blood (PB), cytokine data in PB, and multiparametric flow cytometry (MFC) expression patterns of malignant plasma cells in bone marrow (BM), at every two treatment cycles (Baseline, Cycle-2, Cycle-4, Cycle-6, and Cycle-8), we identified key biomarkers that predict treatment outcomes. After completing the procedures of data merging and normalization,

the criterion used for selecting biomarkers for inclusion in the predictive model was based on whether the p-value of the t-test between negative groups (patients suffered from progression disease, stable disease, and minor response) and positive group (patients have stringent complete remission, complete remission, very good partial response, and partial response) was less than 0.05. **Results:** As a result, lymphocytes count (p=0.0118), percent of CD19+ B-lymphocytes in PB (p< 0.0001), percent of CD3+ T-lymphocytes in PB (p< 0.0001), percent of CD3+CD4+ T-lymphocytes in PB (p=0.0017), ratio of CD4+/CD8+ in PB (p=0.0003), IL-10 in PB (p=0.0017), percent of CD138+/CD38+ PCs in BM by MFC analysis (p=0.0001), and percent of CD27 on PCs (p=0.0131) were finally selected. We made a combination of R-ISS stage and the above dynamic biomarker features to build a Random Forest classifier. Then, we trained and evaluated the model separately for different target variables and dynamic Biomarker combinations at different time points. Finally, the random forest-supported model demonstrated improved accuracy in predicting short-term outcomes (the next treatment cycle). We then employed the following formula for calculating accuracy: Acc = number of correct predictions for positive samples/number of positive samples + number of correct predictions for negative samples/number of negative samples. Additionally, other machine learning algorithms, including Naive Bayes, also supported our predictions, enhancing the robustness of our approach. **Conclusions:** The improved predictive capabilities of our model have practical implications for personalized treatment planning, enabling more timely and precise adjustments to therapy, potentially improving patient outcomes, and optimizing resource allocation. Furthermore, our research uncovered new insights into the role of specific immune cell subsets and cytokine fluctuations in treatment response, offering potential new avenues for therapeutic intervention.

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The Metabolic Profile and Prognostic Model of Multiple Myeloma

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Introduction: Multiple myeloma (MM) patients had improved overall survival rates due to considerable advances in the treatments. However, MM remains to be an incurable disease. There is a need for greater precision in clinical prognostic models. Furthermore, novel strategies are required to ameliorate the poor outcomes of relapsed and refractory patients. Metabolic alterations constitute a hallmark of cancer. Our previous studies revealed that imbalance in amino acids metabolism promotes MM progression. Glycine promotes MM progression through disrupting glutathione balance [1], whereas excessive serine impedes megakaryopoiesis and thrombopoiesis in MM [2]. Furthermore, kidney damage resulting from abnormal amino acid metabolism leads to accumulation of excessive urea, which is utilized by gut microbiota, ultimately resulting in nitrogen-recycling bacteria enrichment in MM [3]. The significance of metabolic alterations in prognostic prediction and enhancement of therapeutic effects in MM requires further investigation. Here, we performed a systematic analysis utilizing target metabolomics, with the aim of optimizing the management of MM patients. **Methods:** The metabolomes of bone marrow and peripheral blood from 113 patients were included in the analysis, among which 20 had metabolomes of CD138 positive cells. Q300 was utilized for the detection of the metabolomes. Written consent was obtained from all patients. Clinical information encompassing demographics, clinical presentation, diagnosis, and OS time was collected. **Results:** Given that malignant plasma cells reside in the bone marrow and absorb metabolites from the tumor microenvironment, our initial focus was on the metabolomes of bone marrow. Utilizing the overall survival time (OS) as a metric, four distinct metabolic clusters were identified in MM patients. Following a maximum follow-up period of 80 months, the median OS for clusters 1 to 4 is not reached, 50.1 months, 41.5 months, and 28.1 months respectively (p=0.011). The amino acids, specifically glycine, serine, and proline, were consistently present in each cluster, indicating their crucial role in MM. The significantly elevated metabolites in each cluster were marked in long chain fatty acid (LCFA), bile acid (BA) and carbohydrate, short chain fatty acid (SCFA), and bile acid (BA). Based on their metabolic characteristics, the four subtypes were categorized as LCFA, BA&Carbon, SCFA, and BA. Furthermore, the metabolic subtypes exhibited a strong correlation with clinical parameters such as monoclonal protein level, albumin, hemoglobin level, and IGH. These findings demonstrate that metabolic class designation serves as a novel predictor of survival in MM. **Conclusions:** We present a metabolic prognostic model for MM patients. Several metabolic targets were identified based on the metabolic profiles. This study plays a significant role in advancing the current MM stratification systems and identifying promising therapeutic targets for MM.

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T-Cell Receptor Repertoire Analysis of Blood and Bone Marrow Samples From Multiple Myeloma Patients

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Introduction: The collection of bone marrow (BM) aspirates from multiple myeloma (MM) patients is the gold-standard method for evaluating both disease burden and for studying the BM

microenvironment. The development of liquid biopsy and blood-based approaches may provide a minimally invasive strategy for monitoring disease, clinical response, and for biomarker discovery. As T-cell targeted therapies are being advanced as earlier lines of therapy in MM, we explored the utility of peripheral blood mononuclear cells (PBMC) as a surrogate tissue for BM immune microenvironment, and specifically T-cells. **Methods:** Baseline and longitudinal visit matched patient-derived samples were obtained from subjects enrolled in the MMRF CoMMpass trial (36 subjects; 91 BM and 100 PBMC samples) and PBMC samples from the MMRF CureCloud study (14 subjects). For bulk TCR focused analyses, subject and visit matched PBMC and BM (CD138-negative BMMC) genomic DNA (gDNA) samples were sequenced using the Adaptive Immunosequencing (Adaptive Biotechnologies, Seattle, WA) to quantitatively profile the TCR (TCRb) repertoire. For single cell analyses (paired scRNAseq/scTCRseq), aliquots of cryopreserved PBMCs were thawed and evenly divided for, (i) selective T-cell enrichment (cocktail of non-T cell targeted magnetic beads) and (ii) no T-cell enrichment, prior to gene expression profiling using the 10X Chromium Next GEM 5' V2 kit. **Results:** TCRb sequences from visit matched, longitudinal, BM and PBMC samples exhibit overlapping profiles and characteristics. TCR repertoire diversity, clonality and richness (dynamics) over time and therapy were highly similar between BM and PBMC samples. Single cell T-cell analyses of PBMCs revealed that T-cell enrichment (TCE) captured a broader diversity of T-cell clones. TCE increased the proportion of T-cells analyzed in the samples to 75% vs 40% in unenriched PBMC. While TCE had no impact on transcript-level expression profiles, T-cell subtypes remained consistent between these two processes. Moreover, we observed a higher abundance of functional subsets of CD8 and CD4 T-cells in TCE samples. Additionally, when mapping TCR clone specificity to common large-scale TCR-epitope databases such as vdjDB or immuneCODE we observed that TCE significantly enhanced the identification of both rare and antigen-specific clones compared to samples without enrichment. **Conclusions:** We confirm that the TCR repertoire in blood and BM are conserved with similar dynamics suggesting that blood could be a possible surrogate to monitor T-cell functional status in the BM of MM patients (contingent ddon therapy). We also demonstrate shared TCR diversity and clonality between PBMC and BM. Detailed single cell analyses of TCE samples identifies rare clonotypes which may be of clinical significance. Future analyses will explore the relationship between T-cell/TCR clonality and diversity associated with specific therapies in matched PBMC and BM samples.

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Impact Of Bone Marrow Fibrosis In Multiple Myeloma At Diagnosis and On DIsease Course

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Introduction: Bone marrow fibrosis (BMF) is found in 8-57% of plasma cell dyscrasias. Increased reticulin in multiple myeloma (MM) is found to be associated with increased plasma cell infiltration and heralds a poorer prognosis. Here we aimed to explore the frequency of BMF at diagnosis and its impact on disease course. **Methods:** We performed a single-center, retrospective analysis of 217 MM patients with available data who had been evaluated for BMF between January 2010 and June 2022 with a follow-up period of at least 1 year. Univariate and multivariate cox-regression analyses and Kaplan-Meier methods were used in survival analysis. **Results:** Of 217 patients evaluable for BMF 137 (63%) had detectable BMF while 80 (37%) had no BMF. The median age of the patients was 63 (range: 37 to 89) and females and males accounted for 50.2% (n=109) and 49.8% (n=108), respectively. The median follow-up time was 44 months (range: 12 to 155). Median progression free survival (PFS) in patients with and without BMF was 20 (95% CI: 13-26) and 24 months (95% CI: 11-36) (p=0.286). Median overall survival (OS) in patients with and without BMF was 93 (95% CI: 83-102) and 95 (95% CI: 85-103) months (p=0.346). We evaluated the morphologic patterns of plasma cell distribution and found out that diffuse patterns were more common in BMF (p< 0.001). Diffuse plasma cell pattern was an independent poor prognostic factor for OS (p< 0.023). Mean hemoglobin values in patients without and with BMF were 11.14±2.32 and 10.18±2.23 g/dL, respectively (p=0.003). International Staging System (ISS) stage I patients built 24% (n=33) of patients with BMF while 40% (n=32) of patients without BMF had stage I disease (p=0.047). When we stratified the cohorts with and without fibrosis by two age levels (< 65 and ≥65 years), patients ≥65 with BMF had worse OS (p=0.001) and PFS (p=0.007) compared to patients < 65 with BMF. OS difference in patients without BMF was not statistically significant (p=0.057) but PFS in patients without BMF was worse in ≥65 patients (p=0.035). In patients with BMF having red blood cell (RBC) transfusion requirements OS (p=0.008) and PFS (p=0.034) were significantly worse than patients without BMF having RBC transfusion requirements. **Conclusions:** Bone marrow microenvironment is an area of interest. In this study we could not find any survival difference between patients with and without BMF at diagnosis. Fibrotic MM patients had lower hemoglobin values, higher ISS stages and tendency to have diffuse plasma cell infiltration similar to previous reports. Older age and RBC transfusion need correlated with worsening PFS and OS in patients with BMF while older age had an impact on PFS in nonfibrotic patients. Evaluation of BMF both at diagnosis and following treatment may provide better prognostic significance.

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A Germline Variant of BNIP1 Gene (rs28199) is Associated with Familial Multiple Myeloma

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Introduction: BNIP1 gene plays a pivotal role in cellular degradation processes, notably apoptosis and autophagy. A variant in BNIP1 gene (NM_001205.3/c.*1208A >G; rs28199) has been reported to be associated with multiple myeloma (MM) risk (OR = 1.18, (95% CI:1.11–1.23), p = 3.18 × 10−10) (Macauda et al. Leukemia 2023, Interlymph-Heidelberg Consortium). It is predicted to affect the binding site of IRF1, STAT2_STAT1and FOXP1 transcription factors, have a strongest effect for IRF1 (interferon regulatory factor 1) and be associated with an increased blood level of Interleukin-6. We have recently reported in our targeted and whole exome sequencing study on familial cases (BJH, 2024) that this variant is present in 13 of 18 familial MM cases (72.2%). In this study, we expanded our familial cases to analyze rs28199 variant and aimed to compare it to non-familial MM patients and healthy population. **Methods:** A total of 32 familial MM and 30 non-familial MM cases were included to the study from hematology centers in Turkey and defined as having one or more first, second or third-degree relatives who have plasma cell diseases. Non-familial MM cases were randomly selected from the samples of the reference hematology center in Ankara University, Faculty of Medicine. Targeted NGS sequencing was utilized to investigate the germline variant from patients' peripheral blood samples. Allele frequencies of the study group was also compared to the Turkiye Genome Project data of the Turkiye National Genome Center. **Results:** 65.6% (n=21) of the familial and 40% (n=12) of the non-familial MM cases were positive for the BNIP1 variant, revealing a significant association between the variant and familial MM (OR: 2.86 (95% CI: 1.02-8.04), p=0.04). Among the variant positive patients, the rates of homozygosity were 47.6% (n=12) in the familial and 8.3% (n=1) in the non-familial MM cases (OR: 10, (95% CI: 1.08-91.98), p=0.02). The variant allele frequencies were 0.48 and 0.22 in familial and non-familial MM cases, respectively (p=0.00). Likewise, rs28199 allele frequency among familial MM cases was also more frequent than the frequency observed within germline whole genome data of healthy population (Turkiye Genome Project) (0.48 vs 0.32, p=0.02). **Conclusions:** This study shows that germline BNIP1 variant (rs28199), when in homozygous state is particularly associated with familial MM. Our data on BNIP1 rs28199 variant among familial cases contributes the findings of the Interlymph-Heidelberg Consortium which suggests this variant to be associated with MM as one of the genetic risk factors.

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Heterogeneity of Osteoclasts in Multiple Myeloma Revealed by Single Nucleus RNA Sequencing

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Introduction: Osteolytic bone lesions are a hallmark of multiple myeloma (MM), affecting up to 80% of patients and leading to chronic pain, pathological fractures, and neurological impairment. These lesions result from excessive osteoclastic bone resorption coupled with suppressed osteoblastic bone formation. Osteoclasts (OCs) have demonstrated phenotypic and functional diversity in other bone-related diseases such as rheumatoid arthritis. However, comprehensive studies exploring the heterogeneity of OCs in MM are still lacking. Here, we utilized in vitro differentiated OCs from the immunocompetent Vk*MYC MM mouse model to investigate OC diversity. **Methods:** To characterize MM bone disease, murine Vk*MYC MM cells were intrafemorally transplanted into the femur of C57BL/6 mice. MM development and bone lesions were confirmed via serum protein electrophoresis and µ-CT imaging. To study OC heterogeneity, an in vitro protocol for differentiating OCs from Vk*MYC bone marrow mononuclear cells (BMMNCs) was developed and validated. BMMNCs were cultured with M-CSF and RANKL for five days to expand and induce fusion of OC precursors (OCPs) to form mature OCs. MM cells were present in the supernatant throughout the entire duration of the OC differentiation culture. Single-nucleus RNA sequencing (snRNA-seq) using the 10x Genomics Chromium 3' platform was performed on day five OCs from Vk*MYC and PBS-injected mice. **Results:** Tartrate-resistant acid phosphatase (TRAP) staining of OCs in femurs revealed an increased number of OCs in Vk*MYC mice relative to PBS-injected mice. OC differentiation from Vk*MYC BMMNCs yielded larger and greater quantities of OCs, as observed under the microscope following TRAP staining, compared to those from PBS-injected mice. On day five of the OC culture system, snRNA-seq revealed high expression of OC marker genes in clusters 1, 5, and 13 in both Vk*MYC and control samples. Notably, genes associated with immune response and phagocytosis pathways were significantly more expressed in Vk*MYC cluster 13 compared to the corresponding control cluster. Additionally, Vk*MYC OC differentiation culture exhibited a higher abundance of M1 macrophages, with significantly increased IL-17 receptor expression compared to the control group. **Conclusions:** Differential expression analysis of identified OC clusters within each sample showed no significant differences in OC marker genes, indicating that the observed diversity is not due to

different stages of differentiation, as OCPs display markedly lower expression of these markers. Cluster 13 in the Vk*MYC sample may suggest the presence of highly activated OCs. M1 macrophages, involved in chronic inflammatory conditions, can differentiate into OCs, and research has shown that IL-17 promotes OCP differentiation. In summary, OCs are a heterogenous population, and a specific MM-related OC subgroup may exist within the bone marrow microenvironment of MM patients with bone lesions.

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B-Cell Profile in Bone Marrow and Peripheral Blood of Multiple Myeloma Patients After Autologous Stem Cell Transplantation

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Introduction: Multiple myeloma (MM) is a clonal plasma cell (cPC) malignancy associated with an impairment of the B cell compartment. Previously, B-cell recovery during therapy has been reported as a prognostic factor in MM and a unique feature of MM patients who attain long-term disease control. The kinetics of B-cell reconstitution in bone marrow (BM) from MM patients during treatment was described. Still, detailed recovery of peripheral blood (PB) B-cell subsets after therapy remains to be investigated. This study aimed to describe B-cell subsets in PB vs. BM of MM patients at D+100 after autologous stem cell transplantation (ASCT) and their potential relationship with minimal residual disease (MRD). **Methods:** A total of 152 paired BM and PB samples were studied from 76 MM patients – 54% males; median age of 61 y (40-70 y) – collected at D+100 post-ASCT. All patients received induction triplet regimens, including immunomodulatory drugs and/or proteasome inhibitors, followed by high-dose melphalan before ASCT. Age-matched healthy donors (HD) were studied as controls. Samples were obtained at two different centers (UFRJ, n= 88; USAL, n= 64) and analyzed by flow cytometry stained with EuroFlow NGF MM MRD two-8 color antibody combinations. **Results:** BM clonal PC (MRD+) was detected in 50/76 (66%) of MM patients, and 7/50 (14%) also presented circulating tumor plasma cells (CTPC+) in PB. All MM BM samples presented B-cell precursors (BCPs) percentage above normal levels, while memory B-cells and normal PC (nPC) were under average percentage (vs. HD). MRD+CTPC+ patients had significantly lower frequencies of nPC CD19- (long-lived plasma cells) on BM compared to MRD+or- patients. In PB, memory B-cell counts were significantly reduced in all groups of MM patients vs. normal. PB nPC CD19+ (plasmablasts) significantly decreased in CTPC+ patients compared to other MM patients (MRD+ and MRD-), which reached average counts. From 38% (29/76) relapsed MM patients, 72% (21/29) were MRD+ compared to 62% (29/47) of MRD+ in non-relapsed ones. Among MRD+ patients, 14% (4/29) of the relapsed group had CTPC+ vs. 6% (3/47) of non-relapsed patients. MRD+CTPC+ patients had a significantly shorter PFS, being 9m vs. 28m in MRD+CTPC- and not reached in MRD-CTPC- patients (p=0.02). Overall, mortality was 14% (11/76), being 8/11 (72%) of MRD+ (6 CTPC- and 2 CTPC+) and 3/11 (27%) in MRD-CTPC- cases. Overall survival was 18m in MRD+CTPC+, 36m in MRD+CTPC- and 50m in MRD-CTPC- patients. **Conclusions:** The presence of CTPC at D+100 post-ASCT was associated with lower recovery of nPC PB counts and worse PFS. Such findings reinforce that CTPC clearance post-ASCT would increase the availability of BM niches for nPC and potentially for BCPs, leading to normal B cell maturation recovery. Further studies with larger cohorts and longer follow-up times are necessary to understand better the effects of B cell recovery on MM survival.

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Testing and Reporting of FISH Studies in Multiple Myeloma: Recommendations from the Cancer Genomics Consortium Myeloma Working Group for Best Practices

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Introduction: Multiple myeloma (MM) is an incurable plasma cell (PC) malignancy with recurrent cytogenetic abnormalities with prognostic and therapeutic implications. The gold standard clilnical assay that detects these cytogenetic abnormalities is fluorescence in situ hybridization (FISH). FISH testing is heterogeneous among clinical laboratories, with variations in FISH panel design and reporting which can lead to confusion among physicians and patients. To assess the variability in MM FISH testing/and reporting, we formed the Cancer Genomics Consortium Plasma Cell Neoplasm Working Group composed of cytogenetic laboratory directors from a variety of clinical laboratory settings. **Methods:** We formed a working group of cytogenetic laboratory directors from the Cancer Genomics Consortium membership. The directors represent a variety of clinical laboratory settings from small academic laboratories to large reference laboratories. We performed an extensive literature

review and created a survey centered around the genetic testing practices and FISH report interpretation among MM clinicians. **Results:** Among 102 respondents, representing 14 countries, most clinicians (74%) utilized in-house FISH laboratories. Nearly all (90%) respondents desired FISH at diagnosis, 72% during disease progression, and 40% for treatment/response assessment. The most-requested probes included TP53 (99%), t(4;14) (92%), 1q gain/amplification (91%), t(14;16) (90%), t(11;14) (85%), t(14;20) (76%), 1p deletion (67%), while FISH for ploidy status, deletion 13q/-13, t(6;14), MYC rearrangement, and other rare IG rearrangements were ranked lower in importance (10-50%). Approximately 65% of respondents were satisfied with the clarity and interpretation of FISH reports. However, when challenged to interpret a particularly difficult FISH report, 20% responders interpreted results correctly while the majority were either unsure or misinterpreted the report. **Conclusions:** Our study highlights the need for significant improvements in MM FISH report clarity by the clinical laboratory directors to benefit both the clinician and patient. We propose solutions to improve standardization and recommend best MM FISH reporting practices that we aim will be adopted by clinical laboratory directors.

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Immunomodulatory Effects of Daratumumab on the Bone Marrow Microenvironment in Multiple Myeloma: Insights from Single-Cell Analyses

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Introduction: Daratumumab (Dara), a monoclonal antibody targeting CD38, is approved for treating multiple myeloma (MM). Its impact on the cellular immune compartment and the relation to response/resistance are not fully understood. Understanding Dara's effects on the immune landscape and its therapeutic mechanisms is crucial for identifying synergistic immunotherapeutic approaches and informing therapy sequencing for long-term efficacy. **Methods:** Mass cytometry (CyTOF) and single-cell RNA sequencing (scRNA-seq) were used to comprehensively characterize the immune microenvironment in MM patients undergoing Dara therapy, either as monotherapy or in combination regimens. CD138-negative fractions of bone marrow mononuclear cells (BMMCs) collected from MM patients at pre-treatment (pre-Dara, n=37), on-treatment (on-Dara; in remission, n=10), and post-treatment (post-Dara; relapsed, n=32) timepoints were analyzed to focus on the non-malignant immune compartment. **Results:** CyTOF and scRNA-seq analyses revealed a consistent decrease in the frequency of CD4+ T cells, B cells, plasma cells, and NK cells by up to 50%, on- and post-Dara compared to pre-Dara, while CD8+ T cells showed a 30% increase. CD38 expression was markedly reduced on- and post-Dara across most immune cell types, confirming the antibody's on-target effects and previously published results. On-Dara samples exhibited increased expression of cell surface markers associated with T cell activation and migration (HLA-DR and CXCR3), compared to pre-Dara samples. This was accompanied by a concomitant downregulation of inflammatory pathways, including TNFα and IL-2 gene signatures, potentially enhancing anti-tumor immune responses during treatment. When comparing patients in remission to relapsed patients, a significant upregulation of a senescence marker (CD57), and immune checkpoint molecules (ICOS, PD-1 and TIGIT) was observed in the T cell compartment, with the highest fold change (FC=1.98) on regulatory T cells in relapsed patients. Additionally, TIM-3 expression was significantly elevated in dendritic cells (FC=2.08) and monocytes (FC=1.44) in relapsed patients, suggesting a potential restraint of anti-tumor immunity. Moreover, interferon-stimulated gene (ISG) pathways were downregulated in NK cells and monocytes in remission but upregulated in relapsed patients, implying a potential pro-tumoral role in disease progression. **Conclusions:** Our comprehensive single-cell analyses unveil distinct immunomodulatory effects of Dara on the bone marrow immune microenvironment, including alterations in immune cell frequencies, activation states, and functional pathways. The observed upregulation of senescence markers, immune checkpoints, and pro-tumoral pathways in relapsed patients highlights potential resistance mechanisms and suggests avenues for therapy combination and sequencing strategies to enhance efficacy, overcome resistance, and improve patient outcomes in MM.

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Artificial Intelligence System To Predict t(11,14) Status in Multiple Myeloma Patients by Leveraging the Correlation of Plasma Cell Morphology and Genetics

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Introduction: The diagnosis of multiple myeloma (MM) is based on the cytomorphological analysis of bone marrow aspirate (BMA), along with cytometry and genetic analysis based on underlying cytogenetic alterations, which have both prognostic and therapeutic implications. An example is the translocation (t)(11;14), which, although it does not have a prognostic impact, serves as a therapeutic target by allowing targeted treatment with venetoclax in these patients. The objective of our study is to develop an artificial intelligence (AI) algorithm to automatically identify plasma cells (PC) with t(11;14) from morphological features of BMA samples analyzed using automated optical microscopy. **Methods:** We digitized 40 fields (100x) from each patient, including healthy controls, controls with MM without t(11;14), and patients with confirmed MM with t(11;14), using a device manufactured with a 3D printer to attach a mobile application to an optical microscope. For each BMA, 40 fields (100x) were digitized and the average of PC analyzed was 174. An AI algorithm was developed based on a database of more than 400,000 triple manually labeled cells, capable of automatically identifying nucleated cells from BMA images and classifying them into PC and non-PC, with an area under the curve (ROC-AUC) of 98%. Subsequently, an AI algorithm was developed to learn morphological patterns of PC associated with t(11;14) and predict its presence. The AI algorithm corresponds to a Multiple Instance Learning (MIL) architecture, which in turn uses features of each cell extracted by a foundational model trained through self-supervised learning on a database of more than 100K BMA cells. This MIL algorithm for predicting t(11;14) was trained using a 3-fold cross-validation technique, thus ensuring a division at the patient level between training and validation sets. **Results:** A total of 881 digitized cases were analyzed, 841 negative [677 healthy controls and 164 MM without t(11;14)] and 40 MM positive for t(11;14). Morphological analysis of plasma cells using the AI algorithm proved effective for detecting PCs with t(11;14) with an area under the ROC curve (ROC-AUC) of 0.88. The algorithm can predict the presence of t(11;14) with a sensitivity of 0.83 and a specificity of 0.74. The false positive rate was 0.26, while the false negative rate was 0.17. **Conclusions:** Our results demonstrate the potential of applying AI models in the morphological analysis of PC in BMA for detecting genetic alterations, confirming the morphology-genetics correlation in PC of MM cases with t(11;14). Our algorithm sensitively identifies the presence of morphological features suggestive of t(11;14); however, it shows more limited specificity, which could likely be resolved by increasing the sample size, refining the model architecture, or exploring alternative models that include other predictive variables.

P-200

Semi-automated Interphase FISH (iFISH) Spot Scoring in CD138-Positive Cells: Validation Study for Genetic Abnormalities Detection in Multiple Myeloma

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Introduction: Genetic abnormalities detected in plasma cells are important predictors of prognosis in myeloma multiple (MM) and interphase Fluorescent in Situ Hybridization (iFISH) in selected plasma cells is the gold standard genetic technique. Manual iFISH analysis is a time-consuming, exhausting, and error-prone process that needs the participation of at least two qualified analysts. Interobserver variability can lead to misunderstandings and scoring discrepancies, while interlaboratory variability makes it difficult to compare data. Automated analysis provides an opportunity to overcome difficulties with manual analysis. Guidelines for manual fluorescent spot analysis already exist but they are not clear for automated scoring. The aim of the study was to validate the automated analysis and to compare the effectiveness of this with standard manual analysis for iFISH in selected CD138 cells. **Methods:** A workstation was optimized based on the manufacturer's configurations. Six commercial probes (CDKN2C/CKS1B, RB1/DLEU1/LAMP1, TP53/CEN17, FGFR3/IGH, CCND1/IGH, and IGH/MAF) were examined to detect gains, losses, and rearrangements of genes across a total of 180 slides (20 samples). Reference values proposed by the European Myeloma Network (10% for rearrangements and 20% for gains and losses) were used to compare the results of manual and semi-automated analyses. The time spent by the biologist for semi-automated and manual analyses was compared in another 10 samples. Statistical analyses were done using the Tau-b of Kendall coefficient (assess the reliability of the percentage of signal classes for each probe and classifier were employed to categorize the classes into normal or abnormal diagnoses), the Kappa coefficient (for accuracy) and paired Wilcoxon test (comparison the time spent for manual and semi-automated per probe). **Results:** The first important data was that automated analysis was not effective, lacked validation and was excluded. The results for the probe CDKN2C/CKS1B showed 5 cases with abnormal signals (4 gain of CKS1B), RB1/DLEU1/LAMP1 probe showed 3 cases with deletion of all probes, TP53/17cen probe detected 1 abnormal case with trisomy 17, FGFR3/IGH probe detected 5 cases with abnormal signals (1 FGFR3::IGH) MAF/IGH probe detected 5 cases with abnormal signals (1 IGH::MAF) and CCND1/IGH probe detected 7 cases with abnormal signals (4 CCND1::IGH). A 100% of accuracy for normal or abnormal signals patterns was found in manual and semi-automated analysis. Less time for analysis occurred in the semi-automated analysis than in the manual one for the CDKN2C/CKS1B probes (2.3 vs 3.9 minutes, p= 0.013) and for CCND1/IGH (2.0 vs 4.7, p=0.009). **Conclusions:** n/a.

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Phosphatidylcholine Deactivates Cytotoxic CD8+ T Cells Through UFMylation Mediated by Exosomal SerpinB9 in Multiple Myeloma

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Introduction: Multiple myeloma (MM), the second most prevalent hematological malignancy, remains challenging to treat due to its resistance to current therapies. This study explores the gut microbiome and blood metabolites' role in influencing the tumor microenvironment (TME), aiming to identify novel therapeutic targets and strategies for MM. It focuses on distinguishing MM patients from healthy individuals by analyzing Lachnospiraceae and phosphatidylcholine (PC), investigating their potential impact on MM pathogenesis and treatment resistance. **Methods:** Employing 16S rRNA gene sequencing and UPLC/Q-TOF MS, the study analyzed the gut microbiome and blood metabolites of MM patients compared to healthy controls. It further investigated the impact of PC on CD8+ T cell cytotoxicity towards MM cells, examining the molecular mechanisms involved. **Results:** The study identified significant differences in the gut microbiome composition between MM patients and healthy controls, with Lachnospiraceae and PC emerging as critical differentiators. In MM patients, increased levels of PC were associated with a diminished cytotoxic response of CD8+ T cells against MM cells. This effect was mediated by the upregulation of SerpinB9 (Sb9) in MM cells, which was induced by PC through the LIN28A/B-LPA pathway. Additionally, PC was found to decrease granzyme B (GZMB) expression in CD8+ T cells via exosomal Sb9 derived from MM cells, further inhibiting the cytotoxic effect. Sb9 also played a role in reducing TP53 expression by blocking TP53 UFMylation, a process facilitated by the competitive interaction between TP53 and the ubiquitin-fold modifier conjugating enzyme 1 (UFC1) in CD8+ T cells. These findings were supported by both in vitro and in vivo experiments, demonstrating the potential of PC and Sb9 as novel targets for MM treatment. **Conclusions:** This study underscores the significance of the gut microbiome and blood metabolites, particularly Lachnospiraceae and phosphatidylcholine, in the pathogenesis and treatment resistance of multiple myeloma. By revealing how PC influences CD8+ T cell cytotoxicity and MM cell survival through the modulation of Sb9, the research opens new avenues for therapeutic intervention in MM. These insights highlight the potential benefits of targeting the gut microbiome and blood metabolites to modulate the TME and improve outcomes for MM patients. Further investigations are warranted to explore the therapeutic implications of these findings in MM treatment strategies.

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Risk Factors Predicting Early Relapse for Newly Diagnosed Multiple Myeloma Patients Treated with Front-Line VRD Regimen

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Introduction: Bortezomib, lenalidomide, and dexamethasone (VRD) is a standard therapy for newly diagnosed multiple myeloma (NDMM), which achieves over 90% response rate. This study intends to explore the predictive factors of early relapse in NDMM patients treated by front VRD regimen. **Methods:** Clinical characteristics of 107 NDMM patients receiving front-line VRD regimen were retrospectively analyzed from September 2019 to May 2024 at Peking Union Medical College Hospital. At baseline, interphase fluorescence in situ hybridization (FISH) analysis was performed in CD138 sorted plasma cells. A Next-generation sequencing (NGS) panel including 290 tumor-related genes was performed in marrow plasma cells. Early relapse was defined as relapse within 12 months. **Results:** The median follow-up time of 107 NDMM patients was 32 months. There were 18 cases in ER group,25 cases relapsed after one year and 64 still with response. The top-five frequently mutated genes were KRAS(28%), NRAS(14%), TP53(7.5%), IGLL(5.6%) and BRAF(3.7%). The mutation rates of there genes in ER group were KRAS(5/30,16.7%), NRAS(3/15,20%), TP53(3/8,37.5%), IGLL(2/6,33.3%) and BRAF(1/4,25%), which were not significantly different from those in other patients. The OS in ER group was inferior ($p< 0.001$). Univariate analysis indicated that the del(17p), hemoglobin level lower than 100g/L, non-ASCT and TP53 mutation were associated with development of ER. Multivariate logistic regression analysis suggested that del(17p) was the independent influencing factor of early relapse (OR =8.578, 95% CI 1.737-42.445, P = 0.0083). As to the analysis of top five mutated genes, we found that PFS in patients with TP53 or IGLL5 mutations was worse, whereas PFS in patients with KRAS,NRAS or BRAF mutations was even longer. **Conclusions:** We found that PFS in NDMM patients treated with front-line VRD regimen was not affected by KRAS, NRAS, or BRAF mutations, although RAS mutation was considered as high-risk factors associated with poor prognosis in MM. The early relapse of NDMM patients after VRD regimen is mainly related to high-risk cytogenetic abnormalities, especially del(17p). TP53 or IGLL5 mutation may contribute to early relapse as alternative factors.

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Ability To Perform Spatial Transcriptomics in FFPE Decalcified Bone Marrow Samples of Patients With Precursor Myeloma

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Introduction: Spatial transcriptomics (ST) provides unprecedented insights into complex multicellular architecture by mapping the expression of hundreds to thousands of genes across spatial coordinates. While ST unravel spatial immune contextures to predict disease progression and (immune)therapy response, its application in bone marrow (BM)-derived hematologic cancers has been limited by RNA degradation resulting from required decalcification processes. To evaluate the feasibility of current technologies, we performed ST on 14 BM formalin-fixed, paraffin-embedded (FFPE) samples from healthy individuals and myeloma precursor patients, comparing four ST platforms (CosMx, Xenium, Visium CytAssist, Visium HD) and two decalcification methods (EDTA, RapidCal Immuno). **Methods:** Samples were collected from participants with MGUS, SMM, or MM upon local IRB approval. Eight archived FFPE sections were decalcified with RapidCal Immuno (Statlab). Four of these were analyzed with the CosMx platform (1000-plex panel), three sections from the same FFPE cores were analyzed with the Xenium platform (377-plex panel), and one independent section with Visium HD. Six additional BM samples were EDTA-decalcified, four of which were analyzed with Xenium, one with Visium CytAssist, and one with Visium HD. **Results:** Matching FFPE blocks enabled direct comparison of CosMx and Xenium platforms. Samples analyzed with CosMx exhibited no tissue detachment, yielding 8,448-12,100 cells each with a median of 72-94 genes per cell. While one sample detached during the Xenium run, the remaining samples yielded 5,027-28,334 cells with a median of 11-17 genes per cell. Despite these differences, both technologies detected all major hematopoietic and stroma-derived cell types after Leiden clustering. Xenium identified minor cell populations (e.g., T cells, megakaryocytes) more robustly than CosMx. Interestingly, we detected CCND1high plasma cells in a patient with t(11;14), unlocking the ability to map distinct myeloma cell clones within their immune microenvironment. Next, we compared the effect of decalcification on ST quality. In Xenium, EDTA increased the signal detection five to ten-fold compared to standard methods. Applying Visium CytAssist to one EDTA-decalcified sample resulted in a median of 1014 genes (maximum 5361 genes) per 50 µm-wide spot. Moreover, in ongoing analyses of two samples analyzed by Visium HD as the most advanced ST capturing ~18,000 genes across single cells, we will evaluate if Visium HD has the potential to be an ultimate solution for BM samples. **Conclusions:** Here, we demonstrate that ST is feasible on decalcified BM samples, while minor technical challenges remain due to tissue detachment and acid-based decalcification. However, despite these limitations, ST technologies can be applied to archival decalcified samples. In the future, improved processing and decalcification strategies can enhance the accessibility of BM samples for advancements in spatial biology.

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Deciphering the Interplay of Immune Alterations and Microbiome Changes Along Multiple Myeloma Evolution From Premalignant Conditions

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Introduction: Multiple myeloma (MM) is an incurable blood cancer marked by the abnormal growth of plasma cells in the bone marrow. It is always preceded by a premalignant stage known as monoclonal gammopathy of undetermined significance (MGUS), often progressing to smoldering MM (SMM). Growing evidence indicates that the immune microenvironment plays a pivotal role in disease progression. Therefore, understanding these immune alterations is crucial for developing immunotherapeutic strategies to prevent disease advancement and improve patient outcomes. This study evaluated changes in the immune landscape and variations in fecal microbiota during the transition from MGUS to MM. **Methods:** To assess the immune composition-including myeloid and lymphoid T, B, and NK cell subpopulations, as well as immune checkpoint distribution—in both bone marrow (BM) and peripheral blood, we analyzed samples from 13 MGUS patients, 12 SMM patients, and 63 newly diagnosed MM (NDMM) patients. This analysis employed 10-color and 8-color flow cytometry panels. Additionally, we measured cytokine and chemokine levels in BM and peripheral blood using a 48-plex Luminex plate on 72 samples from the same patients, along with 4 healthy donors. We also conducted fecal microbiome profiling on samples from 10 MGUS, 15 SMM, and 16 MM patients to explore potential correlations between bacterial composition and MM progression. **Results:** Through unsupervised analysis of T cells by FlowCT, we identified a substantial increase in circulating TEMRA CD8 T cells, particularly CD57+ cells, accompanied by a significant decrease in naïve TIGIT+ and TIGIT+ TIM3+ CD8 T cells. Within CD4 T subsets, a reduction in BM effector memory phenotype and an elevation in IL17-producing BM CD4 T cells were observed throughout disease progression. Concurrently, non-classical monocytes HLA-DR+ CD11c+ and BM mature granulocytes diminished as MM advanced. Subsequently, the evaluation of cytokines and chemokines levels within BM plasma indicated a reduction in GM-CSF, IFN-α2, IFN-γ, IL-1β, IL-2, IL-

2Ra, IL-3, IL-10, IL-13, and MCP-1/CCL2 levels in MM patients, suggesting a potential impairment in their myeloid function and T cell effector activity. Finally, fecal microbiota analysis revealed that in SMM, the Coriobacteriaceae family, part of the Actinobacteria phylum, was prevalent, with a significant presence of the Collinsella species. In MGUS, the dominant bacteria were Clostridia, Enterocloster, Faecalibacillus, and CAG-274, all members of the Firmicutes phylum, contrasting with Ruminococcus prevalence in NDMM. **Conclusions:** This study unveils synchronized immune dysregulation and microbiota shifts in MM evolution, identifying significant indicators of tumor progression and potential therapeutic targets. Data on single cell RNAseq, Abseq, TCRseq and BCRseq from the same patients are currently ongoing and will be presented at the meeting.

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Identification of Therapy Induced Evolution in MRD Clones and Resistance Pathways in Multiple Myeloma Through Single-Cell Sequencing

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Introduction: In multiple myeloma (MM), the leading cause of disease progression, exhibits intratumoral heterogeneity that enables adaptability, limits therapeutic success, and remains incompletely understood. Previous studies have confirmed that clonal evolution frequently occurs at disease follow-up, and the patterns of clonal evolution between diagnosis and relapse correlates with patient outcomes. However, it remains unclear whether clonal evolution occurs as early as after induction therapy. **Methods:** In this study, we analyzed single-cell RNA sequencing from 19 patients with newly diagnosed MM (NDMM), 17 paired bone marrow (BM) samples after 2-4 cycles of proteasome inhibitor (PI) plus immunomodulatory drugs (IMiDS)-based induction therapy were collected and underwent scRNA seq. BM samples from one healthy donor was also collected. By tracing transcriptional and cytogenetic PCs clones over time and performing differential expression analysis, we defined different patterns of clonal evolution and identified potential resistant pathways. **Results:** In our cohort, 12 patients were identified with more than 30 PCs in the BM samples sequenced after induction therapy. Among them, our analysis of the transcriptional and cytogenetic clonal dynamics in MM patients identified three main trajectories: patients with sensitive PC clones or clone that responds to treatment with >90% of the malignant PCs replaced with seemingly health PCs (3/12 patients, 25%); in patients with a resistant clone that did not respond or only very partly responded to treatment, > 50% of the malignant PCs were found in the BM post-treatment (5/12 patients, 42%); and patients with clonal selection, indicating that the major clone has been replaced by a small or undetectable clone at baseline (4/12 patients, 33%). For these four patients identified with clonal selection, one was observed with branching evolution, and the other three were observed with differential evolution. Transcriptional differences among sensitive clones, resistant clones and selective clones were detected based on a pairwise comparison of the gene expressions. A large number of differentially expressed genes with reported MM resistant-related functions were observed in the resistant clones, including previously reported 1q-related genes such as CKS1B, HNRNPU and H3F3A; unfolded protein-stress response-related genes such as NOP56 and HSP90B1; cell cycle- and cell proliferation-related genes such as TUBA1B, STMN1 and HMGB2. For selective clones, an evident activation of NF-kB signaling pathway was observed. Furthermore, an increase in CD74-MIF cellular interaction was found between selective clones and the tumor microenvironment. **Conclusions:** Together, our study confirms that clonal dynamics of the evolving PC clones may occur early after upfront therapy, and reveals that the acquisition of therapeutic resistant pathways is associated with early adaptation to treatment.

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Type I Interferon Response in Monocytes Altered Monocyte Differentiation Pathways and Promotes Multiple Myeloma Proliferation

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Introduction: A growing body of evidence has indicated impaired function or compositional changes of monocytes in inflammatory disorders, such as acute respiratory syndrome and COVID-19. 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. Nevertheless, the mechanisms underlying monocyte defects in MM remain poorly addressed, at least in part due to the lack of large-scale single-cell RNA sequencing (scRNA-seq) studies. **Methods:** We performed scRNA-seq on monocytes of 7 newly diagnosed MM (NDMM) patients and 12 HD. Specifically, 3 and 5 BM samples and 9 and 7 PB samples of 12 HD and 7 NDMM patients were obtained and sequenced, respectively. **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.

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Identification of Uniquely Expressed Proteins in Bone Marrow Mesenchymal Stromal Cells of Multiple Myeloma Patients With Poor Therapeutic Response

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Introduction: Bone marrow microenvironment, especially the bone marrow mesenchymal stromal cells (BMMSCs), have been implicated in modulation of homing, growth, proliferation, egression, and even treatment response of tumor plasma cells in patients of multiple myeloma (MM). The proteomic profiling of cultured-BMMSCs from patients of MM may provide insight into proteins and molecular-pathways associated with risk category of MM and also with their response to therapy. **Methods:** Ten newly diagnosed patients of MM (NDMM) were enrolled. The BMMSCs were isolated and cultured from bone marrow aspirate sample taken at the time of diagnostic work-up. The purity of cultured BMMSCs was confirmed by flow cytometry. Proteomic profiling of cultured BMMSCs was carried out using Liquid Chromatography-Mass Spectrometry. The risk categorization based on cytogenetics (FISH) revealed five patients each in cytogenetic high-risk (cHR) & standard-risk (cSR) categories. The data from proteomic-profiling was statistically compared between the two risk categories. All patients were started with bortezomib-based induction. Treatment response for three cSR and all five cHR patients was available at six months. Four patients, including one from cHR category achieved stringent complete response (sCR) [good responder (GR) group], and the rest four failed to achieve sCR [poor responder (PR) group]. The data from proteomic-profiling was statistically compared between the two response category-groups. **Results:** The cHR patients revealed significantly higher levels of proteins involved in cholesterol biosynthesis, steroid metabolism, lipid metabolism, rRNA processing as compared to cSR patients. Whereas, the proteins involved in glycosaminoglycan & aminoglycan catabolism, and glycosphingolipid metabolism were significantly lower. Analysis amongst PR and GR revealed same results corresponding to cHR & cSR, except for absence of difference in rRNA processing pathway amongst response categories. There were some unique proteins, expressed only in PR and not in GR group, notably, ABCC3, ATXN7L3B ,BCAR3, H2BC12, IREB2, PATL1, RABGAP1L, S100A8, SIRPA, TFB1M, H2BC3, SEPTIN6, NCAM1, MFN1, TSYPL1, NOP14, AKTIP, ABHD5, MPHOSPH10, SLC35B3, IMP3. Conversely, PARVB, APOH, LZTR1, PPP1R14A, CYB561D2, UBTD2, UBTD1, TMEM14A were only present in GR group.Validation of some of these proteins on freshly enrolled NDMM patients was carried out. **Conclusions:** Proteomic profiling of BMMSCs from patients of MM with poor response to therapy reveal expression of unique proteins which may provide more insight into pathobiology of disease, molecular pathways involved in resistance to therapy, and possibly potential new therapeutic targets.

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Clonal Evolution of Multiple Myeloma Following the Mutagenic Impact of Radiotherapy

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Introduction: Ionizing radiotherapy (RT) is a routine treatment of multiple myeloma (MM). RT induces double-strand breaks (DSB) and deletions linked to the ID8 indel mutational signature, but its mutagenic impact on MM relapse patterns is underexplored. **Methods:** We reworked mmsig for indel signatures (https://github.com/UM-Myeloma-Genomics/mmsig) and used 80x whole genome sequencing (WGS) to characterize 266 newly diagnosed (ND) and

98 relapsed/refractory (RR) MM (327 patients). For validation, we included 56 relapsed and 100 untreated large B-cell lymphomas (LBCL). Because chemoRT is often co-administered in patient samples, we validated the mutagenic impact of each individual therapy using treated single-cell-derived colonies. **Results:** Of 514 total WGS, 29 and 16 samples were from MM and LBCL patients exposed to RT. Of 45 cases with prior RT exposure, 41 (91%) also had prior mutagenic chemo (platinum/melphalan). Indel burden was increased in RRMM compared to NDMM (median 596 vs 527, p< 0.001). We performed both indel and single base substitution (SBS) signatures analysis for all samples. SBS signatures include platinum-(SBS31, SBS35, E_SBS37) and melphalan-induced (SBS99) mutagenesis in exposed samples. We deconvoluted a total of 8 indel signatures including ID8. ID8 was seen in 18 relapsed samples (of 154 total, 11.6%) and not in any at baseline. Importantly, while presence of ID8 was strongly correlated with prior RT (p< 0.001), it was also observed in 10 unexposed samples. All of these RT-unexposed cases had evidence of platinum/melphalan mutagenesis. As chemo-induced ID8 has not been reported, we performed a single cell expansion experiment wherein DHL-4 cells were exposed daily to platinum or RT. Single cells from days corresponding to a lethal dose and a half-lethal dose were expanded, and the resulting colony subjected to 60x WGS. An unexposed single cell expansion was performed as control (in triplicate, total 15 WGS). RT and platinum expansions had a higher indel burden (mean, 4247) compared to control (mean, 3065; p = 0.004). Where all RT expansions had evidence of ID8, only lethal dose platinum harbored ID8, implying a higher dose threshold must be met, but that DSB from chemotherapy can indeed cause ID8. Finally, we focused on 2 ID8+ cases from patients with RT exposure, but no chemo signatures. One LBCL case had an irradiated neck node as a bridge prior to CART. At relapse, 9 months later, a biopsy from an inguinal site had ID8. One MM case had irradiation of a clavicular plasmacytoma and a relapse 7 years later with ID8 detected in a marrow biopsy. Given the requisite clonal expansion of unique RT-induced indels required for ID8 detection in WGS, this constitutes evidence that a single cell survived RT and later seeded systemic relapse. **Conclusions:** ID8 is strongly associated with palliative RT in RRMM and LBCL, indicating surviving tumor cells from RT-exposed lesions can seed systemic relapse. Yet, ID8 is not solely the result of RT, and can be induced via DSB from chemo.

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The Influence of the Gut Microbiome on Myeloma Progression

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Introduction: Our understanding of the microbiome's role in cancer has significantly expanded, uncovering how variations in diversity and composition of gut microbiota contribute to treatment response among cancer patients. However, the microbiome's influence on multiple myeloma (MM) progression and resistance to immunotherapy remains incompletely elucidated. We asked whether dysbiosis (loss of diversity, depletion of obligate anaerobes, blooms of pathobionts) is associated with MM progression, immune evasion, and inferior outcomes. **Methods:** N/A. **Results:** We profiled the gut microbiome of 50 newly diagnosed MM patients who underwent high-dose melphalan conditioning and ASCT by 16S rRNA sequencing of the V4-V5 region. We compared pretransplant gut microbiota features in early progressors (EP, n=25) who relapsed in < 43.5 months (range 3-42) to late progressors (LP, n=25) who relapsed or maintained remission at >43.5 months (range 45-85). α-diversity was lower in EP (p< 0.035), whereas there was no significant difference in β-diversity. Using pairwise comparisons, Blautia and Faecalibacterium were significantly enriched in EP and LP respectively. Random Forest prediction classifier method, a supervised machine learning algorithm and Shapley Additive exPlanations (SHAP), a post-hoc explainability algorithm, identified Faecalibacterium and other short chain fatty acid producers as the most significant microbiota features in LP and Blautia had the highest importance in EP, further validating their significance. To establish causality between the gut microbiome and MM severity, we generated isogenic KaLwRij mouse strains harboring differences in richness and complexity of naturally occurring gut microbiota. We observed increased tumor burden and decreased infiltrating CD8 T cells in 5TGM1 mice with low microbiota richness compared to mice with high richness. The median overall survival for 5TGM1 mice with low, intermediate and high richness was 31, 35, and 39 days post-5TGM1 injection, respectively. We performed fecal microbiota transplantation (FMT) in antibiotic-treated KaLwRij mice. Mice were humanized with pretransplant stool from EP (n=3 donors) and LP (n=3 donors). 5TGM1 mice transplanted with gut microbiota from EP showed accelerated MM progression after 21 days compared to mice transplanted with gut microbiota from LP. **Conclusions:** Our findings suggest that lower diversity and specific bacterial taxa prior to ASCT are predictive of early relapse in NDMM patients. We observe that lower microbiota diversity accelerates MM progression, impairs CD8 T cell responses, and worsens survival. This indicates a causal relationship between the gut microbiome and disease severity. Our preliminary FMT studies suggest a cause-and-effect relationship between gut microbiota and early disease progression and further highlight the feasibility and therapeutic potential of microbiota-centered intervention in limiting disease severity.

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Evaluation of IL-6, IL-1β and TNF-α Polymorphisms in Multiple Myeloma Patients

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Introduction: Multiple Myeloma (MM) is a hematological neoplasm characterized by clonal proliferation of plasma cells, resulting from the action of inflammatory cytokines, angiogenic and vasculogenic factors. Genetic alterations related to such factors have been studied in order to understand how these changes modify the onset and evolution of the disease. Aims- To study the polymorphisms in the IL-1β , IL-6 and TNF-α genes and their potential impact on MM biochemical changes. **Methods:** A cross-sectional study was carried out involving 20 patients transplant eligible newly diagnosed MM from the MAXDARA trial a phase 2 study and 55 healthy controls. The genotyping was performed with polymerase chain reaction (PCR) and DNA sequencing by B3500xL Genetic Analyzer for Human Identification (Apllied Biosystems,Massachusetts, EUA). The sequencing results were analyzed by BioEdit (Sequence-Alignment-Editor-7.2.5) and compared with NCBI databases using BLAST. **Results:** Seventy-five % (n=17) of these MM patients were black or mixed race, 63.64% (n=14) were female and 28.5% (n=6) and 33.3% (n=7) were diagnosed with R-ISS- II and III, respectively. Polymorphism analysis in the IL-6 gene -174G/C rs1800795 showed a frequency of 52.38% (n=11) for the homozygous wild type (GG) genotype, 28.57% (n=6) for the heterozygous genotype (GC) and 19.05% (n=4) for the homozygous variant genotype (CC) in the MM group and 79.25% (n=42), 19.87% (n=10) and 1.89% (n=1) for the GG, GC and CC genotypes, respectively in the control group. The analysis with a dominant model demonstrated an odds ratio (OR) of 3.47 (1.17 – 10.25 CI: 95.0%), p-value = 0.042, and the allele frequencies showed an OR of 3.91 (1.62 – 9.43 CI: 95.0%), p-value=0.003. The association of polymorphisms with biochemical markers showed that MM individuals with GA/AA genotypes for the TNF-α rs673 polymorphism had higher levels of calcium than individuals with the GG genotype (p=0.006). For the TNF-α rs1800629 polymorphism, individuals with the GG genotype had higher levels of total protein than GA/AA individuals (p =0.03). **Conclusions:** The present study suggests that the presence of the IL-6 -174 G/C rs1800795 polymorphism appears to be associated with MM. New studies with more MM patients involving polymorphisms in the IL-6 and TNF-α genes are necessary to confirm these results.

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Clinical Characteristics and Prognostic Values of 1p32.3 Deletion in Newly Diagnosed Multiple Myeloma Patients

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Introduction: 1p32.3 deletion is a common cytogenetic abnormality in multiple myeloma, but its clinical significance has not been clearly demonstrated and its detection by FISH has not been widely carried out. This study mainly analyzed the clinical characteristics, treatment response, and prognostic significance of 1p32.3 deletion detected by Cytoscan in newly diagnosed multiple myeloma patients. **Methods:** 345 NDMM patients admitted in The First Affiliated Hospital of Soochow University from September 01, 2018 to August 31, 2022 of a VRD registration study, were retrospectively analyzed. Cytogenetic testing was performed by CD138 sorted fluorescence in situ hybridization (FISH) and Cytoscan. **Results:** The proportion of chromosomal 1 abnormalities was 64.1%, including 189 cases (54.8%) of 1q21 gain/amplification and 88 cases (25.5%) of 1p deletion. Among them, 40 patients had 1p32.3 locus and involved CDKN2C deletion. Del1p32.3 patients had higher urinary protein levels, higher LDH levels and were more likely accompanied with extramedullary disease, strongly correlated with 1q21 gain/amplification and 17p deletion. Cytoscan showed the higher proportion of complex chromosomal abnormalities, different subclonal groups, complex karyotypes and CNV abnormalities. 1p32.3 showed the increased proportion of disease progression and lower achievement of deeper remission after induction therapy. Patients with single monoallelic deletion have significantly poorer survival outcomes compared to those with partial chimeric monoallelic deletion both in 1p12, 1p22 and 1p32.3 locus, with the shortest median PFS of only 15 months, P=0.0110, and the shortest median OS of only 18 months, P=0.0015. The main clone is a clear adverse factor affecting patient prognosis (median PFS 15 months, P=0.0103, median OS not reached, P=0.0167). The accumulation of HRCAs could further deepen the adverse prognosis of high-risk patients in PFS (median PFS 20 months, PFS P=0.0480, OS P=0.1074). Autologous stem cell transplantation can improve the prognosis in Del1p32.3 population in both PFS and OS to some extent (36 months PFS 50.6% vs 37.5%, 36 months OS 82.5% vs 70%). In multivariate analysis, only 1p32.3 was an independent adverse factor affecting the prognosis of PFS in patients with 1p deletion (PFS: HR=1.755, 95% CI 1.060-2.907, P=0.019; OS: HR=1.291, 95% CI 0.608-2.743, P=0.506). **Conclusions:** Patients with 1p32.3 deletion are prone to high-risk cytogenetic abnormalities, and 1p32.3 deletion is an independent high-risk cytogenetic factor for poor prognosis of MM, associated with unstable disease cloning and invasive phenotype of plasma cell diseases, indicating it should be routinely tested in the clinic for newly diagnosed MM patients.

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Single Nucleotide Variants in PTPRD, NOTCH4, SH3RF3, DCC, and CSMD Genes as Potential Prognostic Biomarkers of Newly-Diagnosed Multiple Myeloma

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Introduction: Monoclonal gammopathy of uncertain significance (MGUS) is a premalignant condition that may progress to diverse neoplasms or monoclonal gammopathies, with active multiple myeloma (MM) being the most frequent. Aims: To analyze the differences of single nucleotide variants (SNVs) frequencies between MGUS and MM patients by microarray genomic analysis, and its discriminatory capability. **Methods:** This retrospective study included 56 newly-diagnosed MM (NDMM) patients(median age: 57.5 years, ISS-3: 30.4%), with 57.2% undergoing frontline autologous stemcell transplantation (ASCT). PIR were distributed as follow: complete response (CR) 25%,very good partial response (VGPR) 33.9%, partial response (PR) 26.8%, and stabledisease/ refractory (<PR) 14.3%. Early relapse (ER; within 24 months) occurred in 48.2%cases. Genomic DNA was purified from peripheral blood or bone marrow cells byconventional methods. SNVs were analyzed using the Illumina Infinium GSA on the IlluminaiScan Platform which contains 654,027 markers. Binary Discriminant Analysis (BDA),Principal Components Analysis (PCA), and k-means clustering were employed. The PIR wasassessed per IMWG recommendations. **Results:** The analysis of the entire cohort showed 692 SNVs that were able to differentiatebetween the various PIR groups (Dim1 11.2%, Dim2 6.8%) (t.score > 3). Among the 42 mostsignificant SNVs (t.score > 4), five are for PR, and 33 are for (<PR). Of these, 60% and 12%,respectively, have been associated with tumoral activity. On the other hand, in patients whoreceived ASCT (n=32), 151 SNVs effectively discriminated between ER and non-earlyrelapsed (NER) (Dim1 34.7%, Dim2 6.5%) (t.score > 3). Among them, we found 12overlapping SNVs between ER and ≤PR. Patients hetero- or homozygous for the alternativeallele (Group A; n=9) carrying PTPRD (rs12343415, rs77411943, rs10978084), NOTCH4(rs8192588), SH3RF3 (rs76256617), DCC (rs72920200), and CSMD1 (rs11781684) variantshad a higher ≤PR rate (88.9%) compared to cases homozygous for the reference allele(Group B, n=47) (34%) (p=0.005). Group A also had a higher ER rate (88.9%) versus 40.4% ofGroup B (p=0.021). Additionally, in a multivariate analysis including first-line ASCT and ISS,Group A had worse overall survival (p=0.008) and progression-free survival (p=0.017). **Conclusions:** Our analysis showed that a significant number of SNVs detected by a widegenotyping through microarray technology can classify patients with different PIR groups. Inaddition, even with a limited number of patients, our results suggest that the presence ofalternative alleles in specific SNVs may be associated with inferior induction response, PFS,and OS in NDMM. These findings suggest the potential predictive role of our genomicanalysis and the clinical relevance of SNVs in MM. However, more studies are required tocorroborate our results. Financing.: IMS and The Paula and Rodger Riney Foundation.

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Comparative Genomic Analysis of Active Multiple Myeloma and Monoclonal Gammopathy of Uncertain Significance Using Single Nucleotide Variants Microarray

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Introduction: Monoclonal gammopathy of uncertain significance (MGUS) is a premalignant condition that may progress to diverse neoplasms or monoclonal gammopathies, with active multiple myeloma (MM) being the most frequent. Aims: To analyze the differences of single nucleotide variants (SNVs) frequencies between MGUS and MM patients by microarray genomic analysis, and its discriminatory capability. **Methods:** An analytic and retrospective study of 56 MM patients (median age 57 years, 43.8% females; subtypes IgG 59.3%, IgA 23.4%, others 17.3%; risk staging ISS-1 31.2%, ISS-2 37.5%, and ISS-3 31.3%) and 14 MGUS (71.4% females, median age 65.5 years; subtypes 64.3% IgG, 28.6% IgA, and 7.1% IgM) was performed. Genomic DNA was purified from peripheral blood or bone marrow cells by conventional methods. SNVs were analyzed using the Illumina Infinium GSA on the Illumina iScan Platform which contains 654,027 markers. Binary Discriminant Analysis (BDA), Random forest (RF), Principal Components Analysis (PCA), and k-means clustering were employed. Hg19 genome was used as reference **Results:** Upon several filtering steps, 103,942 SNVs were obtained. Of those, 251 across 193 genes were significant using the BDA algorithm and satisfactorily clustered MM and MGUS through PCA (Dim1 16.9%, Dim2 4.5%). Among these SNVs, 52 were more prevalent in MM, involving genes related to various cellular components, molecular functions, and biological processes by Overrepresentation Analysis of GO pathways. More frequent MM-associated SNVs included CFAP74 rs2803337, FAF1 rs3827730, FSTL1 rs1147696, SORCS2 rs2285778, ARHGEF37 rs4409073, UST rs9390613, NUGGC rs7840091, MMRN2 rs746677, TRPC6 rs4326755, ATP10A rs6576456, UST rs10457838, SGF29 rs4788073, and PCP4 rs9983735. On the other hand, more frequent MGUS associated SNV included OR2W5 rs10925061, PADI2 rs11588995, ATP8B4 rs12915207, KCNN2 rs1487228, ECE1 rs213019, ATP8B4 rs28706888, PGAP6 rs763146, RC3H1 rs80205789. The top ten SNVs by the RF selection were: KIAA1614 rs17302207, ALPK2 rs9967112, TMEM132C rs117202260, NOTCH1 rs10870078, and MYO5B 17714688, MYOD1 rs71484784, ITGA9 rs76052815, ROS1 rs13201929, PLXNA2 rs72739456, and SHISA9 rs153096, with 80% of them being associated with cancer risk or tumoral progression. **Conclusions:** In summary, our study underscores the potential role of extensive SNV genotyping in distinguishing between MGUS and MM. We observed distinct SNV patterns indicating potential associations with prognostic biomarkers for susceptibility to MM progression,

based on genes involved and their biological functions. These findings have implications for personalized therapeutic strategies in clinical practice. Further research is warranted to elucidate the underlying molecular mechanisms and validate the clinical utility of these SNVs in MM management.Funding. IMS and The Paula and Rodger Riney Foundation

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Examining the Role of XRCC1 and BRCA1 Gene Variants on Survival and Treatment Response in Patients With Multiple Myeloma From South America and Spain

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Introduction: Multiple Myeloma (MM) shows differences in epidemiology, clinical evolution, and genetics among different populations. This variation could influence treatment outcomes. We hypothesize that single nucleotide variants (SNVs) in DNA repair genes could impact treatment outcomes. Aims: To analyze the association between SNVs BRCA1 rs799917 and XRCC1 rs2548 with treatment response, overall survival (OS), and progression-free survival (PFS) in MM patients undergoing high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) as first-line consolidative therapy. **Methods:** This retrospective study included 222 newly diagnosed MM patients (median age: 54.3 years; 45% females) from Uruguay (12.2%), Argentina (5.4%), and Spain (82.4%). Response rate, overall survival (OS), and progression-free survival (PFS) were evaluated. DNA was purified from peripheral blood or bone marrow samples. In Uruguay and Argentina, genotyping of SNVs was performed by conventional PCR and Sanger sequencing, whereas in Spain was performed by allelic discrimination with TaqMan probes in an ABI PRISM 7500 Sequence detection system. Statistical analysis was performed using SPSS v.26 and R 4.3.2 software. **Results:** MM subtypes were IgG 57.7%, IgA 23.4%, and other 18.9% with a risk staging: ISS-2 35% and ISS-3 22.7%. Bortezomib-based regimens (BBR) were used in 28.4%. Pre-ASCT responses included: complete response 20.6%, very good partial response (VGPR) 11%, partial response (PR) 45%, and < PR 23.4%. Genotypic frequencies for rs25487 (n=179): AA 30.7%, AG 46.4%, GG 22.9%; allelic: G 46.1%, A 53.9%. For rs799917 (n=210): GG 20%, AG 77.6%, AA 2.4%; allelic: G 58.8%, A 41.2%. The genotypic frequencies among the three countries were significantly different for both SNVs. The median OS (mOS) and PFS (mPFS) for the whole group were 7.52 years (y) and 2.8y, respectively. Factors significantly affecting 10y-OS included ISS, pre-transplant response, and use of BBR. The rates of ≥VGPR according to the SNVs were rs799917 AG/AA 29.7% and GG 45.2% (p >0.05), and rs25487 AA 25%, AG 34.1, and GG 56.1% (p< 0.01). No significant differences in 10y-OS rates for rs799917 AG/AA: 42.6% and GG: 49.2%. Similarly, for 10y-PFS of this SNV, AG/AA 12.9%, while GG 21.3%. For rs25487 AA, 10y-OS 35.7%, AG 47.0%, and GG 68.9%. Likewise, for 10y-PFS, we observed AA 22.1%, AG 12.4%, and GG 12.6%. No significant difference regarding ISS frequency among genotypes. However, rs25487 GG had a higher proportion of BBR (p< 0.05). **Conclusions:** Our findings demonstrate a notable increase in pretransplant ≥VGPR rates for patients carrying rs25487 GG genotype. SNVs XRCC1 rs25487 and BRCA1 rs799917 exhibited non-significant differences in OS and PFS, in agreement with previous studies. While these results hint at the potential impacts of XRCC1 rs25487 on patient outcomes, other variables underlying the clinical phenotype and cofounders must be considered for predictive accuracy. **Funding:** IMS and Paula and Rodger Ridney Foundation.

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Cancer Dynamics of Multiple Myeloma

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Introduction: MM progression,dissemination,and relapse involve multiple driver lesions and exhibit high genomic complexity and heterogeneity. Early drivers,such as cytogenetic abnormalities,chromosomal translocations,and copy number variants (CNV), are detectable in premalignant stages. As the tumor evolves, secondary genomic lesions emerge in subclones,distinguishing them genetically from one another. We present here, the mutational landscape of MM, in cytogenetic,genetic,epigenetic, tumor microenvironment and immunoprofiling terms to identify areas of interest for drug development. **Methods:** n/a. **Results:** Primary events: two non-overlapping pathways initiate plasma cell proliferation: hyperdiploidy and non-hyperdiploidy. Hyperdiploidy, which rarely co-occurs with IgH translocations, generally indicates a better prognosis than IgH-translocated myeloma. Multiple myeloma SET domain protein (MMSET) becomes essential during MM progression with the t(4;14) translocation. Other translocations include t(11;14), t(12;14), t(6;14), t(14;16), and t(14;20), with the latter being less common and along with t(4;14) are associated with genetic instability.Two tumor progression models are proposed: the static progression model, where the malignant clone is defined at the SMM stage, and the spontaneous evolution model, where progression occurs through clonal evolution with secondary events like additional translocations,CNV,mutations,epigenetic changes, and microenvironmental alterations driving progression from MGUS/SMM to MM. Secondary events: the deletion of chromosome 13q, amplification of chromosome 1q ,and deletion of chromosome 1p are significant events.TP53 mutations combined with 17p loss result in poorer outcomes. Concerning the epigenetic changes, the key one in MM pathogenesis is global DNA hypomethylation and

gene-specific hypermethylation during the transformation from MGUS to myeloma. On the other hand, the microenvironment: local "milieu" provides both suppressive and supportive signals to clonal plasma cells, such as increased IL-6 production and enhanced angiogenesis by VEGF. Not all MGUS/SMM patients with similar genetic alterations progress to MM, indicating the microenvironment's key role in disease initiation and progression. Immune evasion and MM progression are influenced by immune checkpoint molecules and immunosuppressive cytokines (IL-10 and TGF-β). Additional factors include bone disease (RANKL production), osteoclast activation,and metabolic changes (Warburg effect). **Conclusions:** While our understanding of MM biology has improved, identifying molecular alterations, microenvironment, and cytokine abnormalities driving MM progression, has not yet fully translated into individualized targeted therapies with large and /or small molecules. On the other hand, promising results are seen with CAR-T cell therapy and developing clinical studies that combine this cell therapy with target drugs may become a game-changer in the natural history of high-risk MM

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IRF2 Inhibition Impairs Cell Migration and Triggers Necroptosis in Multiple Myeloma

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Introduction: Multiple Myeloma (MM) is the second most common hematologic neoplasia, but it remains incurable. A recent study of the epigenome of MM cells described de novo chromatin activation as a unifying factor underlying the disease. These de novo active regions were enriched in specific Transcription Factor Binding Sites (TFBS) suggesting that TFs may exert a significant role in the development and progression of MM. Here we identify and characterize the function of essential TFs involved in the pathogenesis of MM. **Methods:** na. **Results:** CRISPR/CAS9 library screening was conducted against 54 TFs that presented TFBS at de novo active chromatin regions revealing that 22 TFs were essential for MM. Strikingly, there were three members of the IRF family: IRF1, IRF2, and IRF5, along with the positive control IRF4. Single knockdowns identified IRF2 and IRF4 as the most essential TFs. Besides, using the CoMMpass database we detected that MM patients with higher expression of IRF2 had worse progression-free and overall survival, both in univariate and multivariate analyses considering high-risk genetic factors. Then, to characterize the biological function of IRF2 in MM, its chromatin localization was determined by CUT&RUN. IRF1 (non-essential) and IRF4 were also assessed to compare the role of the three IRFs. We identified 16300 chromatin regions bound by IRF2, significantly enriched in active promoters compared to IRF4 (7512 peaks) and IRF1 (5891 peaks). The expression of the IRF2 target genes was analyzed in plasma cells from healthy donors, MGUS, SMM and MM patients, observing a dysregulation from MGUS state that suggests the role of IRF2 in MM development. Moreover, IRF2 co-localized with IRF1/IRF4 in 40% of the chromatin regions and regulated the immune system and GTPases. Whereas most of the regions were regulated exclusively by IRF2 and regulated cell cycle and GTPases. Intriguingly, IRF2 was present in 32% (498/1556) of de novo active chromatin regions, more than IRF1 or IRF4. 201 peaks were unique to IRF2 and regulate genes involved in cell migration and osteoblast differentiation, while 297 peaks co-localized with IRF1/IRF4 and were related to oxidative stress genes. Finally, transcriptome analysis revealed that IRF2 inhibition downregulated the adaptive immune system, cell proliferation, and GTPases were also dysregulated leading to a decrease in cell-cell adhesion and cell migration. Then, we observed an upregulation of the innate immune system, dsRNA responses, membrane biogenesis and necroptosis, which was confirmed by the increase of MLKL phosphorylation. **Conclusions:** IRF2 plays a significant role as a prognostic biomarker and as an essential gene in the pathogenesis of MM by participating in the regulation of relevant signaling pathways such as cell cycle, migration and adhesion. Moreover, the inhibition of IRF2 promotes necroptosis paving the way to the development of new therapeutic strategies.

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The Interaction Between Myeloma Cells and Microenvironment via LILRB4 Signaling Promote Myeloma Progression

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Introduction: LILRB4 is a family member of leukocyte immunoglobulin-like receptors (LILRs), which are known to play critical roles in the regulation of immune tolerance. We have suggested that LILRB4 presented to be an ideal immunotherapy target for MM. In this study, we aimed to investigate the underlying mechanisms by which LILRB4 mediated MM progression remain unknown. **Methods:** To underscore the immune alterations under the impact of

LILRB4 expression in MM cells, we generated LILRB4-overexpressed immunocompetent MM mouse model. A 32-color spectral flow cytometry panel was implemented for deep immunophenotyping of tumor microenvironment in LILRB4-overexpressed MM mouse model. **Results:** We have already suggested that CD38+LILRB4+ MM cells tended to be initiating immature plasma cells by single-cell RNA sequencing analysis. We observed that the level of LILRB4 was significantly increased in precursor stage of plasma cells (pre-PC, CD38+CD138+CD19+CD56+) compared with mature malignant MM cells (MPC, CD38+CD138+CD19-), which were both higher than normal PCs (NPC, CD38+CD138+CD19+CD56-). We hypothesized that LILRB4 might also be a marker for MM-initiating cells. Combining the known MM-initiating marker, CD24, we showed that CD24+LILRB4+ MM cells presented morphologically less mature than the other MM cells. Further, LILRB4+ MM cells could form more and larger cell colonies than LILRB4- MM cells, indicating the tumor-promoting function of endogenous LILRB4. LILRB4 is an important immune modulating molecule. LILRB4 has been known to mediate T cell suppression. Here, we cocultured LILRB4-overexpressed or LILRB4-deleted MM cell lines with peripheral blood mononuclear cells (PBMCs) from healthy donors in vitro. We found that overexpression of LILRB4 in MM cells could induce the generation of MDSCs and decrease the infiltration of CD3+ T cells. Using KaLwRij-5T33 mouse model, the proportion of MDSCs were increased and the proportion of T cells were decreased in bone marrow from 5T33-LILRB4 engrafted animals. Notabaly, 5T33-LILRB4 engrafted mouse displayed more rapid disease progression compared with 5T33-empty vector transfected (EV) engrafted mice. Furthermore, the conditioned medium of LILRB4-overexpressed MM cells had same effect in inducing MDSCs. Interestingly, when we cocultured MM cells with PBMCs, the expression of LILRB4 were also significantly upregulated in MM cells. These results indicated a feedback loop between immune cells and MM cells via LILRB4-related signaling interaction, which promoted the formation of immunosuppressive microenvironment for MM cells. **Conclusions:** We suggested that LILRB4+ MM initiating cells could modulate the microenvironment to enhance the maintenance of these cells. Interfering the LILRB4 signal interaction between MM cells and the microenvironment would be advantageous to MM treatment.

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Inadequacy of MYC Gene Expression Alone as a Risk Determinant in Multiple Myeloma – the Importance of Associated MIZ1 Expression

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Introduction: MYC gene expression has been associated with progression from Monoclonal Gammopathy of Unknown Significance to Multiple Myeloma (MM). Furthermore, a subset of patients with newly diagnosed MM (NDMM) carries secondary MYC rearrangements. Despite several studies showing poor prognosis of NDMM patients with MYC rearrangement, MYC aberration is not part of the International Myeloma Working Group poor risk category. MYC-interacting zinc finger 1 (MIZ1) is a transcription factor that plays a role in oncogenesis. Its interaction with MYC lead to suppression of MIZ1 target genes. We investigate whether MYC and MIZ1 expressions are prognostic in NDMM. **Methods:** Genes' expressions from the MM Research Foundation CoMMpass dataset were used to divide NDMM patients into four groups based on their MYC and MIZ1 tertile gene expressions. Bioinformatics analyses were done using R packages. MIZ1 knockdown was performed using CRISPR dCas9-containing cell lines. Further statistical analyses were done using Prism 10.0. **Results:** A total of 764 NDMM cases were included in the analysis. Of the MYC high group, 92 cases (12.04%) expressed high MIZ1 (HMHM) and 73 cases expressed low MIZ1 (HMLM). Of the MYC low group, 84 cases (10.99%) expressed high MIZ1 (LMHM) and 97 cases (12.70%) expressed low MIZ1 (LMLM). MYC translocation was found more often in the HMHM (21.65%) and HMLM (20.62%) compared to LMHM (0%) and LMLM (4.12%) groups. Survival analysis using Kaplan Meier plot showed worse prognosis in the HMHM group, with HMLM group comparable to the rest. Hence, we focused further analysis on HMHM group against the rest of the cohort (reference/Ref group). We observed less ISS stage 1 disease in HMHM with tendencies towards more ISS stage 2 and 3 diseases. Furthermore, less Black/African American were observed in the HMHM group. To assess the significance of MYC and MIZ1 in-vitro, we knocked down MIZ1 in U266 and H929. MIZ1 knockdown led to reduced cell numbers at days 5 and 7 post transduction of sgRNA in H929 only. **Conclusions:** MYC translocation has been associated with higher gene expression. However, its impact on prognosis is variable, with the poorest prognosis observed when MYC was partnered with IgL gene and better outcome when it was partnered with non-immunoglobulin genes. High MYC gene expression has previously been associated with poor prognosis in the CoMMpass dataset. We have shown that MYC's poor risk is dependent on MIZ1 high gene expression. MIZ1 expression was important in survival and/or proliferation of H929 cells in culture, but not in U266 cells. Interestingly, c-MYC is expressed only in H929 cells while U266 cells expresses L-MYC, which interacts less strongly with MIZ1 compared to c-MYC. Hence, high MYC and MIZ1 gene expressions may be a novel poor risk indicator in MM. Furthermore, MIZ1 suppression may be clinically useful in this high-risk group. Further studies are required to validate these findings in different MM gene expression datasets.

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Longitudinal Analysis of t(11; 14) and t(4; 14) Genomes Reveals Distinct Evolutionary Trajectories in Multiple Myeloma

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Introduction: The t(4;14) and t(11;14) represent the most common translocated multiple myeloma (MM) subtypes and are associated with different clinical behaviours. Although differences in genomic aberrations and expression profiles have been shown at diagnosis, little is known about the genetic mechanisms underlying disease progression. **Methods:** To gain insight, we analysed paired whole genome sequencing (median CD138+ tumour 46X; germline 23X) from longitudinal samples (n=34, median 3 per patient) derived from 8 t(11;14) and 5 t(4;14) MM patients with a median time between samples of 24.8 months. Additionally, we performed long-read RNA sequencing on the same patients for gene expression (n=18; median samples 2 per t(11;14) and 1 per t(4;14) patient). **Results:** Canonical IGH translocations were observed at all timepoints. Regarding other structural variants (SV), there was no difference in breakpoint number and rate of acquisition between subtypes through progression. While copy number (CNA) remained stable in 2/3 evaluable t(4;14) patients, de novo changes were seen in 7/8 t(11;14) patients, with acquisition of gain1q (n=2), del6q (n=4), and del13q (n=1). This could suggest t(11;14) gain more de novo CNA at progression, including del6q associated with plasma cell leukaemia. There was no difference in mutational burden between subtypes but we identified subtype-specific mutational drivers such as PRKD2 in the t(4;14), and IRF4 in the t(11;14), consistent with the literature. Overlaps in driver mutations converged between subtypes to pathways of epigenetic regulation and DNA instability. Mutational signature analysis showed similar contribution of signatures, with clock-like SBS5 and hypermutation SBS9 active in all patients, melphalan-associated SBS-MM1 linked to ASCT rather than subtype, and APOBEC SBS13 remaining stable except one t(11;14) case (appeared at progression). Despite this, the rate of acquisition of both overall mutational burden and SBS9 signature contribution was higher in t(4;14) through progression (linear regression, p=0.04 and p=0.019 respectively).Subtypes also displayed distinct transcriptomic profiles, with 206 differentially expressed genes reported between the subtypes (log2FC > ±2, p< 0.05). t(4;14) patients exhibited increased expression of genes on 1q whereas t(11;14) overexpressed genes on chromosome 11. As expected, t(11;14) was associated with a B cell phenotype, expressing a signature of B cell-associated genes, of which MS4A1 (CD20), CD79A, and RGS1 decreased in expression in 3/4 patients through progression. **Conclusions:** Overall, we show marked differences in the mechanisms of progression between t(11;14) and t(4;14). Whilst SVs and mutational processes show similar patterns between subtypes, our data suggests t(4;14) have a higher rate of mutational acquisition whereas t(11;14) develop more high-risk copy number aberrations and lose B cell signature expression with progression. This could help inform subgroup-specific management through disease progression.

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Profiling of Immune Checkpoints in the Myeloma Microenvironment

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Introduction: The immune tumor microenvironment (TME) in multiple myeloma (MM) is a complex and dynamic ecosystem characterized by interactions between malignant plasma cells and various immune cell populations, which collectively contribute to disease progression, immune evasion, and therapeutic resistance. Modulation of immune responses by immune checkpoint molecules expressed on malignant cells and immune cells within the TME helps the cancer evade immune surveillance and promotes tumor survival. **Methods:** In this study, we mapped inhibitory and costimulatory immune checkpoints in the TME of patients with MGUS and active MM using multiparameter flow cytometry. Our pipeline was designed to profile the expression of inhibitory and costimulatory immune checkpoint molecules on various subsets of immune cell types within the adaptive and innate TME in bone marrow samples from patients with MGUS and active MM, as well as from healthy donors (HD). **Results:** By profiling the adaptive TME, we observed a significantly higher expression of CD27 on cytotoxic T cells, helper T cell subtypes, and γδ T cells. Conversely, the expression levels of OX40 and PD-1 were significantly downregulated on T cell subsets in both MGUS and active MM compared to HD. However, we noted significantly higher expressions of TIGIT, 2B4, and DNAM-1, in contrast to the low levels of receptors 4-1BB, CTLA-4, TIM-3, LAG-3, and BTLA. Moreover, statistically significant differences between the MGUS stage and active MM were observed in the expression of TIGIT, PD-1, CD27, and 2B4 on cytotoxic T cells and helper T cell subtypes. On NK cells of innate immunity, we observed a decrease in OX40 and PD-1 in both MGUS and MM, as well as a decrease in TIM-3 only in MM, and an increase in CD27 in MM compared to HD. The expression level of CTLA-4 was significantly lower in MGUS patients compared to active MM. Upregulation of TIGIT was detected on NKT cells in active MM compared to HD. On B lymphocytes, we observed upregulation of CD27 and downregulation of PD-1, LAG-3, and 4-1BB, along with a decrease in TIM-3 expression in MGUS and OX40 in MM compared to HD. The expression profile of malignant plasma cells showed high levels of the immune checkpoints PD-1, CD27, BTLA, ICOS, CTLA-4, DNAM-1, TIM-3, and TIGIT, compared to low levels of LAG-3, 2B4, 4-1BB, and OX40. **Conclusions:** In conclusion, we observed a significantly higher expression of CD27 on T cell subsets

in the premalignant MGUS stage. In contrast, in active MM, we found increased expression of inhibitory immune checkpoints 2B4, PD-1, and TIGIT on T cells, suggesting their involvement in the transformation from MGUS to MM. A better understanding of the TME, including both inhibitory and costimulatory immune checkpoints in precursor conditions and active MM, may provide the basis for new therapeutic approaches. This study was supported by SRDA grants APVV-16-0484 (JJ), APVV-20-0183 (JJ), APVV-19-0212 (DC), and NextGenerationEU project No. 09I03-03-V02-00031 (DC & KS).

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Plasma Cell Lineage and Driver Heterogeneity Associated With Multiple Myeloma Progression

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Introduction: Multiple myeloma (MM) is characterized by aberrant clonal plasma cell growth in the bone marrow (BM). Despite advances in therapeutic options and identification of prognostic factors, patients still relapse. We aim to delineate tumor heterogeneity and map cell state transitions between B and plasma cells (PCs) to understand tumor intrinsic (genomic drivers) and extrinsic (BM microenvironment) changes facilitating MM progression. **Methods:** We studied PCs from patients in the Multiple Myeloma Research Foundation (MMRF) CoMMpass study, integrating data from CD138-sorted and unsorted sequencing datasets to reveal the landscape of PCs in MM. BM Mononuclear cells were sorted into a CD138 enriched fraction for whole exome sequencing (WES), whole genome sequencing (WGS), and bulk RNA-seq to characterize the tumor genomic and transcriptome. We utilized single-cell (scRNA-seq) from 361 samples (263 at diagnosis) on the non-enriched remaining cells to characterize the BM microenvironment; We characterize these PCs, their unique features relative to bulk RNA expression, and interactions with genomic drivers. This dataset was further integrated with external unsorted datasets including normal BM (n=12), monoclonal gammopathy of undetermined significance (n=3), smoldering MM (n=12), and newly diagnosed MM (n=18). **Results:** Within the scRNA-seq, we detect an average of 10% of PC cells across patients, totaling ~90,000 cells. By integrating findings from matched WES data, we mapped somatic drivers and copy number alterations to over 21 transcriptionally distinct plasma cell clusters. We identified a specific PC cluster with significantly more somatic mutations, including 64% non-driver mutations and another cluster with CCND1 mutations in 38.9% of its cells. Transcriptionally, CCND1 expression is higher in non-progressors than rapid progressors, highlighting the prognostic value of CCND1 alterations in MM. Relapsed patients (n=50) exhibited an enrichment of a PC cluster harboring DIS3 mutations, compared to baseline patients. Analyzing over 900 cases based on WES, we found TP53 (10.4% vs. 1.8%) and BRAF (9.4% vs. 4.8%) mutations more enriched in White than Black patients, a pattern also observed in scRNA-seq data. These findings suggest an epidemiological contribution to MM predisposition influencing prognosis and treatment outcomes. Finally, we integrated genomic alteration mapping and trajectory analysis, revealing two PCs exhibiting joint expression of B and plasma markers and genomic alterations, suggesting a potential early/precancer state. **Conclusions:** In summary we identified distinct PC subclusters with unique transcriptional and mutational profiles. Further by incorporating external datasets, we traced the B to plasma cell trajectory and characterized novel pre-cancer states at single-cell resolution. Understanding the interplay between genomic drivers and the BM microenvironment will reveal novel targets and underpinnings of MM disease progression.

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Analysis of Normal Plasma Cell Distribution Across Distinct Age Cohorts Reveals Age Dependent Changes

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Introduction: Plasma cells (PCs) are terminally differentiated cells that secrete large amounts of immunoglobulin (Ig). Following their generation, many PCs enter the bone marrow (BM), which provides unique niches that promote the longevity of PCs. The BM also plays a key role in the clonal PC malignancy, multiple myeloma, as well as its precursor condition, monoclonal gammopathy of undetermined significance (MGUS). MGUS is an asymptomatic condition characterized by a clonal population of abnormal PCs that reside in the BM and has a 1% risk of progression to MM per year. The incidence of MGUS increases with age, which has important implications for MGUS pathogenesis. To begin to understand if aging results in a more permissive BM microenvironment that may predispose to the development of MGUS, we investigated if the number and spatial distribution of human BMPCs change as a function of age in healthy individuals. **Methods:** Bone marrow core biopsies (BMCBs) selected for analysis in this study were determined by hematopathologists to have normocellular bone marrow, normal trilineage hematopoiesis, and no morphologic features of metastatic malignant cells. Ten BMCBs were analyzed for each of the following age ranges: 5 months-9 years; 10-19 years; 20-39 years; 40-59 years; 60-79 years; and 80-99 years. Multi-color immunofluorescence was performed to determine number and spatial localization of kappa and lambda Ig light chain expressing PCs. We also assessed expression of Ig heavy chain, TNFSF13, CXCL12, and CD271 expression in a subset of BMCBs. **Results:** Quantification of PCs and clustering in BM sections across six different age groups revealed that fewer

PCs and PC clusters were observed in the youngest and oldest age groups. PC clustering increased with age until the sixth decade and then began to decrease. A positive correlation between the number of PCs and PC clusters was observed across all age groups. Although our examination was limited, PC clusters were typically found to be comprised of both kappa and lambda LC-expressing cells with various combinations of heavy chain isotypes. Thus, PC clustering did not tend to involve local in situ clonal PCs in any of the age groups tested and suggests that clustering results instead from the ability of several PCs to contact supportive stromal cells that may secrete factors that promote PC survival and retention in the BM. In this regard, we observed that both single PCs and PC clusters were typically located adjacent to a CD271+ cell, a cell type that is known to also express CXCL12. **Conclusions:** The current findings suggest that PCs can arrange in clusters within the BM at any age and that PC clustering is positively correlated with the number of BMPCs. PC clustering increased with age but then diminished in older adults. Further studies to understand the mechanisms responsible for PC clustering in normal BM are warranted. Studies of this nature are needed to better understand the role of the BM microenvironment in MGUS progression.

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Clinicopathologic Features of 73 Patients with TP53 Mutated Multiple Myeloma

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Introduction: Risk stratification in multiple myeloma (MM) patients remains challenging despite the currently available models. TP53 deletion/monosomy 17 detected by conventional cytogenetics and fluorescence in situ hybridization (FISH) is commonly regarded as an adverse risk factor. However, the clinicopathologic features of MM patients with TP53 mutations detected by sequencing and the prognostic impact of these mutations have not been well studied. We summarize the clinicopathologic features of 73 patients with TP53 mutated MM. **Methods:** We searched our institutional database for patients with TP53 mutated MM. The clinicopathologic and laboratory data were collected from the medical record. A separate group of 61 TP53 wild type MM patients served as control. TP53 mutations were detected and analyzed by next generation sequencing (NGS). **Results:** The 73 study cohort patients had a median age of 64 years (range, 36-94 yrs). TP53 was the sole mutation detected in MM in 44 (60.2%) patients. The most common co-occurring mutations detected in MM included KRAS (n=16, 21.9%) and NRAS (n=12, 16.4%). The most common co-occurring cytogenetic aberrations included RB1 deletion (n=67, 91.8%), CKS1B gain (n=58, 79.4%), TP53 deletion/monosomy 17 (n=38, 52%) and CCND1::IGH fusion (n=35, 47.9%). TP53 mutated MM patients had more advanced R-ISS stage and a shorter overall survival compared with TP53 wild type MM patients (p=0.006 and p=0.02 respectively). **Conclusions:** TP53 mutations in MM are associated with a higher R-ISS stage, are frequently associated with CKS1B gains and affected patients have shorter overall survival. Our data confirm that TP53 mutations carry adverse prognostic significance, similar to TP53 deletion/monosomy 17, and need to be incorporated into risk assessment and treatment planning of MM patients.

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Autologous Transplantation Is the Strongest Prognostic Factor for Overall Survival in Multiple Myeloma Patients With Deletion 17p: 20-Year Real-World Experience of the Greek Myeloma Study Group

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Introduction: Deletion 17p (del17p) is a strong negative prognostic factor for survival in Multiple Myeloma (MM), and it is included in both the revised international staging system (RISS) and its 2nd revision (R2-ISS). Our aim was to compare characteristics and outcomes of MM patients with or without del17p, and to explore possible other adverse prognostic factors for overall survival (OS) in patients with del17p, in the real-world setting. **Methods:** We analyzed 1337 MM patients (M/F: 665/672, median age: 66, range: 33-92, IgG: 786, IgA: 350, light chain: 177, IgD: 8, non-secretory: 14, IgM: 2) who were diagnosed from 2003-2023, and included in the Greek Myeloma Study Group registry. Of those, 129 (9.6%) patients had del17p (median age: 65, range: 38-85; M/F: 67/62); 74/129 (57.4%) had del17p as a single abnormality (del17p-s), whereas 55 (42.6%) had del17p plus ≥1 other high-risk abnormality (del17p-plus). **Results:** Age, eGFR, calcium, albumin, platelet counts, and bone marrow infiltration did not differ between del17p vs others (control group); LDH and β2-microglobulin were higher, while hemoglobin was lower in del17p patients (p< 0.05). Expectedly, R-ISS3 and R2-ISS4 were more common in patients

with del 17p (31 vs 9% and 41% vs 26%, respectively; p< 0.001). All patients were treated with novel anti-myeloma combinations; 487 (36.5%) received lenalidomide-based triplets (LBT i.e. lenalidomide-proteasome inhibitor-dexamethasone) or daratumumab-based regimens (DBR). Regarding del17p patients, 41/129 (32%) received LBT/DBR and 40 (31%) underwent autologous transplantation (ASCT) upfront; induction therapy did not differ between groups. After a median follow up of 57 months (95% CI: 53-61), 80/129 (62.0%) patients with del17p vs 479/1208 (39.6%) of controls deceased (p< 0.001). Median PFS and OS of patients with del17p vs others was 19 (95% CI: 15-23) vs 34 months (95% CI: 31-37), and 36.8 (95% CI: 26-47.6) vs 83 months (95% CI: 75-91), respectively (p< 0.001). PFS and OS did not differ between del17p-s vs del17p-plus patients. In the multivariate analysis for the whole population del17p, eGFR< 40mL/min/1.73m2, R2-ISS, LBT/DBR induction and ASCT were significant prognosticators for OS. High-risk abnormalities other than del17p had no impact on OS. In multivariate analysis for the del17p cohort, ASCT was the only independent prognostic factor for OS (p< 0.001; HzR: 0.26 95% CI: 0.18-0.40). Median OS for patients who underwent ASCT vs others was 52.3 (95% CI: 25.9-78.7) vs 30 months (95% CI: 24.6-35.3), respectively (p=0.003). **Conclusions:** We conclude that, in the real-world setting, del17p remains an independent prognostic factor for OS, surpassing the predictive value of other high-risk abnormalities. For patients with del17p, neither baseline prognostic markers/staging systems or current upfront regimens predicted for OS; ASCT remains a strong prognosticator underscoring its established therapeutic value in this high-risk population.

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Risk Factors and Prognosis of Extramedullary Disease in Newly-Diagnosed Multiple Myeloma Patients

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Introduction: Extramedullary Disease (EMD) in Multiple Myeloma (MM) is detected in 4-7% of patients at the time of diagnosis and increases to 6-20% in relapsed/refractory patients. The prognosis of extramedullary involvement in myeloma is quite poor. In our retrospective study, we aimed to determine the risk factors for EMD, to investigate the relationship between bone marrow (BM) fibrosis and EMD, and the effects of BM fibrosis on survival in newly diagnosed MM patients presenting with EMD at the time of diagnosis. **Methods:** A total of 189 MM patients who were newly diagnosed between November 2016 and September 2023 were included in the present study. EMD is defined as soft tissue

Table 1 (abstract P-225)

	Non-Extramedullary Disease (n=168)	Extramedullary Disease (n=21)	P value
Age (Median), years	64.5 (40-86)	67 (37-78)	0.849
Gender			
Male	103 (61.3%)	12 (57.1%)	0.712
Female	65 (38.7%)	9 (42.9%)	
WBC, x10^9/L	6.1 (1.6-26)	8.4 (3-20)	0.013
LDH, U/L	189 (60-1210)	208 (160-540)	0.123
Albumin, g/dl	3.5 (1.8-5.2)	3.5 (2.4-4.4)	0.829
β_2 Microglobulin, mg/L	5.6 (1.1-55)	5.7 (2.2-30)	0.538
Type of M protein			
IgG	102 (60.7%)	14 (66.7%)	0.475
Non-IgG	66 (39.3%)	7 (33.3%)	
Revised-International Staging System (R-ISS)			
I	29 (17.3%)	5 (23.8%)	
II	116 (69%)	11 (52.4%)	0.839
III	23 (13.7%)	5 (23.8%)	
High Risk Cytogenetics*			
Yes	18 (10.7%)	2 (9.5%)	0.801
Bone Marrow Plasma Cell Percentage	50% (10-90)	45%(10-80)	0.805
Bone Marrow Fibrosis (Grade I-III)			
No	77 (45.8%)	4 (19%)	0.019
Yes	91 (54.2%)	17 (81%)	

plasmacytomas that occur due to hematogenous spread and have no contact with bone structures. **Results:** EMD was detected in 21 (11.1%) of the 189 patients who were included in the present study. A significant relationship was detected between the median White Blood Cell Count (WBC) at diagnosis and the presence of fibrosis in the BM in the univariate analysis of factors that might affect the presence of EMD. In multivariate analysis, the median WBC count at diagnosis (OR 1.15, 95% CI 1.03-1.28, p=0.015) and the presence of fibrosis in the BM (OR 3.45, 95% CI 1.09-10.89, p=0.032) were found to be independent risk factors for EMD. After a median follow-up period of 36 months, the median overall survival (OS) in patients with EMD was 13 months, and the median OS in those without extramedullary involvement was 77 months (HR: 3.09, 95% CI 1.52-6.26, p = 0.002). No difference in OS was observed between patients with BM fibrosis (Grade 1-3) and patients without fibrosis (HR:1.04, 95% CI 0.60-1.79, p=0.885). **Conclusions:** As a result of the present study, it was found that BM fibrosis might be a predictive factor for the presence of EMD. A detailed examination for EMD might be required in newly diagnosed MM patients in case of BM fibrosis. We think that it will contribute to the improvement of prognosis, especially if the definition of EMD is standardized, risk factors are determined fully with prospective studies with a larger number of patients, and treatment standardization is identified.

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Study of T Cell Receptor (TCR) Dynamics in Smouldering Myeloma (SMM) Using TCR Sequence Clustering To Infer Contribution of the Immune Microenvironment to Progression to Multiple Myeloma (MM)

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Introduction: The drivers of progression from SMM to MM are not fully explained by tumour-intrinsic factors. We hypothesise that T cells maintain disease equilibrium in SMM and that a reduction in tumour-targeting clones contributes to progression. We analysed longitudinal samples from SMM patients to study T cell clonal dynamics. **Methods:** Bulk TCR sequencing was performed on cryopreserved peripheral blood (PB) and bone marrow (BM) mononuclear cells. Simpson's normalised reciprocal index was calculated and then structurally similar TCRs were grouped by TCRdist3. Clusters with significant abundance changes between timepoints were identified. **Results:** Patient samples from the COSMOS observational SMM study (progressors=4, non-progressors=3) at successive timepoints were analysed (median samples per patient=5, median time from first to last=14m, range=7-28). We calculated Simpson's index for each timepoint (per patient), seeking global changes in TCR repertoire diversity at progression. We found no consistent trends in progressors vs non-progressors. We hypothesise that clustering TCRs with similar sequences would better reveal changes in tumour directed clonotypes. Similarity in TCR sequences implies shared antigen specificity. We identified a median of 1316 (range=37-9508) unique clusters per patient. Focussing our analysis on the tumour niche, we selected patients with good quality (reads >1500) BM samples (2 progressors, 1 non-progressor), and identified clusters that significantly changed in abundance from baseline to progression/final timepoint (ie. deviated from calculated normal distribution); median significant clusters per patient=126 (range=62-1017). We calculated fold change in these clusters over time. No significant change in cluster abundance was observed in the non-progressor. In contrast, both progressors displayed significantly reduced abundance in several TCR clusters at progression ($p< 0.05$, n=23, n=8) but no clusters increased in abundance at progression. This indicates loss of structurally similar TCRs (hypothesised to bind the same tumour antigen) at progression, thus a loss of tumour-specific T cell immunity which could contribute to a loss of disease control and progression. We analysed these TCR clusters in corresponding PB samples. The reduction in BM cluster proportion was mirrored in PB in one progressor, but not in the other, indicating variability in the BM/PB TCR repertoire between patients and favouring the importance of tumour niche immunity to disease control. **Conclusions:** Progression to MM may involve alterations in tumour specific T cell immunity, not revealed by studying global TCR diversity. Our analysis employing TCR sequence clustering to infer tumour directed clonotypes identified a subset of TCR clusters that reduced in abundance at progression, consistent with loss of immune control. This approach will aid our understanding of how T cell immunity alters at progression, forming the basis for immune interception strategies.

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The Significance of Complex Karyotype in Multiple Myeloma

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Introduction: Cytogenetic abnormalities in patients with multiple myeloma play undoubtedly a crucial role in terms of disease staging and prognosis. While hyperploidy is considered a standard risk factor and hypodiploidy an adverse one, the significance of the number and type of chromosomal abnormalities is unclear.

Although complex karyotype (both quantitative and structural abnormalities are required) is not considered as a high risk disease factor in myeloma, in contrast to AML, it has been reported to affect prognosis. Additionally, the coexistence /cumulative role of cytogenetic abnormalities detected from FISH studies in complex karyotype remains vague. **Methods:** We retrospectively studied 37 patients (women n=14, men n=23) with a median age of 64 (40-82) who had a complex karyotype and were treated in our center during the last 6 years. All patients underwent classic bone marrow chromosomal analysis, whereas 33/37 patients had also a result from FISH analysis. **Results:** Hyperdiploidy (48-65 chromosomes) was found in 24 patients, whereas hypodiploidy (< 44 chromosomes) was found in 13. Concurrent structural abnormalities were diverse and were more frequent in hyplodiploidy with a median number of 6 (2-9) abnormalities found per patient, whereas in hyperdiploidy the respective median number was 3 (1-10). Interestingly, 9 patients with hyperdiploidy had only 1 structural abnormality. Furthermore, high-risk cytogenetic abnormalities detected by FISH were scarcer in patients with hyperdiploidy 7/21 (33%, 1p/1q n= 5, del17p n=2) versus 9/12 (75%, 1p/1q: 9, IGH/FGFR3: 2, IGH/MAF: 2, del17p: 4) of patients with hypodiploidy, p=0.02. As expected, disease outcome was worse in patients with hypodiploidy compared to patients with hyperdiploidy. Median PFS was 15 vs 31 months (p=0.003) and median OS was 19 vs 92 months respectively, (p=0.004). Notably, and in contrast to bibliographic reports, patients with only 1 structural abnormality did not have a more favorable prognosis. Concerning patients < 70 years old, PFS and OS were found significantly improved in those that underwent autologous stem cell transplant (ASCT), whereas no other factors effecting prognosis were found statistically significant from the multivariate analysis. **Conclusions:** Among myeloma patients with complex karyotype, hypodiploidy compared to hyperdiploidy is a more complex disease genetically, with more concurrent structural abnormalities and coexistence of high-risk FISH abnormalities in the majority of patients, thus explaining its inferior prognosis. Structural abnormalities were fewer in hyperploidy, as were high-risk FISH abnormalities. Finally, ASCT enhances the disease outcome in patients with complex karyotype.

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The Detection of PR Minor Clones at Single Cell Level Identifies High Risk Disease in Multiple Myeloma

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Introduction: The development of new treatments has improved the outcome of Multiple Myeloma (MM) patients. However, MM remains an incurable disease and a subset of patients has suboptimal response to therapy, short survival, and are defined as high-risk (HR). Despite great efforts to understand the biology of MM, it remains difficult to identify HR disease and prognostic and predictive biomarkers to identify these patients are not well established. In this study, we have evaluated in relapsed/refractory (RR) MM and newly diagnosed (ND) MM patients a new method to identify HR disease based on the presence of highly proliferative (PR) subclones. We also aimed to characterize the transcriptomic signature of the PR cells and identify potential therapeutic targets for HR patients. **Methods:** Single-cell RNA analyses were performed on bone marrow sorted CD138+ MM cells obtained from 58 ND and 78 RR MM patients with available serial samples. Unbiased mRNA profiling was conducted using the 10x GemCode system and sequencing performed on an Illumina platform. Cell Ranger and Seurat were used for data processing and analysis. Cells were classified as PR and non-PR based on a single-cell GSEA score obtained by using the Zhan gene dataset. Kaplan-Meier survival analysis was performed to evaluate the effect of PR cells on PFS. P values were calculated using the log-rank test. **Results:** A PR signature identified in at least 5% of cells was found in 27% of ND and 50% of RR cases and found also in standard-risk patients based on FISH cytogenetics. Importantly, poor PFS was observed in all patients carrying PR subclones. In ND, the median PFS was 30 mos in PR patients and 43 mos in the non-PR patients (p=0.004). As expected, patients with TP53 mutations or chr17p deletion had a shorter PFS (17 mos). In RR, PR patients had a poor PFS of 6 mos when compared to 36 mos in non-PR patients (p=0.003). Of note, all PR patients retained their PR signature over time, and in 44% of patients an enrichment of PR cells was observed at subsequent progression, consistent with Darwinian clonal evolution due to therapeutic pressure. Furthermore, pathway enrichment analysis of PR cells revealed in both groups enrichment of MTORC1 signature, MYC targets, and DNA repair pathways with overexpression of LDH4, PPA1, TPI1, PPIA, ENO1, EIF4A1, and NPM1. Among the identified DEGs, high ENO1 (alpha-enolase) expression was associated with poor PFS in both groups (p=0.005 and 0.002), suggesting a potential role of ENO1 in HR disease. **Conclusions:** In this study we have shown that the presence of PR cells identifies HR disease and patients with poor survival. We have also demonstrated that these PR subclones are enriched at time of progression. Therefore, their identification should be considered for better disease prognosis. Lastly, we were able to provide insight into the molecular signature of PR cells and identify some markers that may be used to detect HR disease and guide therapeutic intervention.

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Osteoblastic Cells Maintain Bone Forming Capacity in Fractured Vertebrae of Patients With Myeloma Bone Disease: Evidence From In Vivo and In Vitro Studies

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Introduction: In multiple myeloma (MM), malignant plasma cells interact with the bone marrow microenvironment, causing defective osteoblastic cell differentiation and function, which contribute to the development of osteolytic lesions and myeloma bone disease (MBD). It has been speculated that lytic lesions in MM do not heal, partly due to osteoblast impairment, however little is known about osteoblast function directly in the setting of a fracture. Thus, we examined osteoblastic bone forming capacity following vertebral fracture in patients with MBD. **Methods:** Two biopsies were collected from the fractured vertebral body of 22 MM patients undergoing vertebroplasty, using a 13G bone biopsy needle. The first biopsy was formalin-fixed, paraffin-embedded, sectioned at 3.5-µm thickness and Masson's Trichrome stained. Whole-tissue slide scans were histomorphometrically analyzed for signs of sclerotic bone formation. The second biopsy was fixed in culture wells and incubated in cell culture medium to establish explant cultures. Function of outgrowing osteoblastic cells was determined by measuring mineralization capacity as alizarin staining of mineralized matrix (AZR) and alkaline phosphatase (ALP) activity. **Results:** New bone formation was seen in 17/22 patients (77%), but the newly formed bone volume (NBV) per total bone volume (BV) varied widely between patients (median 33%, IQR 3-58%). NBV/BV was positively correlated to BV per total tissue volume (BV/TV, r=0.48, p=0.025). Clinical confounders e.g. age, gender, International Staging System (ISS) stage, Revised-ISS stage, treatment response, time from diagnosis, and number of fractures did not differ in patients with little or no new bone formation (NBV/BV < 5%, 7/22, 32%) compared to patients with evidence of new bone formation, nor did clinical characteristics correlate to NBV/BV. Most patients were newly diagnosed or newly symptomatic and had received ≤1 treatment lines (21/22, 95%). Interestingly, the estimated fracture age showed no correlation to NBV/BV, and patients with 0% NBV/BV experienced fractures up to 113 days prior to vertebroplasty. In vitro, cultured osteoblasts demonstrated mineralization capacity and ALP activity, but with large interpatient variation (AZR median 84.3 AU IQR 59-109 AU; ALP median 1.41 IQR 0.83-1.99). Osteoblastic functional readouts did not correlate with NBV/BV, however mineralized matrix formation negatively correlated the degree of plasma cell infiltration at patients' diagnostic iliac crest biopsy (r=-0.52, p= 0.038). **Conclusions:** Our preliminary findings demonstrate patients with MM can form new bone following bone fracture and that osteoblastic cells at fracture site may maintain intrinsic bone forming capacity, suggesting the presence of factors within the bone microenvironment that impair osteoblastic function. Ongoing molecular studies focus on identifying these negative regulators.

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t(11; 14) Alone Represents a Group of Multiple Myeloma With Slow Remission but Long-Term Survival

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Introduction: Presence of t(11;14) on plasma cells is considered a standard-risk prognostic factor per IMWG risk-stratification. However, recent studies suggest inferior PFS and OS observed among t(11;14) patients relative to the standard-risk myeloma patients. **Methods:** This study aimed to evaluate the impact of t(11;14) in newly diagnosed multiple myeloma (NDMM) patients on treatment response rate, response kinetics, and survival based on mutually exclusive risk groups. We describe 790 patients with newly diagnosed myeloma treated with available baseline FISH data (within 90 days post-diagnosis) from January 2010 until June 2021, including 99 patients with t(11;14) alone, 58 with t(11;14) plus other high-risk cytogenetic abnormalities [t(11;14)+HR] including chromosome 1 abnormalities [C1A1, including gain/amp1q and/or del(1p)] and/or del(17p), 224 standard-risk (SR) patients without t(11;14) and 409 in the high-risk cytogenetic abnormality (HRCA) group including t(4;14), t(14;16), t(14;20), C1A1 and/or del(17p) but without t(11;14). **Results:** Comparison of t(11;14)alone patients with the SR group revealed no statistically significant differences in PFS (49.3 vs. 50.7 months; P= 0.392), or OS (112.4 vs. NR months; P= 0.982). Prognosis of t(11;14)+HR patients was significantly worse than t(11;14)alone group (PFS: P=0.029; OS: P=0.002), but similar to that of the HRCA group [mPFS: 33.1 vs. 30.8 months; P= 0.862; mOS: 69.8 vs. 75.4 months; P= 0.333)]. The t(11;14)alone group achieved a significantly worse response than SR group: ≥VGPR 72.9% vs. 85.2% (OR 0.47 [95% CI, 0.26–0.85]; P= 0.011), ≥CR 50.0% vs. 66.8% (OR 0.50 [95% CI, 0.30–0.82]; P= 0.005), and MRD-negative (37.5% vs. 63.1%, P=0.001, sensitivity of 10-5), respectively, which was inconsistent with its favourable prognosis.

Response kinetics analyses found that the cumulative incidence curve of VGPR onset was flatter in the t(11;14)alone group compared to the SR group (P=0.036), and the time to VGPR (mean time to VGPR, mTVGPR=4.93 months) was significantly longer in the t(11;14)alone group than in the SR group (mTVGPR=3.01 months; P=0.017). Similar results were found in the analyses of reaching CR and reaching MRD negativity. **Conclusions:** Our study have showed t(11;14)alone was characterized by the slowest timing of onset and lowest plateau of remission but long PFS and OS. The slow rate of remission may correlate with its favourable prognosis. In the new drug era, the prognosis of t(11;14) with other high-risk cytogenetic abnormalities patients remains poor. BCL-2 inhibitors may be incorporated earlier into myeloma therapy to improve the prognosis of patients with t(11;14), especially t(11;14) with other high-risk cytogenetic abnormalities.

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Whole Genome Sequencing Reveals Lower APOBEC-Mutational Activity in Multiple Myeloma Patients With African Ancestry Compared With Those of Non-African Ancestry

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Introduction: It remains unknown if multiple myeloma (MM) in patients with African Ancestry (AA) has a different spectrum of genomic aberrations when compared to patients with non-African Ancestry. Previous studies in patients with AA suggest an excess of t(11;14) and a deficiency of TP53 mutations. **Methods:** Together with the New York Genome Center / Polyethnic-1000 consortium, we performed whole genome sequencing (WGS) in patients with diverse ethnic backgrounds. Combined with our previously published WGS and CoMMpass, the cohort comprised 1488 WGS with 208 self-declared AA. We used a comprehensive pipeline for somatic variant calling (mgp1000), together with admixture analysis to estimate ancestry using geographically-distinct reference populations (Africa; AFR, Europe; EUR, America; AMR, East Asia; EAS and South Asia; SAS). **Results:** We identified 5 clusters corresponding to single continent-level reference population, together with a cluster characterized by highly admixed individuals with no dominant ancestry. 5% self-identifying as AA were assigned to other clusters, while only 34% self-identifying as Hispanic were assigned to the AMR-dominant group.The prevalence of t(11;14), t(4;14) and t(14;16) were not significantly different between clusters. For somatic mutations, the tumor mutational burden (TMB) was lower in AFR cluster (median 2.21 mutations per Mb) than the EUR cluster (2.94, FDR adj. p=4.3x10-6), without differences in high-incidence mutations including TP53. There were also no significant differences in copy number aberration. The most striking difference was observed in mutational signatures; AFR had lower contribution from clock-like signatures (SBS1/SBS5) and lower APOBEC-mutational activity (SBS2/SBS13), which were responsible for the difference in TMB. Mutational timing analysis, using the corrected ratio between duplicated and non-duplicated mutations to estimate the timing of chromosomal gains, did not reveal differences in the estimated timing of cancer initiation between clusters. As no differences in age, tumor purity or coverage were observed, this suggests a different mutational rate between clusters. Interestingly, WGS from the Pancancer Analysis of Whole Genomes dataset in bladder and cervical cancer, (associated with APOBEC activity in pathogenesis), also had lower APOBEC-activity in AFR-dominant clusters. Further, leveraging both single cell WGS (DLP+ platform) and a validation cohort from EUR-dominant patients (GMMG-HD6 trial), we found that 34% of AFR lacked any APOBEC activity at either clonal or subclonal levels, compared with only 16% in EUR (p=0.03) and < 5% in the GMMG-HD6 dataset. **Conclusions:** In the largest series of WGS from racially diverse MM patients to date, integrating genomic data with comprehensive ancestry information, MM in patients with AFR-dominant admixture emerged as biologically different. Differential mutational signature contribution, particularly APOBEC- mutational activity, appears to result in distinct genomic evolution over time.

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Comprehensive Genomic Sequencing Predicts Sub-Optimal Response to Bispecific Antibodies (BsAb) and Chimeric Antigen Receptor T Cells (CAR-T) in Multiple Myeloma (MM)

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Introduction: BsAb and CAR-T provide impressive response rates in relapsed MM, however, some patients are either primary refractory or have short remission durations. Small cohorts have demonstrated target antigen loss and immune dysregulation contributing to resistance, requiring assays not routinely available in clinical practice. Response prediction in newly diagnosed MM is improved using extended targeted sequencing, with estimation of the structural variant chromothripsis using copy number variant (CNV) signatures (Maclachlan et al. Blood 2023). **Methods:** We assessed genomic risk factors (RF) and treatment response in patients having received commercially available BsAb or CAR-T at MSKCC; combining FISH, SNP-array, and a clinical sequencing panel (MSK-IMPACT-Heme). If patients received >1 agent, each therapy response was evaluated. Survival was assessed by Kaplan-Meier, and GISTIC analysis examined significantly aberrant CNV. **Results:** 221 patients were assessed; 126 received CAR-T, 133 BsAb, with 32 receiving >1 therapy. Median follow-up time was 194d (IQR 92-369), with 108 progression events. Genomic data was available in 191 (86%); FISH in 191, SNP array in 168 and MSK-IMPACT-Heme in 119. Samples were collected pre-therapy in the majority, post-therapy in 20 and at both timepoints in 15.While t(14;16) predicted shorter PFS with both CAR-T (median 83d, p=0.007) and BsAb (median 24d, p=0.03), none of t(4;14), gain1q, amp1q, del1p or MYC aberration were significant in univariate analysis. In BsAb patients only, TP53mut predicted adverse PFS (median 66d, p=0.0004), as did del17p (median 58d, p=0.0003) and biallelic TP53 aberration (median 34d, p< 0.0001). Mutations in KRAS, NRAS or DNA-damage-response genes were not associated with short PFS.GISTIC analysis in those who had progression or death within 3m showed an enrichment of focal gains at 7p12.1, 8q22.2, 16q22.1 and 17q22. Complex genomics, defined by CNV suggesting chromothripsis, showed a trend to significance, which when combined with biallelic TP53 aberration, predicted a median PFS of 21d. Considering the effect of multiple RF; for those reaching progression or death within 3m, 46/68 (68%) had ≥2 standard RF, which increased to 51 (75%) with the inclusion of TP53mut, MYC aberration and complex genomics.Broad monoallelic CN loss at BCMA/TNFRSF17 (del16p13) or GPRC5D (del12p13) was detected in 22% and 24% pre-therapy and did not predict resistance to the relevant targeted agent. Post-therapy genomic evolution was observed in paired samples, with emerging TP53 and KRAS mutations, gain8q (MYC), focal deletion of GPRC5D and CNV suggesting chromothripsis affecting chr16. **Conclusions:** BsAb and CAR-T may overcome individual standard genomic RF, however harboring multiple genomic RF remains adverse. Clinically available extended genomic characterization predicts response better than FISH alone in this large cohort treated with BsAb/CAR-T. This work will extend into pre-/post-therapy whole genome sequencing for more granular data analysis.

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Comparative Analysis of CXCL12-Abundant Reticular (CAR) Cell Subpopulations in the Bone Marrow of Healthy Individuals Versus MGUS and Multiple Myeloma Patients

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Introduction: Studies demonstrate that MM cells present constitutive activation of the canonical Wnt pathway, inducing cell proliferation, disease progression, dissemination, and drug resistance. Mechanistically, the oncogenic activity of canonical Wnt in MM is due to the abnormal secretion of R-spondins (RSPOs) within the BM, which promotes the stabilization of the Wnt receptor at the plasma membrane of MM cells and increases their responsiveness to Wnts. Nevertheless, the BM microenvironment is heterogeneous, and it is currently unknown what the specific stromal cell type responsible for RSPO secretion is. Considering that CAR cells are the main constituents of the hematopoietic niche and that murine CAR cells express RSPOs, we hypothesized that these cells would be the primary source of RSPOs in human BM, contributing to MM progression. Therefore, this study aimed to map the distribution of the distinct CAR cell subpopulations, identified by the differential expression of leptin receptor (LEPR) and CD56, in BM samples of healthy individuals (sustaining orthopedic conditions) versus MGUS and MM patients. **Methods:** Healthy BM samples were collected from bone discards of patients undergoing primary hip arthroplasty. MM and MGUS samples were collected from patients undergoing BM aspiration for diagnostic examination. Nucleated cells were isolated and incubated for 30 minutes with fluorochrome-conjugated primary antibodies against CD3, CD31, CD45, CD235a, CD71, LEPR, and CD56. Immunophenotyping was performed using a FACS Canto II flow cytometer. Analysis was performed with the DIVA software. **Results:** Flow cytometry analysis of healthy BM samples (n=6) revealed the presence of two CAR cell subpopulations - LEPR+/CD56- and LEPR+/CD56+ - at similar frequencies. In MGUS (n=3), an expansion of the LEPR+/CD56- population was verified, accompanied by a decrease in the LEPR+/CD56+ pool. As for the MM samples (n=6), we observed two patient profiles: one group with an increase in the LEPR+/CD56+ fraction and another in which this population was decreased. **Conclusions:** Considering the literature, evidence points out that the expression of CD56 in cells of the BM is a distinguishing criterion between MM and MGUS, and CD56 expression is related to the presence of lytic bone lesions in MM. Our results suggest that (i) the CAR cell compartment is altered in MGUS and MM; (ii) the level of CD56 expression in CAR cells might serve as a criterion to stratify MM stages; (iii) the LEPR+/CD56+ CAR pool might be the primary source of RPSOs that promote MM progression. Additional flow cytometry and qRT-PCR analysis are ongoing to evaluate the correlation of CD56 expression in CAR cells to the MM stage and the expression of RSPOs in each CAR cell subpopulation.

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Autocrine IL6 Signaling in Stromal Cells in Multiple Myeloma Influences the Bone Marrow Microenvironment

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Introduction: The bone marrow microenvironment can have a profound influence in multiple myeloma (MM) and interleukin-6 is a well-established mediator of these effects. To further investigate the role of IL6 in the interactions between stromal cells (MSCs) and MM cells we used CRISPR/Cas9 to delete IL6 from the HS5 MSC line and determine effects on co-culture-induced protection. **Methods:** IL6 gene editing was confirmed by NGS and ELISA. In co-culture (CC) and conditioned media (CM) assays, MM cells were preincubated for 30-60 min before addition of drug or T cells. Cell death was measured using Annexin V staining. MM cells were identified by CD38 staining, HS5 by mCherry and T cells via CD3. RNA isolated from HS5 Cas9 and IL6KO cells was analyzed by RNAseq. STAT3 phosphorylation was determined by Western blot. **Results:** IL6KO HS5 cells do not offer protection against venetoclax-induced cell death in tested human myeloma cell lines (HCML). We also tested the effects of CC on BCMA CAR-T cell killing. We found that CC could protect HCMLs from CAR-T killing and this protection was not significantly different with CC of IL6KO cells. Results with CM from Cas9 and IL6KO cells were similar, suggesting that soluble factors independent of IL6 can protect MM cells from BCMA CAR-T killing. To identify these soluble factors, we performed RNAseq comparing the HS5 Cas9 and IL6KO cells. We found 1637 genes were differentially expressed (633 significantly up- and 1004 down-regulated in IL6KO cells, FDR< 0.01). GSEA indicated that gene sets associated with inflammatory and IFNα signaling were upregulated in IL6KO cells and several growth and survival cytokines were downregulated. Interestingly IL6R is upregulated. We confirmed that HS5 cells express IL6R by flow cytometry and that it is upregulated in IL6KO cells. We also observed IL6R on MSCs cultured from a patient sample. Expression of IL6 signaling component genes IL6ST, JAK1 and STAT3 along with target gene SOCS3 was also detected, suggesting that IL6R may signal in HS5. Control and IL6KO cells express similar levels of total STAT3 protein, however phospho-STAT3 was lost in IL6KO cells. For validation in patient samples we queried bulk RNAseq from MSCs purified from MM patients and confirmed that IL6R, IL6ST, JAK1 and STAT3 were expressed in cells isolated from normal, newly diagnosed and post-induction therapy patients. Finally, previous scRNAseq has indicated that MSCs fall into 5 unique transcriptional clusters, with 2 of these clusters unique to MM patients (De Jong et al., Nature Immunology, 2021). We find that like IL6 itself, IL6-regulated genes are enriched in myeloma-induced MSCs. **Conclusions:** These data indicate that myeloma-induced MSCs utilize IL6 in an autocrine-dependent fashion to produce factors that can influence the bone marrow microenvironment, suggesting blocking IL6 or IL6R could influence therapeutic response by reprogramming the microenvironment.

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Isatuximab as Post-ASCT Therapy in MRD-positive Patients Augments CD8 Effector T Cell Differentiation: Insights from the UKMRA Phase 3 RADAR Study

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Introduction: Addition of the anti-CD38 Ab Daratumumab to lenalidomide maintenance (R) improved depth of response and PFS in the PERSEUS study. We hypothesized that this relates in part to alterations in cellular immune function in the bone marrow (BM). In the Phase 3 RADAR study, standard risk patients who are MRD-positive post-ASCT are treated on one of 4 consolidation/maintenance arms (A-D): A, R; B, R+Isatuximab (R-Isa); C, R-Bortezomib + Dex (R-BorD) consolidation (cons) followed by R; or D, R-Isa-BorD cons followed by R-Isa. **Methods:** We used flow cytometric-based immune profiling with a 10-colour antibody panel on fresh BM cells to assess immune cell populations. We aimed to define the effect of Isa on the BM immune microenvironment. **Results:** We analysed the immune profile of 78 patients [40 Isa-treated (B, D) and 38 non-Isa treated (A, C); median age 60, 64.1% male, 87.2% white] after 3 months of cons/main. Isa-treated patients had a larger CD3+ T cell compartment (p=0.008), with a trend to proportionately more CD8+ cells (p=0.089). Within the CD8+ population, Isa treatment was associated with a relative loss of the early differentiated CD127+ subset (p=0.013), and increase in the terminally differentiated CD57+ subset (p=0.078). T regulatory cells did not differ between Isa and non-Isa arms. We tracked changes in T cell subsets between 3 and 6 months post-ASCT in 57 patients with paired samples. In absence of Isa, post-ASCT immune reconstitution follows a normal pattern, with earlier recovery of CD8+ T cells (3m) followed by later (6m) rise in CD4+ T cells resulting in a rise in CD4:8 ratio over time (paired Wilcoxon, p< 0.0001). With the addition of Isa, the low CD4:8 ratio seen early post-ASCT persists, with maintained dominance of CD8 effectors.

NK cells express high levels of CD38 and, as expected, Isa-exposed BM contained markedly less NK cells (p< 0.001). However there was a disproportionate loss of the CD56dimCD57+ terminally differentiated subset (p=0.001), with relative sparing of CD56bright NK cells (p=0.122), suggesting skewing toward a less mature subset with Isa treatment. Furthermore, comparing pre- and post-treatment BMs in Isa-treated patients did not reveal the skewing over time towards the mature CD56dim subset (p=0.6506) which was observed in the absence of Isa (p=0.005). We observed little difference on myeloid cells. Interestingly Isa-exposed BM showed a rise in NK-T Like cells (p=0.0326) which was not observed without Isa. **Conclusions:** Isa treatment alters immune cell compartments post-ASCT including patterns of terminal T cell differentiation. Further work on T cell states and TCR dynamics, as well as NK function, will reveal how cons/main strategies can maximise anti-tumour immunity in the post-ASCT setting.

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Integrated Coding and Non-Coding Transcriptomic Atlas Reveals How Malignant Plasma Cells Shape the Bone Marrow Microenvironment in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is a highly heterogeneous cancer, posing challenges for prognosis and treatment. The bone marrow microenvironment (BMME) has emerged as a significant factor driving MM progression and response to therapy, with dysregulated immune populations significantly shaping the BMME. We propose that these dysregulated populations correlate with specific malignant plasma cell phenotypes, collectively influencing patient outcomes. Given the emerging role of noncoding RNAs (ncRNAs) in regulating cellular phenotypes, we constructed the first combined coding and non-coding transcriptomic atlas of the MM-BMME to elucidate how distinct malignant cell phenotypes alter the immune landscape. **Methods:** We performed single-cell RNA-seq on 481 bone marrow samples from MM patients enrolled in the MMRF CoMMpass study. The sequencing data was aligned to the GRCh38 genome expanded with noncoding transcripts from LncBook2.0 and GENECODEv34, followed by QC, batch correction, clustering, and supervised analysis. **Results:** Approximately 1.9 million cells were captured from immune, plasma, and stromal compartments, with ncRNAs comprising 46% of represented genes: 22,102 long ncRNAs (lncRNAs) and 3,112 small ncRNAs. Major immune compartments (B lymphoid, myeloid, and NK and T lymphoid) were further divided into 70 subclusters, with ncRNAs representing 24-38 of the top 100 and 10-24% of the total differentially expressed genes within each compartment, highlighting the ability of ncRNAs to differentiate immune subtypes. Thirty of these subclusters were differentially abundant (P < 0.05) between patients with different specific cytogenetic abnormalities, suggesting that malignant plasma cell genotypes shape the immune microenvironment. Most notably, among patients with 1q21 gain and 17p53 deletion, an increase in TGFβ-stimulated monocytes and a decrease in cytotoxic CD8+ T and CD56dim NK cells, respectively, were observed.Examining the malignant plasma cell profiles, we identified 14 ncRNAs differentially expressed across cytogenetic abnormalities, of which 6 lncRNAs were associated with poor overall survival. Combined high expression of these lncRNAs in plasma cells was linked to poor survival (P < 0.05, HR = 3.7). Stratifying patients based on enrichment of these outcome-associated lncRNAs revealed changes in immune composition, including an increase in CD4+ Tregs (P < 0.05), further supporting our hypothesis that malignant cell phenotypes shape the BMME. Lastly, by constructing regulatory networks, we identify how key ncRNAs putatively modulate the phenotypes of plasma and immune cells. **Conclusions:** Integrating coding and noncoding RNAs, we present the first high-resolution transcriptomic atlas of the MM-BMME, revealing distinct immune subpopulations associated with specific malignant plasma cell phenotypes. Collectively, this work highlights a central role for ncRNAs in shaping the MM-BMME, highlighting their potential as therapeutic targets and prognostic markers for MM.

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Mapping Racial Disparities in Immune Cell Dysregulations and Multiple Myeloma Outcomes Using Single-Cell Profiling

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Introduction: Multiple Myeloma (MM) is one of the most common malignancies and is disproportionally diagnosed in Black populations relative to white or European. This increased incidence

is associated with variations in frequencies of certain cytogenetic events, and age of onset. We propose that differences in MM incidence and outcomes in Black patients may be influenced by immune bone marrow microenvironment (BME) dysregulations, which we explored using single-cell RNA sequencing data from the MMRF Immune Atlas. **Methods:** We analyzed scRNA-seq data from the MMRF Immune Atlas, a sub-cohort of the MMRF CoMMpass study. The data yielded 106 manually annotated cell populations, spanning myeloid, lymphoid, and erythroid lineages. Associations of the immune population with self-identified race were assessed using univariate and multivariate models and differential expressions, adjusting for patient sex, age, and ISS stage. **Results:** Of the 263 NDMM patients in the Immune Atlas, 46 self-identified as 'Black' or 'African American', while 205 self-identified as 'White'. Black patients had significantly higher ISS stages at diagnosis (ISS3: 42% Black, 23% White, p< 0.05), and were less likely to receive triplet therapy (50% Black, 73% White, p< 0.05), though no significant association with race and progression-free survival was observed. Significant alterations were identified in the T, NK, and Myeloid compartments adjusting for age, sex, and ISS stage. The T cell compartment in Black patients had a significantly higher cytotoxicity signature enrichment (PRF1, FGFBP2, GNLY) (p< 0.05), and higher abundances of cytotoxic CD4+ and CD8+ cell states (p< 0.001). Treg populations were slightly enriched in white patients (p< 0.05), though no differences in Naïve populations were observed. In Black patients, NK cells showed enrichment of an adaptive NK signature (KLRC2+, FCER1G-, p< 0.01), a cytotoxic CD56dim population with memory-like properties often observed in certain viral infections such as CMV. These NK cells also show enrichment of MHC-II antigen presentation pathways. Lastly, Black patients also showed significant enrichment of CD16+ non-classical monocytes (nCM, p< 0.05) with overexpression of FCGR3A and CX3CR1 markers. **Conclusions:** Multiple significant alterations in the immune microenvironment are present in Black versus White NDMM patients. Some of these alterations in Black populations, such as adaptive NK cells, have been associated with either decreased relapse, or stronger responses to therapies such as Daratumumab and ASCT, which historically have been vastly underutilized in the US Black population, especially in the first lines of therapy. Overall, this indicates that there are some alterations in the immune microenvironment with respect to self-identified race. As the immune compartment plays a significant role in therapeutic efficacy, it's important to ensure under-represented minorities are fairly included in clinical trials to assess therapeutic responses.

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Prognostic Impact of Cytogenetic Abnormalities and R2-ISS in Multiple Myeloma: Experience in a Brazilian Private Hospital

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Introduction: Advances in cytogenetic techniques, notably the Fluorescence In Situ Hybridization (FISH), has brought important data about the clinical and biological behavior of multiple myeloma (MM). Cytogenetic abnormalities are useful for risk stratification and therapeutic decisions. The incorporation of 1q+ into the R2-ISS prognostic tool revealed a new subgroup of very high-risk patients, not previously found in the R-ISS model. Cytogenetic analysis is still not widely available in many countries. This work objective was describe the experience of incorporating cytogenetic analysis and the R2-ISS classification MM patients from a Brazilian private hospital. **Methods:** This is an observational, retrospective and descriptive study. Patient's data collected from January 2022 to January 2024. Patients eligible for autologous stem-cell transplantation (autoSCT) were treated with the PERSEUS protocol (Dara-VRd), with 93% of patients achieving responses superior than partial responses. Patients ineligible for autoSCT receveid the MAIA protocol (Dara-Rd). Patients were required to have a complete risk stratification for R-ISS and R2-ISS, including FISH from a bone marrow sample. **Results:** 25 patients (of which 16 eligible for autoSCT) were included. Average age was 63 years. The most common type was IgG Kappa (52%). Median follow-up of 15 months (12-70). 13/25 (52%) cases had detectable cytogenetic abnormality on FISH. More than 90% of all findings were classified as high risk by the mSMART 3.0 model. 7/16 and 3/9 patients had at least one high-risk cytogenetic mutation in the transplant eligible and ineligible groups, respectively. The most common findings were +1q in 9 cases (36%) and del(13q) in 5 cases. 30% of all cases had a prognostic classification shift when R2-ISS was compared to R-ISS. Most shifts occurred in the R-ISS III group. Of the 10 patients in this classification, 50% received up-staging to R2-ISS IV. The median overall survival (mOS) of all R-ISS III patients was 21.3 months (2-75). With R2-ISS, the mOS of the III group was 36 mo (4-75) and 8.8 mo (2-19) in the IV subset. The progression-free survival (PFS) for the R-ISS III patients was 17.12 mo (1-60). The same population classified with R2-IPSS had a PFS of 21.3 mo (8-60) in group III and 5 mo (1-13) in group IV. **Conclusions:** Real-life data suggests that applying R2-ISS reveals a subgroup of patients at higher risk (IV), not previously found in the R-ISS III stage. The group IV seems to have a lower mOS and mPFS when compared to the other stages. There is a need of prospective studies with large cohorts and standardization of FISH reports and methodologies for the better understanding of prognosis and clinical outcome of multiple myeloma.

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The Burden of Circulating Tumor Plasma Cells Is Associated With the Quantity of Mesenchymal Stromal Cells and CXCR4-Expressing Plasma Cells in Bone Marrow of Newly Diagnosed Multiple Myeloma

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Introduction: Bone marrow mesenchymal stromal cells (BMMSC) are known to influence the homing, survival, proliferation, and exit of tumor plasma cells (TPC) in plasma cell neoplasms (PCN) including multiple myeloma (MM). The dynamic interaction between CXCR4 expressed on bone marrow TPC (BMTPC) and its ligand CXCL12, secreted by the BMMSC, is important for homing followed by egress of plasma cells into the peripheral blood circulation. The load of circulating TPC (CTPC) at the time of diagnosis is likely to be associated with quantity of CXCR4-expressing-BMTPC (CXCR4+BMTPC) and BMMSC in patients with newly diagnosed MM (NDMM). **Methods:** The study prospectively enrolled NDMM-patients over a duration of one year. Multicolour flow cytometry (MFC) was used to quantify CTPC from 6ml EDTA-anticoagulated peripheral blood, and percentages of BMMSC & CXCR4+BMTPC from bone marrow aspirate sample. CTPC were enumerated using CD19, CD27, CD38, CD45, CD56, CD81, CD117/CD200, CD138, and cytoplasmic-kappa & lambda expression. BMMSC were gated based on CD105, CD73, CD90, and CD271 expression with negativity for CD45 and lineage-markers. The samples were processed & acquired on Navios-Ex flow cytometer and analyzed using Kaluza 2.2 software (Beckman Coulter, USA). The percentage of CTPC, and the percentages of BMMSC & CXCR4+BMTPC were statistically analyzed to evaluate their association with each other. **Results:** Sixty-six patients of NDMM were enrolled. The median % of CTPC was 0.0345 (IQR 0.0016 to 0.3)%. The median BMMSC and CXCR4+BMTPC were 0.0034 (IQR 0.0015 to 0.01248)% and 84.87 (IQR 55.54 to 95.16)%, respectively. There was a trend toward an inverse correlation between CTPC% and BMMSC% ($r = -0.056$, $P = 0.6$). Conversely, a trend toward a positive correlation was noted between CTPC% and CXCR4+BMTPC% ($r = 0.064$, $P = 0.6$). Also, CXCR4+BMTPC% was higher in the patient group with a BMMSC% ≥ 0.024% when compared to the group with BMMSC% < 0.024% ($P = 0.03$). CTPC% showed a significant positive correlation with BMPC% on light microscopy ($P = 0.001$). In addition, the median BMMSC% was lower in patients with TP53 deletion ($P = 0.03$). **Conclusions:** The load of CTPC in patients of NDMM showed a trend towards inverse correlation with quantity of BMMSC and conversely a positive correlation with quantity of CXCR4-expressing-BMTPC. Interestingly, BMMSC% was lower in patients with TP53 deletion. The quantity of BMMSC may influence the load of CTPC and may also be associated with other prognostic markers in patients of NDMM. Data from larger cohorts may yield corroborative evidence and have implications in understanding disease biology as well as proposing alternate therapeutic intervention strategies.

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Survival Analysis and Transcriptomic Profiling Unveil Key Genes in Multiple Myeloma: Insights from MMRF CoMMpass Data

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Introduction: Multiple myeloma (MM) is a heterogeneous hematological malignancy characterized by clonal proliferation of plasma cells in the bone marrow. Despite advancements in treatment, MM remains incurable in most cases, necessitating a deeper understanding of its molecular mechanisms and prognostic factors. Transcriptomic profiling has emerged as a powerful tool for identifying biomarkers and therapeutic targets in MM. In this study, we conducted a comprehensive analysis of gene expression data from MM patients to elucidate the role of specific genes in MM prognosis and pathogenesis. **Methods:** We obtained gene expression data from the Multiple Myeloma Research Foundation (MMRF) CoMMpass study, which includes transcriptomic profiles of MM patients. Survival analysis was performed to compare the expression levels of various genes between survived and deceased patients. Differential expression analysis was conducted to identify genes with significant fold changes and p-values. Drug-associated genes were identified from the Drug Gene Interaction Database and examined for potential adverse event (AE) clinical features using OMIM. Additionally, gene-gene interaction analysis was performed using STRING to explore potential pathways and networks underlying MM pathogenesis. Signaling pathways were compared using QIAGEN Ingenuity Pathway Analysis (IPA) to elucidate molecular mechanisms associated with MM progression and treatment response. **Results:** Our analysis revealed significant associations between survival outcomes and the expression levels of several genes in MM patients. Notably, BRCA1 ($p < 0.0001$), ATM ($p = 0.00023$), CYBA ($p = 0.019$), IFNG ($p = 0.023$), NR3C1 ($p = 0.00055$), PIK3CA ($p = 0.00039$), PIK3CG ($p = 0.049$), CTLA4 ($p = 0.0049$), NFE2L2 ($p = 0.035$), and RPS19 ($p = 0.029$) exhibited significant prognostic value. Differential expression analysis identified potential biomarkers associated with MM prognosis, providing insights into disease biology and treatment response. Moreover, gene-gene interaction analysis revealed intricate networks and pathways implicated in MM pathogenesis. **Conclusions:** Our study sheds light on the molecular landscape of MM and highlights the prognostic significance of specific genes in disease progression. The integration of transcriptomic data with clinical outcomes offers valuable insights into disease biology and therapeutic targets. These findings have implications for personalized medicine approaches and the development of novel therapies to improve outcomes for MM patients. Further research is warranted to validate the prognostic value of identified genes and explore their therapeutic potential in MM management.

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Progression From Smouldering Myeloma to Myeloma Is Accompanied by an Increase in CD56bright Bone Marrow Resident NK Cells With Reduced NK Cell Cytotoxic Capacity

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Introduction: Natural killer (NK) cells are crucial in the innate immune response against tumour progression. Whilst the immune microenvironment in myeloma (MM) is reported to be increasingly dysfunctional through disease evolution, information on whether and how the NK cell compartment alters with progression is limited. We aimed to study NK cell phenotype and function in disease progression, based on primary samples from trial patients, using single-cell RNA-sequencing (scRNAseq) and functional studies. **Methods:** Freshly isolated bone marrow (BM) mononuclear cells from precursors and newly diagnosed MM enrolled in clinical trials (COSMOS, Smouldering Myeloma (SMM) n=88 and Monoclonal Gammopathy of Undetermined Significance (MGUS) n=17), and MM (RADAR, n=48) were analysed by flow cytometry for tumour infiltration (CD138+) and NK cell subsets (CD3-CD56+). Functional capacity of patient NK cells toward tumour target was assessed by cytotoxicity assays against the NK sensitive cell line K562 (n=16). Finally, we performed scRNAseq on 18 patients and integrated our data with previously published studies of BM and peripheral blood to analyse a total of 68,665 NK cells from 191 subjects, including samples from healthy donors and individuals with MGUS, SMM and MM. **Results:** We observed a stepwise increase in the proportion of BM NK cells with a CD56bright phenotype through progression from MGUS through SMM to MM using flow cytometry. Interestingly, there was a positive correlation between abundance of the NK CD56bright subset, and tumour infiltration in precursor conditions (r=0.39, p< 0.001) but not in MM. Functional studies revealed a reduced cytotoxic response towards tumour target in BM NK cells of MM patients when compared to SMM, with reduced expression of the degranulation marker CD107a (p=0.002). Immunomodulatory response of MM NK cells was also significantly lower, with reduced expression of XCL1/2 (p=0.02) and CCL4 (p=0.01) compared to SMM NK cells. Using scRNA-seq, we identified a subset of CD56bright NK cells found only in BM samples. In addition to XCL1 and GZMH, found on the classical CD56bright population, this subset also had high expression of CD69 and CXCR6, consistent with BM residency. These resident NK cells had a significantly lower score for a cytotoxic gene set, including cytolytic molecules PRF1, GZMB and GNLY, compared to the classical CD56bright population (p=5.6x10-11) suggesting reduced cytotoxic capacity. With disease progression, we found an increase in the proportion of this BM-specific CD56bright population which was significant between SMM and MM (padj=0.008). **Conclusions:** We show for the first time that progression to myeloma is accompanied by an enrichment of the CD56bright NK cell compartment, specifically the BM-specific NK CD56bright CXCR6+ CD69+ subset with a reduced cytotoxic profile. Further work will clarify if these changes in the NK compartment contribute to the loss of host immune control at disease progression.

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Clonal Hematopoiesis of Indeterminate Potential (CHIP) is Associated with Shorter Overall Survival (OS) in Patients with Multiple Myeloma

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Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is frequently observed in patients with multiple myeloma (MM). Previous studies demonstrated that CHIP is associated with shorter survival in MM patients undergoing autologous stem cell transplantation (ASCT), particularly those who do not receive maintenance therapy with an immunomodulatory agent. This study aims to evaluate the implications of CHIP on both clinical characteristics and survival outcomes in a large cohort of MM patients. We present our preliminary findings describing the impact of CHIP on OS. **Methods:** Study participants include MM patients evaluated at the Massachusetts General Hospital between January 2019 and December 2022 who underwent targeted exome sequencing (i.e., Heme SNaPshot) on DNA extracted from bone marrow for CHIP-associated somatic mutations. The patient population included in this analysis consented to mutational testing and did not include all consecutive patients seen at our institution. The presence of CHIP was defined by the presence of a leukemia-associated mutation with a variant allele fraction >2% in unselected bone marrow aspirate samples. Medical records were manually reviewed for all patients to extract data on baseline clinical characteristics and survival outcomes. The Kaplan-Meier method was used to estimate OS, and univariate comparisons between groups were made with the log-rank test. Updated results will be presented at the meeting with multivariate analyses for OS after accounting for baseline clinical characteristics. **Results:** A total of 317 patients underwent gene sequencing, of whom 167 (53%) had CHIP. Preliminary findings show that patients with CHIP had significantly shorter OS from the time of MM diagnosis compared to patients without CHIP (8.6 vs. 14.5 years; p=0.007). Five patients (1.6%) also had myelodysplastic

syndrome (MDS) or acute myeloid leukemia (AML). Among these patients, three patients developed MDS/AML after the diagnosis of MM, whereas two patients had MDS/AML prior to the diagnosis of MM. There was no statistical difference in the incidence of MDS/AML after the diagnosis of MM when accounting for death as a competing risk between patients with and without CHIP (Fine-Gray p=0.81). Four out of five of these patients harbored CHIP-associated mutations and two out of the five patients had an ASCT. Cytogenetic testing of two MDS patients also revealed a t (11;14) mutation. **Conclusions:** The present study supports previous data that the presence of CHIP is associated with shorter OS in MM patients. The high incidence of CHIP in our patients may be biased given that mutational testing was not performed on all consecutive patients. Updated multivariate analyses for OS will be presented at the meeting with a detailed analysis on patients with MDS/AML.

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Cytogenetics Abnormalities in Patients With Newly Diagnosed Multiple Myeloma Analyzed by Fluorescent In Situ Hybridization in Chilean Patients

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Introduction: One of the most relevant points at diagnosis of multiple myeloma (MM) is the identification of adverse prognostic characteristics of the disease, such as clinical features, patient fitness, tumor burden and high risk cytogenetic abnormalities. The use of fluorescence in situ hybridization (FISH) for the genetic classification of newly diagnosed MM (NDMM) has become an essential tool. There are multiple definitions, but currently patients are considered to have high-risk disease if FISH studies demonstrate one of the following abnormalities: t(4;14), t(14;16), del17p, t(14;20) and gain/amplification of 1q. The occurrence of any two high risk factors is considered double-hit myeloma and three or more high risk factors as triple-hit myeloma. We aimed to determine the frequency of high risk cytogenetic abnormalities in patients with NDMM in a large cohort of Chilean patients. **Methods:** Observational, retrospective, descriptive study based on data recovered from the Cytogenetics Laboratory of at a National Reference Center for FISH testing from January 2018 to December 2023. FISH is made by immune-magnetic cell sorting. Descriptive statistics were used. **Results:** Bone marrow samples from 462 patients were referred for study; 55.4% (n=256) were male, and the mean age of presentation was 63.1 years. Only 51.7% (n=239) were processed. The most frequent alterations were those involving the immunoglobulin heavy chain (IGH) locus at the chromosome 14q32 region with 39.7% (n= 91/229), including t(11;14) with 15,8% (n=6/38), t(4;14) with 15.6% (n= 30/206) and t(14;16) with 1.5% (n=3/205). The deletion of 17p was observed in 19.8% of the patients (n= 47/237). Gain or amplification of 1q21 occurred in 63% (n=23/36) of the samples tested, 47% (n=11/23) of them being amp(1q), one with seven extra copies. Deletion of the short arm of chromosome 1, 1p32, was observed in 11% (n=4/35). The proportion of patients labeled as high risk disease were 31% (n=74/239), double-hit myeloma 7,5% (n=18/239) and triple-hit myeloma 0.8% (n=2/239). **Conclusions:** This is the most extensive report of cytogenetics alterations in NDMM in the Chilean population so far. Most of our results are similar to those reported in the literature. Until the end of this study, there were no cases of t(14;20) in our patients. We found a high frequency of chromosome 1 abnormalities. This probe has recently been added to our myeloma panel, and few tests were performed during the studied period, which may explain the high rate of positivity. The most striking finding is that almost half of the samples could not be tested, whether for technical reasons or due to an imposed age limit at the public health system. It is critical that all patients with NDMM be properly stratified.In conclusion the results are similar to that previously described, except for a higher incidence of gain/amp 1q. We have to optimize the technique and expand the indications for FISH testing.

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Effects of Daratumumab(dara), Cyclophosphamide (C), Thalidomide (T) and Dexamethasone (D) Combination on Lymphocyte Populations of Transplant Eligible Newly Diagnose Multiple Myeloma Patients

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Introduction: Multiple Myeloma (MM) is the second most common hematological malignancy, resulting from the proliferation of monoclonal protein-producing plasma cells, predominantly affecting the elderly population. In the last decade, therapeutic advances have led to an increase in the overall survival of patients, however the disease remains incurable. Therapeutic protocols combining alkylating agents, immunomodulators, immunosuppressants, and immunotherapy induce an immunological shift that is still not fully understood. The aim of this study was to quantify lymphocytes subpopulations and B cells subsets in patients with Newly diagnosed Multiple Myeloma (NDMM) eligible for Autologous Stem Cell Transplant (ASCT) using first-line therapy with cyclophosphamide, thalidomide, dexamethasone combined with daratumumab (Dara-CTd), an anti-CD38 monoclonal antibody. **Methods:** Between 2018 and 2022, 23 NDMM patients from the MAXDARA clinical phase 2 trial had their lymphocyte profiles analyzed at five distinct time points: at diagnosis, after induction therapy, after two consolidation cycles post-ASCT, before maintenance therapy, and one year after the start of the maintenance phase. Flow cytometry was used to detect lymphocyte subsets by surface molecules including CD3,

CD4, CD5, CD8, CD16, CD19, CD20, CD38, CD45 and CD56 in the scatter plot. B cells were isolated and subpopulations (naïve B cells, non-class switched memory B cells, class switched memory B cells, IgD-CD27- memory B cells and plasmablasts) were detected by CD20, CD24, CD27, CD38, CD45 and IgD. Statistics was performed using the SPSS® v25.0. **Results:** The patients median age was 58 (range 37 – 67) years old, and 57% were female. It was observed that the treatment induced significant changes in the lymphocyte profile, with emphasis on the decrease in B cells and NK cells (p≤0,05). The composition of the B cell subsets changed significantly throughout the treatment. T cells had a significant decrease after the induction phase, but recovered soon post-ASCT. Although not statistically significant, higher lymphocyte counts were associated with higher overall free survival and measurable residual disease undetectable by next-generation flow (NGF). **Conclusions:** Lymphopenia have been shown with different protocols using Dara as single agent or in combination. The present study confirmed that Dara-CTd induces a decrease in the number of different lymphocytes populations (T, B and NK) after induction therapy with Dara-CTD. The T cells number recovery after two consolidation cycles post-ASCT, but B and NK cells remains at low levels during treatment, with slow recovery.

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Taking a Peek Into the Cytogenetic Profile of an Indian Cohort

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Introduction: Multiple myeloma is a genetically heterogeneous disease with varied presentations. Besides patients' related factors and treatment used, biological characteristics of malignant plasma cells determine outcomes and cytogenetics is part of currently used risk stratification models. This study focuses on the cytogenetic patterns and their relations to the presentation, prognosis and outcomes in multiple myeloma. This study also aims to compare the old IWMG classification of high risk stratification to the 2024 IMS consensus recommendations. **Methods:** We have used electronic medical records from a tertiary health care hospital in India to collect data. FISH analysis was performed on sorted BM plasma cells. Data pertaining to 221 patients was entered systematically into an excel sheet out of which 178 had reports available to cytogenetic testing. Retrospective analysis was conducted using Chi-square to find significant associations, univariate and multivariate analysis were further done on these findings. **Results:** Incidence of cytogenetic patterns in our study were as follows: 13(7.3%) patients showed t(4:14), 5(2.8%) had t(14:16), 5(2.8%) had 17p deletion, 29(16.4%) with 1q-gain, 21(11.9%) with 1q-amplification, 7(4%) with 1p deletion, IgH translocation to unknown partner was seen in 37(20.9%) patients, 7(4%) had t(11:14), 4(2.3%) had t(6:14), 62(35.07%) with deletion 13/monosomy, 90(50.8%) had hyperdiploidy, 21(11.9%) had high risk cytogenetics (t(4:14), t(14:16) and/or del17P). Double hit and triple hit were noted in 10 patients (5.6%) and 1 (0.56%) patients respectively. High risk cytogenetics markers were associated with hypoalbuminemia at presentation (p< 0.001), extramedullary and paramedullary disease (p=0.01), serological progression (p< 0.001), death (p=0.011). According to the new high risk stratification 21 patients out of 178 were high risk (11.79%) and predicted early mortality (p=0.006) and hypoalbuminemia at presentation(p=0.008). There was no difference between the overall response rates (66.7% Vs 68% of VGPR or better) of high risk patients according to either old or new high risk stratification systems. t(4:14) was associated with paramedullary disease (p< 0.001) and with serological progression after initial therapy (p< 0.001). **Conclusions:** This study suggests the lower incidence of some of recurring cytogenetic abnormalities in our patient cohort possibly due to prior treatment and a better diagnostic modalities should be evalauted.

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Exploring the Link Between High-Risk Cytogenetics and Skeletal Lytic Lesions in African American (AA) Multiple Myeloma (MM) Patients: Insights from a Decade-Long Study

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Introduction: MM involves the clonal proliferation of plasma cells within the bone marrow, often resulting in destructive skeletal lesions. This study aims to investigate the association between high-risk cytogenetics(CG) and the presence of lytic lesions observed in a minority population with MM. **Methods:** We retrospectively reviewed records of biopsy-confirmed MM patients at a cancer center in Brooklyn between 2013 and 2024. Inclusion criteria were the availability of Fluorescence in situ Hybridization (FISH) results and radiology records, including bone surveys, MRI, or PET/CT scans. We calculated the relative risk (RR) to investigate the association between high-risk CG and the presence of lytic lesions. **Results:** Among 97 patients with MM, 42 patients were included in the study, with a median age of 69 years (range: 36-90), with 23 (54.7%) males and 19 (45.3%) females, 35 (83.3%) of whom were AA. Patients were stratified into high, standard, and low-risk CG based on FISH analysis. Radiological reports were reviewed to document the presence of lytic lesions. High-risk CG included: del(17p), t(4;14), t(14;16), t(14;20), gain 1q, or p53 mutation. Standard-risk CG included: t(11;14) IGH/CCND1 and isolated hyperploidy. Normal CG on FISH was categorized as low-risk. Among 42 patients, 19 (38.8%) had positive lytic lesions. Among

these, ten patients (52.6%) exhibited high-risk CG, 6 (31.6%) standard-risk, and 3 (15.8%) low-risk CG on FISH. Among 23 (61.2%) patients without lytic lesions, 9 (39.13%) presented with high-risk CG, while standard-risk & low-risk CG were seen in 7 (30.4%) patients each. The presence of high-risk CG was associated with the presence of positive lytic lesions with an RR of 1.35. **Conclusions:** Our findings indicate that patients with high-risk CG have a 35% higher risk of presenting with lytic lesions than patients with non-high-risk CG. The study's primary limitation was the sample size, highlighting the need for further research.

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Increased WEE1 Expression Is Predictive of Short Progression-Free Survival, Independent of Standard Prognostic Factors in Multiple Myeloma

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Introduction: Current prognostic scores in multiple myeloma (MM) rely on disease burden and a limited set of genomic alterations. Gene expression panels have been reported to be prognostic but are not currently utilized in clinical settings. Recently, we applied a novel measure of network robustness, Ollivier-Ricci curvature, to examine patterns of gene-gene interactions in MM and identified novel pathways and genes associated with poor prognosis (Simhal, Maclachlan et al. BCJ 2023). To facilitate clinical application, we focused on the expression of the most prognostic gene highlighted — the tyrosine kinase WEE1, a G2M checkpoint regulator, which has a targeted therapy in trials in ovarian cancer. **Methods:** We analyzed the MMRF CoMMpass RNA-Seq, WES, and WGS dataset (overlap; n=659) comparing with two independent datasets having microarray gene expression profiling (GEP) data from the Total Therapy 2 (N=341) and 3 (N=214) trials. WEE1 gene-neighborhood information was extracted from the STRING database for network analysis. Gene set enrichment analysis (GSEA) was conducted to compute hallmark pathway membership. Multivariate modeling was performed using Cox proportional hazards (CPH) models, random forests (RF) regression models to predict WEE1 expression, and random survival forests (RSF) to compute the concordance index (c-index). **Results:** From the CoMMpass dataset, the mean age was 62.5 ± 10.7 years; 60% were male, ISS distribution was 35/35/30%, and 53% received an autologous stem cell transplant (ASCT). WEE1 expression defined a high-risk (HR) group by top tertile and a low-risk (LR) group by bottom tertile. PFS was significantly different ($p < 1e-9$) between the groups, which was validated in the GEP datasets. In multivariate CPH modeling, PFS prediction was independent of both standard biomarkers (hyperdiploidy, t(4;14), t(11;14), t(14;16), TP53 status) and emerging risk factors (the complex structural variant chromothripsis and APOBEC mutational activity). WEE1 expression also remained prognostic when stratifying by treatment type, including ASCT. RSF modeling on WEE1 and its neighboring genes resulted in a c-index for PFS prediction of 0.63±0.04, comparable to either ISS or R-ISS with measurement of a single gene expression. The increase in WEE1 expression between the risk groups was not correlated with known interacting genes determined via RF. RF modeling showed a 3.2x rise in mean error when using interacting genes to predict WEE1 expression between the HR and LR groups. Differential GSEA showed dysregulation in the hallmark p53 pathway, suggesting elevated WEE1 expression is associated with TP53 aberration. **Conclusions:** We showed that WEE1 is (1) prognostic independent of known biomarkers, (2) differentiates outcomes associated with known markers, (3) upregulated independently of its interacting neighbors, and (4) dysregulates P53 and proliferation pathways. Determining the causes of abnormal WEE1 expression may uncover therapeutic targets.

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CRISPR-Based Functional Genomics Studies Identify Mechanisms of Multiple Myeloma (MM) Cell Response to vs. Resistance Against Novel Pharmacological Mutant-Specific KRAS Inhibitors

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Introduction: RAS genes are frequently mutated oncogenic drivers in MM. Several novel pharmacological inhibitors targeting specific KRAS mutations have become available. We previously reported that G12C or G12D mutation-specific KRAS inhibitors, which are clinically active in solid tumors with these mutations, are also potently active in vitro against MM lines with the respective mutations. Here, we performed 8 genome-wide CRISPR gene editing (knockout, KO) or gene activation studies to assess the mechanisms of sensitization vs. resistance against these inhibitors in KRAS-mutant MM cells. **Methods:** The KRAS G12D-mutant MM cell lines KP-6 and KARPAS620 and the KRAS G12C-mutant lines XG-7 and KHM-1B were treated with the small molecule KRAS inhibitors MRTX1133 (G12D-specific) and MRTX1257 (G12C-specific), respectively, in different concentrations within the clinically achievable concentration range in patients with solid

tumors. A total of 8 genome-scale CRISPR-based gene activation or editing screens were conducted to identify genomic perturbations altering response to KRAS inhibitors. The in vitro activity of both compounds as single agents or in combination with clinically established anti-MM drugs was assessed with bioluminescence assays and flow cytometry, analyzing cell viability/proliferation and cell cycle distribution/apoptosis induction, respectively. Downstream RAS signaling was assessed by Western blotting. **Results:** The KRAS inhibitors showed strong and specific activity in their respective cell lines (IC50 of 5-150 nM) and downstream signaling (pERK1/2 and pAKT) was effectively abrogated. Apoptosis induction was most prominent in G12D-mutant cells. CRISPR activation studies identified KRAS itself, upstream surface receptors (e.g., EGFR), SHOC2 (a positive regulator of RAS-MAPK signaling) as key genes promoting MM cell resistance against KRAS inhibitor treatment. CRISPR gene KO studies suggest a role of the KEAP1/NF2L1 pathway (regulating cell homeostasis), GTPase-activating proteins as well as negative regulators of RAS-MAPK (e.g. LZTR1) as molecular determinants of MM cell response to KRAS inhibition. **Conclusions:** Mutant-specific KRAS G12C and G12D inhibitors show strong in vitro activity in MM cells with these mutations. CRISPR KO or gene activation studies provide functional insights into the pharmacological inhibition of KRAS in MM, identifying potential targets which regulate the response vs. resistance of MM cells to KRAS inhibitors.

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Spatial Transcriptomics Unveils Novel Disease Mechanisms Associated With the Microenvironment in Multiple Myeloma

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Introduction: Single-cell sequencing has been the major technology used to understand the transcriptional features of malignant plasma cells (MM-PC) responsible for developing Multiple Myeloma (MM). These findings underscore the significant genetic and genomic heterogeneity both between patients and among individual patients. The spatial distribution in the tissue of the different cellular types is hypothesized to be critical to the niche-specific regulatory programs involved in the tumor's relapse, drug resistance, or aggressiveness. **Methods:** To elucidate the Bone Marrow`s (BM) topographical distribution and cellular interactions of BM components, we performed Visium Spatial Gene Expression analysis (10x Genomics) in YFPcγ1 (healthy) and MIcγ1 mice strains (a model that recapitulates the principal characteristics of human MM), and in clinical human healthy and MM samples. The formalin-fixed paraffin-embedded (FFPE) BM tissues were decalcified and transcriptionally characterized, applying deconvolution analysis with CARD based on public and own single-cell RNA-seq data to estimate cell composition per spot. Top marker genes associated with MM-PC were used to locate the areas enriched in this cell type. Besides, to define the MM-PC heterogeneity, a pseudo-bulk-based analysis identified the most variable genes and pathways between different groups of MM-PC. To better understand the importance of T cells in MM samples, we performed a targeted analysis looking for specific profiles and additional microenvironmental signatures in the disease. **Results:** Significant differences between healthy and pathological samples were determined using cell deconvolution analysis. After identifying the top marker genes associated with MM-PC in our model, different areas, based on the proportions of MM-PC, were delineated. We differentiate between hotspots (areas with high MM-PC scores), border zones (areas surrounding the Hotspots), and remote zones (low MM-PC scores). Interestingly, different distributions of T cell effector and exhaustion profiles was observed in the border zone and hotspots upon investigating the defined MM-PC density gradient. Additionally, an increase in neutrophil extracellular traps (NETs) pathway, typically observed in solid tumors, was observed within the remote and border zones of MM samples.The application of spatial transcriptomics to FFPE human BM biopsies, healthy and MM (with varying degrees of PC infiltration), confirmed the presence of the equivalent areas and T-cell profiles observed in the mouse model. **Conclusions:** Our findings demonstrate that spatially resolved transcriptomics provides a systematic approach to establishing unbiased gene expression within a spatial context. We identified different T cell profiles in MM and patients. This approach may have broad future potential applications in understanding the performance of advanced therapies such as CAR T cells.

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Alteration of the m6A Regulatory Genes, With the Special Implication of Virma, Is Crucial for Multiple Myeloma Development

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Introduction: Epitranscriptomics has emerged as a crucial field uncovering RNA modifications that play a vital role in human diseases, being the methylation of N6-adenosine (m6A) the one that suffers the most prevalent alterations in human tumors. Therefore, the study of the levels and the associated genes regulating m6A may provide a different perspective for a deeper understanding of the biology of multiple myeloma (MM) and the potential impact as a biomarker or therapeutic target in this disease. We aimed to elucidate the role of the m6A and its regulatory genes in the prognosis and pathogenesis of MM. **Methods:** We analyzed the m6A levels and the status of its 20 regulatory genes based on RNA-seq, ATAC-seq, and ChIP-seq data, in plasma cells (PCs) from healthy donors and MM patients. RNA-seq data from 619 MM patients from the CoMMPass dataset (IA18) were used. VIRMA inhibition was carried out by CRISPR-Cas9 technology. VIRMA levels (western blot), global m6A levels (m6A-ELISA), cell proliferation (flow cytometry), and whole proteome (mass spectrometry) were analyzed. **Results:** m6A global levels were significantly increased in plasma cells from patients with SMM and MM, which correlated with the overexpression of 18 of the 20 genes that regulate m6A. Interestingly, the expression of these genes was epigenetically regulated as demonstrated by greater accessibility and activation (H3K27Ac) of the chromatin in their promoter region. In terms of prognosis, MM patients with a higher number of m6A genes upregulated (ESMEG score: Expression Signature of m6A Epitranscriptomic Genes) showed significantly poorer progression-free (PFS) and overall survival (OS) in the univariate and multivariate study. Finally, we focused on VIRMA, as we identified that VIRMA inhibition was essential in virtually all MM cell lines included in the Dep-MAP-Achilles project. We demonstrated that the inhibition of VIRMA decreased significantly the m6A level and cell proliferation of MM cells. Inhibition of VIRMA was associated with proteome change in which IKBKB downregulation was highlighted. Lack of IKBKB was hypothesized to reduce NF-kb translocation to the cell nucleus, and consequently, to lower NF-kb signaling, decreasing cell survival, and anti-apoptotic effects. These results demonstrate the alteration of the m6A profile in the disease, where the m6A genes, especially VIRMA, have a critical role in MM pathophysiology. **Conclusions:** Our results demonstrate that MM is characterized by an epigenetically deregulated epitranscriptome. Moreover, the expression score of genes that regulate the m6A emerges as a promising biomarker for refining the stratification of MM patients. Notably, within m6A genes, VIRMA plays an essential role in the pathogenesis of MM via reverting the overactivation of the NF-kb signaling pathway observed in MM plasma cells, indicating its potential for the development of targeted therapies to improve the treatment response of MM patients.

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Bone Marrow Immune Ecosystem Shapes Acquired Daratumumab Resistance in Plasma Cell Myeloma

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Introduction: Daratumumab (dara), a monoclonal antibody to CD38, is an effective therapy of multiple myeloma. However, most initial responders relapse or progress. Several possible mechanisms underlying this have been described, but the potential impact of changes in the bone marrow immune ecosystem are still poorly-defined. **Methods:** Here, we studied the cellular composition of the bone marrow immune ecosystem associated with loss of response to daratumumab therapy, using scRNA-seq, DSP technology, validated by PrimeFlow RNA flow cytometry and in vitro and in vivo experiments. **Results:** We compared the differences in the percentage of T-cells before therapy and after acquired resistance. Variations were further examined using PrimeFlow in another cohort. Higher GZMK MFI expression in CD8+ T-cells was correlated with anti-CD38 treatment resistance but decreased expression in subjects with a complete response, while CCR7 showed the opposite trend. Three of the predominantly terminal CD8+ T-cell subsets identified by trajectory analysis had higher transcriptional signatures for cytotoxicity and exhaustion. CD8+ T-cells had an increased exhausted signature, increased cytotoxic signature and decreased naïve signature upon resistance. Expression levels of most checkpoint markers increased after acquiring resistance. We also analyzed B-cells, myeloid cells and NK/NKT-cells phenotype alterations. Then we focused more on plastic plasma cells. Neoplastic

plasma cells clusters 2, 5, 7 and 8 increased in numbers after acquiring dara resistance. Combined with GO/KEGG enrichment analysis, we found cluster 2, 5, 7 and 8 characterized by different pathways. CD138+ and CD45+ cells marked in the DSP were also evaluated and adjusted based on H&E and IHC staining. The ssGSEA algorithm based on the altered immune subset signature showed signatures of various cells decreased in the cancer centre regions. Plasma cell cluster 8 was elevated in parallel with acquiring dara resistance. Resistance associated neoplastic plasma cell cluster 8 signatures were also prognostic in 4 databases. We integrated module analysis and GO/KEGG enrichment analysis and found that MYC regulon was identified as the key. We further studied whether IFN-γ produced by consistently activated cytotoxic immune cells activates MYC associated with acquired resistance. IFN-γ exposure stimulated MYC expression and increased phosphorylation of MYC in two plasma cell myeloma cell lines. MYCi975 reversed resistance to dara-mediate ADCC. After giving dara and NK-cells mean FLuc signal of MYC OE cohort mice was significantly higher compare with NC cohort. Combining MYCi975 and dara reversed acquired dara resistance in MYC OE mice. **Conclusions:** Mechanisms underlying acquired daratumumab resistance are complex involving crosstalk between immune cells and neoplastic plasma cells. Increased activation of MYC may be an important mechanism promoting acquired daratumumab resistance.

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Critical Roles of LILRB4 in Promoting STAT3/PIM1 Mediated Metabolism in Multiple Myeloma

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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 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:** N/A. **Results:** Methods and resultsOur clinical data showed that MM patients with LILRB4 overexpression had poor prognosis and decreased overall survival. Compared with newly-diagnosed MM patients, expression of LILRB4 was higher in the MM patients relapsed after treatment, indicating the critical role of LILRB4 in MM progression and drug resistance. In vitro experiment showed that MM cells with LILRB4 overexpression enhanced the cell colony-forming ability and promoted cell proliferation. Conversely, knocking-out LILRB4 induced cell apoptosis. We used MM cells that overexpressed LILRB4 to establish myeloma xenograft model and results showed that compared with LILRB4neg MM cells, mice injected with LILRB4high MM cells displayed higher tumor formation rate and lower survival rate. Then, we analyzed RNA-seq data to investigate the mechanisms of LILRB4 in MM proliferation. Transcriptome analysis indicated that overexpression of LILRB4 in MM cell lines activated NF-kB, glycolysis, hypoxia and MTORC1 signaling pathways. Among these, NF-kB pathway has been proved in previous studies. More important, RNA-seq data suggested the upregulation of PIM1 in MM cells with LILRB4 overexpression, which has been confirmed in our in vitro experiments. We also found that LILRB4 upregulated the expression of PIM1 through activating SHP2 and STAT3, indicating the underlying mechanism of MM cell proliferation. In addition, in our RNA-seq data, MM cells with LILRB4 overexpression exhibited the enrichment of fatty acid metabolism genes. Interestingly, we found that the amount of lipid droplet increased significantly in LILRB4 overexpressed MM cells as well as the uptake of fatty acid, indicating the correlation between LILRB4 and fatty acid metabolism reprogramming. **Conclusions:** In conclusion, LILRB4 is highly associated with poor prognosis of MM patients and has the ability of tumorigenesis. LILRB4 promotes MM cell proliferation by activating SHP2 and STAT3 to upregulate the expression of PIM1, which plays critical roles in MM pathogenesis.

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Proteogenomic Analysis of Hyperdiploid Multiple Myeloma

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Introduction: The major primary genetic events in multiple myeloma (MM) include translocations of immunoglobulin genes, and a hyperdiploidy (HRD) karyotype. HRD MM has historically been categorized as a subgroup of MM with a more favorable prognosis, but some patients may have more aggressive disease. Further research is needed in this subgroup. Proteogenomics integrates proteomic and genomic data; we employed it here to determine whether any given trisomy may lead to a selective advantage. **Methods:** Protein and mRNA were extracted from CD138+ isolated cells from 47 HRD MM samples using the Qiagen AllPrep Kit. RNA-seq data was processed using MAPR-Seq pipeline using default parameters and gene-wise raw counts were extracted for each sample. Protein samples were digested with trypsin. Proteomics data was processed using Specranaut and protein-wise intensities were extracted for each sample. A multivariate analysis of gene expression data was performed using edgeR software configured to assess the effect of each chromosomal arm-level abnormality on each gene's expression when accounting for other copy number variant (CNV) events. Genes with an adjusted p-value of < =0.05 were considered significantly associated with the corresponding CNV event. A similar method was

followed for performing multivariate analysis with proteomics data with slight modifications. **Results:** We found gene dosage effects with increased relative RNA expression and protein abundance of genes on trisomic chromosomes when compared to genes/proteins on all chromosomes (sum relative frequency 14.4 vs 8.8 for RNA and 49.0 vs 30.0 for protein, respectively). We focused on trisomies 5, 9, 11, 15, and 19 as these are common in HRD MM. KIF2A, which was found to be significantly more abundant in trisomy 5 samples (Rank 13.1, p=0.02), regulates spindle organization and chromosome movement during mitosis, and knockout experiments lead to chromosome misalignment and mitotic arrest. The mechanism for trisomy in HRD MM is unknown and defects in chromosome alignment genes may play a role. Trisomy 9 samples had significantly higher abundance of MLLT3, a known oncogene in AML (Rank 15.8, p=0.003). We found increased expression of CCND1 in samples with trisomy 11 compared to those without trisomy 11 (Rank 10.3, p=0.04) but this was not significant at the protein level (Rank 2.52, p=0.56). Trisomy 11 also had increased protein abundance of PSMD1 (Rank 14.1, p=0.007); mutations are increased in MM refractory to proteasome inhibitors. SNAPC5, a protein important for transcription, was elevated in samples with trisomy 15 (Rank 25.6, p=< 0.001). Trisomy 19 by far had the highest protein abundance in zinc fingers (n=7), which have a known role in MM progression. **Conclusions:** Proteins are the final effectors of most cellular processes. Proteogenomics can improve our understanding of the drivers of HRD MM. Using a proteogenomic approach we found gene dosage effects and identified proteins that may lead to selective advantage of trisomies in HRD MM.

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Synergistic Induction of Senescence-Driven Immune Responses and Myeloma Cell Cytotoxicity by CDK4/6 Inhibitors and Daratumumab Combination Therapy

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Introduction: Progressive immunosuppression is associated with the development of multiple myeloma (MM) and strategies aimed at enhancing immune function, including antibody-based therapy, have important therapeutic significance. While CD38-directed monoclonal antibody Daratumumab (DARA) is highly effective as single agents and in combination regimens by leveraging natural killer (NK) cells as key effectors, disease relapse persists. Therefore, strategies to further enhance efficacy and overcome drug resistance are needed. In this study we show that CDK4/6 inhibitors (Abemaciclib and Palbociclib) induce cell cycle arrest and a senescent phenotype in MM cells, and act in combination with Daratumumab to provoke an NK cell surveillance program leading to myeloma cell death. **Methods:** We evaluated the response of MM cell lines and primary bone marrow samples from MM patients to CDK4/6 inhibition using both Abemaciclib (Abe) and Palbociclib (Pal). Transcriptional changes were investigated with bulk RNA sequencing and qPCR; while flow cytometry analysis was used to investigate the changes in NK cell receptors and ligands. Senescence and SASP induction were evaluated by C12FDG (β-galactosidase staining) and cytokine array respectively. The synergistic effect of Abe/Pal and DARA was measured in vivo in a NSG mouse model reconstituted with human-derived NK cells and engrafted with RPMI-8226-Luc MM cells. **Results:** We observed significant senescence-associated beta-galactosidase (SA-β-gal) activity and potent SASP induction. RNA-seq analysis of MM cell lines after drug treatment revealed a reduction in proliferation genes and increase in SASP factor expression, including type I interferon (IFN I) signaling and enhanced expression of IFN-stimulated genes, compared with control cells. Genes and cytokines related to innate immune responses were significantly increased. Moreover, the NK cell ligands required for activation of NK cell cytotoxicity and tumor cell targeting -NKG2D and -DNAM-1 were increased preferentially on βGalhigh compared to βGallow cells. Overall, these data suggest that, in addition to more stable cell cycle arrest conferred by RB-mediated senescence, CDK4/6 inhibition may promote NK cell immune surveillance through induction of the SASP program. We indeed observed an increase in NK cell degranulation and IFN-γ production using an in vitro NK-MM coculture assay. Importantly, combination with DARA significantly increased DARA -induced MM cell lysis by NK cells both in vitro and in vivo in a humanized model of MM. **Conclusions:** Strategies to exploit and enhance NK cell immune surveillance may complement existing efforts to harness adaptive immune surveillance in MM. Our results suggest that cytostatic agents inducing senescence such as CDK4/6 inhibitors can be combined in MM with CD38 antibody-based therapy to enhance NK cell activity and the clearance of senescent cells, providing the basis for clinical evaluation of this combination therapy to further improve patient outcome in MM.

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The Specific Transcriptional Profile and Clonal Selection of MGUS-like Behavior Predict an Exceptionally Favorable Prognosis in Multiple Myeloma

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Introduction: Achieving persistent undetectable minimal residual disease (MRD) status is considered the cornerstone of

functional cure in myeloma. It is interesting to note that some myeloma patients do not achieve complete response or undetectable MRD after systematic treatment, but can achieve a plateau in their survival curve, which has been hypothesized as monoclonal gammopathy of undetermined significance-like (MGUS-like) behavior. However, this unusual MGUS-like behavior is not well-known and is poorly understood. **Methods:** To address this issue, we retrospectively identified 35 (6.4%) MGUS-like patients from the National Longitudinal Cohort of Hematological Diseases in China (NICHE, NCT04645199) who have a progression-free period of ≥5 years but persistent detectable MRD or M-protein. We used a multi-omics approach including DNA and RNA sequencing to investigate the distinct clinical features, transcriptional profile, genomic landscape, and clonal evolution patterns that contribute to MGUS-like behavior. **Results:** These patients exhibiting MGUS-like behavior demonstrated infrequent anemia and bone lesions, achieving a significantly good prognosis even with suboptimal remission. Transcriptional analysis unveiled a distinct transcriptome resembling the earliest precursor condition (MGUS), enriched in immune response and low proliferation pathways, and showed a tendency towards CD-2 classification and dormant state, indicating an indolent clinical course. Based on differentially expressed genes, we constructed a specific gene signature predicting MGUS-like status and validated its excellent performance in the MMRF cohort. Whole-exome sequencing of paired diagnostic and MRD/first relapse tumor samples revealed two distinct clonal evolution patterns: the majority exhibited stable evolution, while a few patients experienced differential clonal response evolution, both leading to MGUS-like behavior. These findings suggest that MGUS-like behavior not only arises from the unique transcriptional profile of tumor cells but also results from clonal evolution under treatment pressure. **Conclusions:** In summary, we identified a distinct myeloma subgroup that shows unexpectedly long progression-free period but with persistent residual tumor, exhibiting MGUS-like status. This distinctive MGUS-like behavior seems to not only arise from the specific transcriptional profile of tumor cells at diagnosis but also be attributed by the tumor clonal selection under treatment pressure. Furthermore, we have developed and validated a 44-gene signature which can predict potential MGUS-like status characterizing by a favorable prognosis irrespective of response depth.

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Causal Roles of Monocyte in Mediating Effects of Gut Microbiota in Multiple Myeloma Suggested by a Genetic Study

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Introduction: Multiple myeloma (MM) is a tumor of plasma cells primarily within the bone marrow, which accounts for 20% of deaths in adults diagnosed with a hematological malignancy. An essential phase in developing myeloma is the evasion and inhibition of antitumor immunity. Lately, multiple results indicated that the gut dysbiosis was caused by inflammation induced by immune cells. Herein, we performed a two-step mendelian randomization (MR) to determine the relation of GM to the genetically predicted risk of MM and whether immune cell signatures could mediate this association. **Methods:** The datasets comprise data on MM, 412 gut microbiota species, and 731 immune cells. MM GWAS summary data comprising 1249 cases were obtained from FinnGen Release 9. Data on 412 gut microbiota species came from the Dutch Microbiome Project study. In this research, a GWAS was conducted on a population of 7,738 participants, covering 207 microbial taxa and 205 pathways representing microbial composition and function. The original GWAS on 731 immunophenotypes used information from 3,757 European individuals. It contains 4 trait types,7 panels, and 731 traits. All statistical analysis were implemented with R 4.3.1. $P < 0.05$ was considered to have a significant association between exposure and outcome. **Results:** In the two-sample MR analysis, PWY.5097 was associated with higher risk of MM. The MR estimates of weighted median indicated that it was also positively correlated with MM. Our BWMR results showed similar positive effects. The reverse MR analysis revealed no evidence of a causal effect of MM on the identified PWY.5097. Among the final selection of 731 immune cell phenotypes, PWY.5097 was correlated to 34 immune phenotypes. Next, we put these phenotypes into two-sample MR analysis, to screen the association between immune cells and MM. After FDR correction and sensitivity analysis, we observed protective effects for 3 immunophenotypes against MM, including IgD on IgD+ CD24+ B cell, HLA DR on CD14+ CD16- monocyte, HLA DR on CD14+ monocyte, and HLA DR on monocyte. The BWMR model as well proved that the most significant protective cell type was HLA DR on monocyte. In our results, genetically predicted PMY.5097 was associated with increased risk of MM whereas genetically predicted HLA DR on monocyte was associated with reduced risk of MM. We first selected HLA DR on monocyte as representative immune cells for subsequent mediation analysis. The mediation effect of HLA DR on monocyte in the causal pathway from PWY.5097 to MM was -0.019 (95% CI: -0.053-0.157). **Conclusions:** In conclusion, this study thoroughly examined the causal links between circulating GM, immune cells, and MM. Our study identified that HLA DR on monocyte was mediation linking gut bacterial pathway with MM. According to our findings, immune cell-targeting monocyte subset harmonies may be a viable intervention strategy for the prevention of MM.

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LGR4 Promotes Plasma Cell Malignancy and Myeloma Cell Homing by Activating NF-κB Signaling Pathway

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation in the bone marrow. The mechanism of cell homing and migration which critical for myeloma tumorigenesis and progression. As the fourth member

of the G protein-coupled receptors (GPCRs), LGR4 is involved in a variety of physiological and pathological processes. Study shows LGR4 is involved in early haematopoietic fractionation, while high expression of LGR4 is associated with poor prognosis in variety of cancer. LGR4 can promote breast cancer bone metastasis and it is highly expressed in MM patients. However, the unique function and mechanism of LGR4 in plasma cell malignancy and in MM remined unclear. **Methods:** LGR4 conditional knockout mice confirmed LGR4 deletion inhibits plasma cell differentiation. Gene editing technology and adoptive B cell transplantation mouse model to verify the malignant transformation effect of LGR4. Overexpression and knockdown of LGR4 in MM cell line verified the function and mechanism in MM both in vivo and in vitro. **Results:** Firstly, In vitro induced plasma cell differentiation results show interference with LGR4 expression inhibited B cell proliferation and plasma cell differentiation by used LGR4 conditional knockout mice and Cas9 tag mice. Interestingly, the adoptive B cell transplantation by VκMYC mice confirmed that over expression of LGR4 promotes B cell malignant transformation and bone destruction. Taken together, our earlier findings suggested LGR4 promotes plasma cell malignant transformation. Simultaneously, to identify the unique function and mechanism of LGR4 in myeloma, we have determined high-expression of LGR4 is associated with cell adhesion in MM and linked to poor prognosis. Overexpression of LGR4 promotes cell adhesion, migration and homing in MM cells, while knockdown of LGR4 suppresses both in vitro and in vivo. Mechanistically, we established that high expression of LGR4 in MM cells activated NF-κB signaling pathway and promoted the expression of migration-related adhesion molecule, thus accelerated the MM cell homing and tumor progression both in vitro and in vivo. **Conclusions:** In conclusion, evidence from our study show that LGR4 promotes plasma cell malignancy transformation both in vivo and in vitro. Meanwhile, our results show LGR4 in MM cells contribute to MM progression by modulating cell-adhesion to promote MM cell homing to BM. LGR4 activates NF-κB signaling which facilitates cell homing and the inhibition of NF-κB signaling pathway in MM. Taken together, our findings highlight the mechanistic role of LGR4 in plasma cell malignancy transformation and MM cell homing, revealed a therapeutic strategy for MM by targeting LGR4.

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Real-World Treatment Tendencies in Multiple Myeloma: Analysis of Drug Utilization Over Time in Brazil and Argentina

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Introduction: Limited data are available on treatment sequencing and drug use patterns among patients with multiple myeloma (MM) in Latin America. The TOTEMM study was conducted to describe treatment patterns and clinical outcomes of patients with MM in clinical practice in Argentina (TOTEMM-A) and Brazil (TOTEMM-B). Here, a preliminary analysis of treatment tendencies, accumulated per calendar year, is described. **Methods:** Both studies comprised a retrospective database analysis. TOTEMM-A used private electronic medical records from Hospital Italiano between January 2010 and December 2021, and TOTEMM-B used administrative claims data from Orizon between January 2015 and June 2021. Index was defined as a proxy of diagnosis and could be the first MM-related health term/ICD-10 code, or any related procedure, exam, or treatment for MM. In both studies, eligible patients included adults (≥18 years) with ≥1 MM ICD-10 code (C.90)/MM-related health term and any treatment (stem cell transplant and/or antineoplastic drug). Patients should have ≥12 months of follow-up after index. Frequency of treatment use, accumulated per calendar year, for all treated patients with MM was described. **Results:** In TOTEMM-A and TOTEMM-B, 195 and 1075 patients with MM, respectively, were eligible for inclusion. Mean (standard deviation [SD]) age of patients in TOTEMM-A was 70.6 (11.1) years and in TOTEMM-B was 62.0 (12.0) years. Mean (SD) follow-up time in TOTEMM-A was 62.0 (38.3) months and in TOTEMM-B was 34.6 (18.2) months. Changes in the treatment tendencies for MM were observed across the study years in both countries, including a numerical reduction in the proportion of patients receiving cyclophosphamide (TOTEMM-A: 49.1% to 32.4%; TOTEMM-B: 49.3% to 5.6%), bortezomib (the most frequently used proteasome inhibitor [PI]) (TOTEMM-A: 41.5% to 10.3%; TOTEMM-B: 80.6% to 25.0%) and thalidomide (the most frequently used immunomodulatory drug [IMiD] in TOTEMM-A; data only available for TOTEMM-A: 47.2% to 1.5%). Lenalidomide (the most frequently used IMiD in TOTEMM-B) increased overtime (TOTEMM-A: 11.3% to 41.2%; TOTEMM-B: 3.8% to 43.7%). Among monoclonal antibodies, a trend of increased use was shown for daratumumab (since 2017) (TOTEMM-A: 2.6% to 11.8%; TOTEMM-B: 12.6% to 36.6%). **Conclusions:** The treatment landscape for MM in Brazil and Argentina followed similar trends, with an increase in IMiD and monoclonal antibody use and a reduction in chemotherapy and PI use. Understanding the current treatment patterns and trends in Brazil and Argentina will help to raise awareness, identify unmet needs, and optimize the therapeutic strategies for MM.

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MagnetisMM-30: A Phase 1B, Open-Label Study of Elranatamab in Combination With Iberdomide in Patients With Relapsed or Refractory Multiple Myeloma (RRMM)

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Introduction: Trial in Progress. Elranatamab (ELRA) is a humanized BCMA–CD3 bispecific antibody. Single-agent ELRA induced deep and durable responses with a manageable safety profile in patients (pts) with RRMM enrolled in the phase 2 registrational MagnetisMM-3 study (NCT04649359; Lesokhin et al, Nat Med 2023). Iberdomide (IBER) is a novel CELMoDTM agent that induces enhanced antimyeloma tumoricidal and immunomodulatory activity in pts with RRMM (Lonial et al, Lancet Haematol 2022). While IBER in combination with ELRA has not been evaluated clinically, it may provide additional benefit to pts with RRMM based on the mechanisms of action of this novel combination. **Methods:** MagnetisMM-30 is a phase 1b, open-label, prospective study evaluating the safety, efficacy, and pharmacokinetics of ELRA in combination with IBER in pts with RRMM. The study has 2 parts: Part 1 for dose-escalation and Part 2, randomized for dose optimization. After 2 step-up priming doses of ELRA, pts will receive subcutaneous ELRA weekly with IBER given daily for 21 days of each 28-day cycle. After ≥6 months (cycles) of treatment, pts with a partial response or better for ≥2 months are eligible for reduced dosing frequency of ELRA. Once the 2 combination dose levels (dose levels A and B) are selected from Part 1 as the recommended phase 2 doses for ELRA and IBER, pts in Part 2 will be randomized 1:1 (stratified by the number of prior lines of therapy [LOTs; 1 vs >1]) to dose levels A and B. Key inclusion criteria are pts aged ≥18 years with a MM diagnosis per IMWG criteria, Eastern Cooperative Oncology Group performance status of 0-1, adequate organ and bone marrow function, and disease relapsed or refractory to the last antimyeloma regimen per IMWG response criteria. Pts who received 2-4 or 1-3 prior LOTs, including ≥1 immunomodulatory drug (IMiD) and ≥1 proteasome inhibitor (PI), are eligible for Parts 1 and 2, respectively. All pts must have received ≥2 consecutive cycles of an IMiD-containing regimen and ≥2 consecutive cycles of a PI or PI-containing regimen. Key exclusion criteria are pts with stem cell transplant ≤12 weeks prior to enrollment; active, uncontrolled infection; prior treatment with BCMA-directed or CD3 redirecting therapy or prior CELMoD agents (ie, IBER or mezigdomide). This study is ongoing; Part 1 and Part 2 will enroll approximately 27 and 60 pts, respectively. The primary endpoints are dose-limiting toxicities (Part 1) and AEs and lab abnormalities (Part 2). Secondary endpoints include AEs and lab abnormalities (Part 1 only), ORR, CRR, time-to-event outcomes, pharmacokinetics, minimal residual disease negativity rate, and immunogenicity. Clinical trial information: NCT06215118. Study funding: Pfizer. **Results:** NA – trial in progress. **Conclusions:** NA – trial in progress.

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Multiple Myeloma in the Era of Novel Agents: A Single-Center Study

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Introduction: Novel drugs for multiple myeloma (MM), as IMIDs, new proteasome inhibitors, monoclonal antibodies, and CAR-T cells, have expanded the range of available therapies for this disease. Both transplant-eligible and ineligible patients have consistently benefited from these novel therapies.From 2015 to 2022, carfilzomib, daratumumab, elotuzumab, ixazomib, isatuximab, and pomalidomide have been approved in Brazil. This study aimed to evaluate the outcomes of MM patients with access to novel drugs approved in a developing country. **Methods:** This prospective single center study included all newly diagnosed (ND) MM patients treated at Hospital Israelita Albert Einstein, Sao Paulo, Brazil, from 2019 to 2022. Overall (OS) and progression-free (PFS) survival curves were built with the Kaplan-Meier method. Cumulative incidence of progression and non-relapse mortality were built with the Gray method. Uni and multivariable analyses were carried out with Cox models. The impact of autologous HCT was measured with time-dependent Cox model. **Results:** With a median follow-up of 1.6 years, 112 patients were included (19 had HCT). Median age was 67 y/o and most patients were International Staging System (ISS)-1 (32%) and ISS-2 (36%) and 17% were ISS-3.Respectively, 1-year OS and PFS were 83% and 66% and for the autologous HCT group,100% and 79%. Age (p = 0.03) and hemoglobin at diagnosis were associated with OS (p = 0.004). Both high ISS and autologous HCT were (not significantly) associated with lower OS, and improved OS (HR = 0.30), respectively. Only hemoglobin at diagnosis was associated with PFS (p = 0.009).One-year rates of progression and non-relapse mortality were 21% and 13%. Only lytic lesions were associated with relapse (p = 0.0008), while age (p = 0.05) and hemoglobin (p = 0.04) were independently associated with non-relapse mortality. **Conclusions:** We have shown OS and PFS in patients treated with novel drugs for MM, comparable to those achieved in recent randomized trials. The leading cause of treatment failure was relapse. OS and PFS were 83% and 66% and in the HCT patients, 1-y OS was 100%. A recent real-world European study from high Human Development Index countries reported a 90% 1-y OS, which is similar to our results.A remarkable finding of our study is the adverse impact of anemia at diagnosis, with the risk of death 28% higher, mainly due to non-relapse mortality. However, anemia is not included in any of the International Staging Systems (ISS, R-ISS, R2-ISS). The relatively small number of patients in our study hampered some analyses, as the impact of high-dose chemotherapy. Nonetheless, the data was prospectively collected, and it reflects current practices in MM, including just-approved

novel drugs.In summary, we achieved excellent outcomes in a recent cohort of patients with MM and have also shown the independent impact of anemia at diagnosis and the importance of such finding should be tested in a large cohort of patients.

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Metabolism-Associated Genes As Biomarkers and Potential Therapeutic Targets for Hyperdiploid Multiple Myeloma

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Introduction: Aberrant metabolism is a key hallmark of cancer. The recently available large-scale transcriptomic datasets in MM provide a different way to study metabolism-related genes by analyzing their expression. Therefore, the aim of our work was to analyze the alterations in the metabolic transcriptome of MM patients. **Methods:** We analyzed the transcriptome data of 619 MM patients (MMRF-CoMMpass cohort) and focus on the expression of 2753 metabolic genes (metabolic transcriptome) (acquired from Possemato et al., 2011). Non-negative matrix factorization was performed to define metabolic profiles. **Results:** We analyzed the metabolic transcriptome of normal B cell subpopulations (naive, centroblasts, centrocytes, memory, tonsillar plasma cells and bone marrow plasma cells) and plasma cells obtained from bone marrow samples of MM patients. Principal component analysis revealed that the metabolic transcriptome of plasma cells from MM clustered separate from normal B cell subpopulations, also indicating a great MM inter-patient metabolic transcriptome heterogeneity. MM patients were classified in six distinct metabolic groups each one showing a well-defined metabolic pathway affected and a clear association with the main cytogenetic alterations in MM. These results were confirmed in two other independent cohorts of MM patients. Interestingly, hyperdiploid patients were characterized by 2 different metabolic transcriptional profiles, defined as MM5 and MM6, as well as a significantly worse Progression Free (PFS) and Overall Survival (OS) for patients in MM5. A transcriptional analysis of patients MM5 (not restricted to metabolic genes) showed a significant enrichment of 1) pathways related to myeloid categories and myeloid progenitor cell markers, 2) dormant cell gene expression signature and 3) regulons showing transcription factors (TFs) related with myeloid cells differentiation, like CEPBE and NFE2, regulating the expression of specific metabolic, myeloid and dormant cells related genes overexpressed in MM5 group. Among these specific genes of MM5 group, we focused in two genes that regulate lipid metabolism, ACSL1 and ALOX5AP. We observed that the inhibition of ACSL1 and ALOX5AP genes by CRISPR-CAS9 decreased MM cell proliferation, underscoring their essentiality and highlighting their potential as promising therapeutic targets for the treatment of MM patients of MM5 group. **Conclusions:** We have demonstrated that MM patients have a different metabolic transcriptome than normal B cell subpopulations. MM patients also show a heterogeneous metabolic transcriptome, classifying them in 6 distinct groups, associated with specific MM genetic alterations. Among these 6 groups, we focus on MM5 hyperdiploid group that shows a poor prognosis related to its myeloid and dormant cells characteristics. Moreover, we have identified the metabolic genes ACSL1 and ALOX5AP as promising metabolic therapeutic targets for the treatment of MM patients in the MM5 group.

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Disrupting the Lysosome and Autophagy via PIKfyve Inhibition is a Potential Novel Therapeutic Approach in Multiple Myeloma

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Introduction: Sustainable immunoglobulin synthesis by plasma cells and multiple myeloma (MM) cells depends on intricate pathways that manage excessive unfolded or misfolded proteins, notably including autophagy. While autophagy regulation is critical for MM cell survival, the dependence of MM cells on this pathway underscores its potential for therapeutic intervention. One pivotal regulator of autophagy is PIKfyve kinase, which controls cellular functions including intracellular trafficking, lysosomal acidification and thus disrupts autophagy. Using tool compounds, we previously characterized the potent activity of PIKfyve inhibitors in 25 human myeloma cell lines (HMCLs) and > 100 ex vivo patient-derived primary samples. **Methods:** We synthesized new chemical entities with clinical potential starting from the novel PIKfyve inhibitor PIK001: ~10% of these meet criteria for further lead advancement. In vitro PIK001 activity was tested on the NCI60 cancer cell line panel and in multiple HMCLs as a single agent and in combination. To better dissect the mechanism of action of PIKfyve inhibitors in MM, isogenic PIK001-sensitive and resistant HMCLs were generated (KMS26, JJN3, and KMS11). Multi-omic characterization of the sensitive/resistant pairs was performed by whole genome, transcriptome, proteome and metabolome. Lastly, we evaluated the ex vivo downstream effects of 500nM of PIK001 for 16h in six primary MM patient samples through single cell RNA sequencing. **Results:** PIK001 and its analogues inhibit PIKfyve with exquisite selectivity and high potency. In addition to anti-MM activity, PIK001 demonstrated activity in B cell lymphomas and

AML, while sparing of normal blood mononuclear cells. Synergy in HMCLs was evident when combined with commonly utilized MM agents including cereblon binding IMiDs, selinexor, and venetoclax. Multi-omic characterization of the PIK001 resistant HMCLs showed a PIKFYVEN1939K kinase domain mutation (allelic frequency = 38%) in KMS26 resistant, also previously described in a resistant diffuse large B-cell lymphoma cell line. Alterations in gene expression of PIKFYVE and TFEB (a master regulator of autophagy) were identified in the other generated resistant lines. Furthermore, short exposure to PIK001 in the primary MM patient samples demonstrated an enrichment of genes associated to lysosomes and autophagy, as expected, as well as cholesterol homeostasis. Strikingly, we identified an increase in MHC Class I and II expression in the PIK001 resistant HMCLs and in the PIK001 treated ex vivo samples. **Conclusions:** Our findings confirm PIK001 and analogues as potent and specific PIKfyve inhibitors with clinical potential alone or in combinations. Targeting plasma cell biology has historically represented an important therapeutic strategy for the implementation of effective anti-MM therapies, and we propose targeting lysosomal biogenesis and autophagy as another promising approach.

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Mezigdomide (MEZI) Reverses T-cell Exhaustion (Tex) Through Degradation of Aiolos/Ikaros and Reinvigoration of Cytokine Production Pathways

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Introduction: Tex is characterized by a progressive decline in T-cell activation and proliferation and has been implicated as a major resistance mechanism of T-cell immunotherapies approved for multiple myeloma (eg. BCMA-directed T-cell engagers [TCEs]). Here, by using the CELMoD™ agent MEZI, we revealed that Aiolos/Ikaros contribute to the regulation of the Tex phenotype and their degradation reverses the negative impact on activation, proliferation, and tumor cell killing. **Methods:** Tex were generated ex vivo from healthy donors through rounds of CD3/CD28 Dynabead™ stimulations over 14 days, with unstimulated or transiently stimulated T cells (Tact) used for differential comparisons. Comprehensive genomic analyses were used to compare the 3 groups of T cells using RNAseq, ATACseq, whole genome bisulfite sequencing, and ChIPseq for Aiolos/Ikaros and histone modifications, ±MEZI treatment for 72 hrs. Cytokine/chemokines, exhaustion markers, and MEZI effect on Tex-mediating tumor cell killing with a BCMA TCE were also assessed. **Results:** After multiple rounds of stimulation, the viability of Tex remained over 90%, with proliferation decreased from 3–6-fold in initial stimulation to 1–1.4-fold in the last stimulation, as well as 98% reduction in IL-2 secretion. RNAseq showed proinflammatory cytokine expression from Tex was significantly downregulated vs Tact. Expression of exhaustion markers was significantly increased after initial activation, then maintained, and/or increased with further re-stimulations. MEZI treatment significantly downregulated PD1, TIM3, TIGIT, and upregulated proinflammatory cytokines/chemokines, cell surface interaction-related integrins, RAS signaling, and proliferation-related pathways. Gained or lost ATAC-seq peaks in Tex at promoters and distal sites were significantly correlated with gene expression changes from RNAseq, with the strongest effect seen at promoters. Canonical RUNX1/2/3 binding motifs were significantly enriched in the gained peaks in Tex vs Tact, with RUNX2/3 also showing increased mRNA expression. After MEZI, Tex-gained peaks were enriched with NFATC2 and RUNX3 binding sites whose gene expression levels were also increased. Enrichment analysis of the cis-regulated genes of the Tex-gained peaks after treatment highlighted biological processes related to cell-cell adhesion, cytokine production, and other T-cell activation processes. Notably, Ikaros motifs were enriched in the Tex-gained peaks after treatment. Tex cells had the highest expression of Ikaros. In co-cultures of Tex cells with BCMA-expressing tumor cells plus a BCMA TCE, MEZI treatment significantly enhanced Tex killing of tumor cells and reduced the BCMA TCE EC50 5–10-fold vs DMSO controls. **Conclusions:** MEZI-mediated degradation of Aiolos/Ikaros resulted in enhanced proinflammatory cytokine expression and reduction of exhaustion markers, and enhanced Tex killing of BCMA-expressing tumor cells in combination with a BCMA TCE. Previously presented at ASH 2023.

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MAF-Driven Metabolic Reprogramming Mediates H3K27 Hyperacetylation To Regulate Super Enhancer-Associated Genes

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Introduction: Overexpression of transcription factor MAF is found in about 50% of multiple myeloma cases and associated with the prognostically unfavorable t(14;16) translocation subtype. Genetic alterations can modify the epigenome through metabolite availability acting as substrates in histone modifications, but how this translates into specificities in gene regulation is unclear. **Methods:** We performed multi-omics analysis with mass spectrometry-based metabolomics, ChIP-sequencing and RNA-sequencing to understand the altered metabolic state and the underlying mechanism. Seahorse and various metabolic assays were used in validation experiments, and functional studies were performed. **Results:** Here, we report a novel involvement of MAF in metabolically-driven histone acetylation, including the superenhancer (SE) mark H3K27ac, through altering acetyl-CoA metabolism. To sustain a hyperacetylated chromatin state, MAF acquired the metabolic plasticity to induce high influx of glutamine through upregulating amino acid transporter SLC7A5, feeding metabolites into the tricarboxylic acid (TCA) cycle as acetyl-CoA sources. Systematic loss-of-function studies indicated that metabolic enzymes citrate synthase (CS) and ATP-citrate lyase (ACLY) are central to this process, and blocking citrate export from mitochondrial via CRISPR/Cas9 targeting of SLC25A1 synonymously abolished H3K27ac. Silencing of MAF displayed defective mitochondrial oxidative phosphorylation attributed to reduced metabolic flux through TCA cycle and downregulation of

electron transport chain complex I/II expression. ChIP-seq profiling of MAF oncogenic epigenome segregated by promoter- and SE-regulated genes revealed broad H3K27ac signal, H3K4me1 and chromatin accessibility overlapping with MAF-bound regions in cis-regulatory elements. Lastly, we identified novel MAF-regulated common SE genes across t(14;16) subtype by imposing stepwise filtering criteria on our published SE datasets and overlapping with MAF RNA-seq, leading to the prioritization of ZC3H3 for further investigation. Dependency experiments suggested that ZC3H3 is unconditionally required for t(14;16) myeloma cell growth and the robust abrogation of ZC3H3 could be pharmacologically achieved by targeting p300 histone acetyltransferase. **Conclusions:** Altogether, we delineated a non-canonical epitranscriptional role of MAF in connection to its altered metabolic state, and suggest metabolic disruptions or epigenetic modifiers as a new direction in t(14;16) myeloma therapy.

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A Novel Dual HDAC6 and Proteasome Inhibitor Elicits Outstanding Cytotoxicity Against Multiple Myeloma

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Introduction: Proteostasis is an important survival mechanism in multiple myeloma (MM) cells. Histone deacetylase 6 (HDAC6) is involved in the autophagy degradation pathway of malformed proteins. Our previous research highlighted indirubin-3-monoxime (I3MO) as a promising therapeutic agent for MM due to its ability to inhibit proteasome activity. Therefore, we synthesized a novel I3MO derivative, 8b, by coupling an HDAC6 inhibitor to the I3MO structure. **Methods:** The anti-MM effects of 8b both in vivo and in vitro were investigated. RNA-seq were performed to identify downstream pathway after 8b treatment. Autophagy and proteasome inhibition phenotypes were determined. Synergistic effect of 8b with bortezomib was tested both in vivo and in vitro. **Results:** The cytotoxicity of 8b was detected in both MM cell lines and MM patient samples. 8b also displayed cell cytotoxic effect on bortezomib (BTZ) resistance cell lines KMS11-BR. 8b treatment significantly induced the apoptosis and cell cycle arrest in MM cells in a dose and time dependent manner. Furthermore, treatment with 8b (6.25 mg/kg) caused a significant tumor reduction in myeloma murine model. RNA-seq analysis showed that 8b treatment led to down regulation of both proteasome and autophagy pathway in all four MMCLs. Decreased proteasome activities, specifically chymotrypsin-like (CT-L) and caspase-like (C-L) activities, were observed in ARP1 and U266 cell lines following 8b treatment. At the same time, Confocal microscopy analysis and flow cytometry analysis revealed a decrease in aggresome formation in MM cells with 8b treatment. After aggresome formation, it will further undergo degradation through downstream autophagy pathways. Consistent with our RNA-seq data, 8b treatment led to a decreased fraction of autophagosomes and suppressed autophagy level in MM cells. Furthermore, 8b significantly enhanced the sensitivity of MM cells to BTZ-induced apoptosis, indicating synergistic effects between 8b and BTZ in vitro. A xenograft myeloma murine model showed that the combination treatment group, consisting of 8b (6.25 mg/kg) and BTZ (0.5 mg/kg), synergistically suppressed tumor burden compared to treatment with either 8b or BTZ alone. Recent studies have suggested that bortezomib-induced autophagy is one of the mechanisms responsible for acquired drug resistance in MM cells. Interestingly, treatment with 8b efficiently suppressed autophagy induced by bortezomib in MM cell lines. These findings suggest that 8b synergistically enhances PIs cytotoxicity against MM by inhibiting the proteasome activity and suppressing the induced autophagy triggered by PIs. **Conclusions:** Our study demonstrated that novel dual HDAC6 and proteasome inhibitor 8b is an agent triggering dual inhibition of proteasome and autophagy, which represents a promising therapeutic strategy to improve patient outcomes in MM.

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Targeting Ubiquitin Pathway: Novel Therapeutic Approaches for Multiple Myeloma

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Introduction: Our submission highlights groundbreaking research at UB Therapeutics on cyclic peptides UB4A and CP15 for multiple myeloma treatment. These peptides target critical pathways, showing potent anti-tumor activity and potential against drug resistance. We'll detail their mechanisms and preclinical efficacy, offering hope for improved outcomes. Sharing at IMS aims to advance oncology and benefit patients globally. Keywords: Multiple Myeloma, Cyclic Peptides, UB4A, CP15, Therapeutics, Drug Resistance, Preclinical Studies. **Methods:** Our submission showcases UB4A and CP15, novel cyclic peptides for treating multiple myeloma. They target key pathways, combat drug resistance, and offer promising preclinical efficacy. Sharing at IMS advances oncology, benefiting patients worldwide. Keywords: Multiple Myeloma, Cyclic Peptides, UB4A, CP15, Therapeutics, Drug Resistance, Preclinical Studies. **Results:** In vitro studies evaluating the efficacy of UB4A and CP15 on multiple myeloma cell lines have demonstrated promising therapeutic potential. Treatment with both peptides exhibited notable efficacy, particularly in cell lines resistant to Bortezomib, a standard therapy for multiple myeloma. Furthermore, PK studies revealed favorable pharmacokinetic profiles for both peptides, with CP15 demonstrating no significant toxicity except at high doses, where a slight reduction in cell number was observed in normal cells. In vivo efficacy studies with UB4A revealed a significant attenuation in tumor growth, particularly in cell lines resistant to Bortezomib, with a remarkable 48% reduction in tumor size. Additionally, in vitro studies with CP15 exhibited even greater efficacy compared to UB4A, warranting further investigation through in vivo studies. These results underscore the promising

therapeutic potential of UB4A and CP15 as novel treatments for multiple myeloma, with the potential to overcome resistance to existing therapies and improve patient outcomes. **Conclusions:** In conclusion, the comprehensive characterization of UB4A and CP15 through a series of rigorous methodologies has provided valuable insights into their potential as promising therapeutic candidates for multiple myeloma. The successful synthesis and formulation of these cyclic peptides, coupled with their favorable pharmacokinetic profiles and demonstrated efficacy in preclinical models, underscore their promising therapeutic potential. These findings highlight the significance of UB4A and CP15 as innovative treatment modalities that hold promise for addressing the unmet medical needs of patients with multiple myeloma. Moving forward, further preclinical investigations and translational studies are warranted to validate and optimize these peptides for clinical development, ultimately advancing the landscape of multiple myeloma therapeutics and improving patient outcomes.

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Defining the Rates of Cytokine Release Syndrome Associated with Talquetamab Step-up Doses

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Introduction: Talquetamab (Talq) is a first-in-class bispecific T-cell engager antibody directed against G protein-coupled receptor class C group 5 member D (GPRC5D), approved to treat relapsed/refractory multiple myeloma (RRMM). In the MonumenTAL-1 study, an overall response rate was noted in 70% of patients with 23% achieving a complete response. Cytokine release syndrome (CRS) occurred during the step-up dosing phase at a rate of 77%; however, there was no breakdown by step-up dose (SUD). This study sought to characterize CRS rates after each Talq SUD in a real-world setting to discern whether patient hospitalization is required for the entire period of the step-up dosing schedule. **Methods:** In this retrospective study, patients with RRMM who received Talq between September 2023 and May 2024 were identified via the institutional plasma disorders database; patients were selected if they completed the step-up dosing phase for the weekly or biweekly dosing schedule. Chart review was performed to collect patient demographics, disease features, prior lines of therapy (LOT), start dates of Talq SUDs, and CRS onset/grades. The Chi-square/Fisher exact test was used to compare CRS rates after each Talq SUD. Differences in time to onset of CRS between the SUDs were compared using the Kruskal Wallis test. Logistic regression analysis was performed to assess the impact of prior exposure to T-cell redirection therapy (TCRT) on CRS incidence. All statistical analyses were performed in SPSS (version 29). **Results:** 36 patients completed the Talq step-up dosing phase; of whom 16 received the biweekly step-up dosing schedule. The median age was 65 years (range: 41-85 years), and 42% (n=15) were male. The median number of prior LOT was 7 (range: 4-16), and 69% (n=25) had prior TCRT. High risk cytogenetic features [t(4;14), t(14;16), t(14;20), TP53 mutations, del(17p) and 1q amplification] were present in 50% (n= 18) of patients. With an overall incidence of 77%, CRS occurred at a rate of 33% (n=12), 31% (n=11), 11% (n=4) and 6% (n=1) with SUD1, SUD2, SUD3 and first full dose (FFD, p=0.03), respectively. Pairwise comparisons revealed statistically significant differences in CRS rates between SUD1 and SUD3 (p=0.04), SUD1 and FFD (p=0.04) as well as SUD2 and FFD (p=0.04). Grade 2 CRS occurred in 6% of patients with SUD1, 14% with SUD2, 6% with SUD3 and 0% with FFD (p=0.40). Logistic regression analysis indicated no association between prior exposure to TCRT and CRS incidence (OR: 0.62, 95% CI: 0.13-2.60; p=0.61). The median time to onset of first CRS event was 20 hours (range: 11-40 hours), 13 hours (8-34 hours), 28 hours (24-31 hours) and 31 hours with SUDs 1, 2, 3 and FFD (p=0.33), respectively. **Conclusions:** Our real-world data indicated that the Talq FFD was well tolerated, characterized by a significantly low incidence/severity of CRS events. Reducing length of hospital stay with the Talq step-up dosing schedule, and administration of Talq FFD in outpatient settings could be considered in clinical practice.

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Pygo2 Is Overexpressed in Myeloma Cells With 1q21 Amplification Being Involved in Carfilzomib Resistance

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Introduction: Copy number alteration (CNA) of the 1q21 region (1q21+) is one of the most frequent cytogenetic abnormalities in Multiple Myeloma (MM) patients. The presence of 1q21+ in MM cells is associated with a shorter progression-free survival in MM patients particularly in those treated with Bortezomib and Carfilzomib (CFZ)-based regimens. Therefore, the identification in the 1q21 region of druggable targets is an emerging unmet medical need in MM patients for a personalized approach. **Methods:** In this study firstly, we evaluated purified CD138+ bone

marrow (BM) plasma cells (PCs) from 18 newly diagnosed MM (MMD) patients. All the patients underwent fluorescence in situ hybridization (FISH) analysis to detect 1q21 CNA in 1q21 region. The expression profile of all samples was generated using GeneChip ClariomD arrays (Affymetrix Inc.). The Sam R package was used to identify differentially expressed genes between the 1q21+ and control samples. Thereafter we evaluated the expression levels of the identified targets genes by RT-PCR in a validation cohort of MMD (n°=22) and relapsed-refractory MM (MMRR) (n°=29) with or without 1q21+ and in CFZ-resistant human myeloma cell lines (HMCL) (CFZ-R). Finally, we generated a knockdown (KD) gene system by shRNA lentivectors in HMCLs. **Results:** Among the possible targets genes in 1q21 region we observed a significant upregulation of PYGOPUS2 (PYGO2) in 1q21+ MM patients compared to controls. PYGO2 is a gene belonging to Wnt signaling and involved in tumor progression and drug resistance, by promoting a downstream target, as drug resistance polypeptide 1 (MDR1,) in several solid cancers. However, the expression profile of PYGO2 in MM patients and its potential role in CFZ resistance are still unexplored. Interestingly, we observed a positive correlation between PYGO2 and the copy number of the 1q21 region. In a validation cohort, we found overexpression of PYGO2 in patients with MMD and MMR 1q21+ compared to controls (MMD w/o 1q21). MDR1 expression is also upregulated in patients with MMD 1q21+ and even more so in MMR 1q21+, confirming the relationship between MDR1 and drug resistance. Interestingly, we found a significant positive correlation between PYGO2 and MDR1 expression levels in both MMD and MMR patients. Accordingly, we generated a JJN3 PYGO2-KD cell line and downregulation of PYGO2 led to reduced cell viability and significantly reduced MDR1 expression. In parallel, in CFZ-R HMCL, we noted that PYGO2 and MDR1 were upregulated compared to CFZ-sensitive HMCL. To translate in a clinical perspective, we develop a specific chemical inhibitor of PYGO2 (JBC117) to test in vitro and ex vivo on primary mononuclear cell of MM patients. **Conclusions:** These results show, for the first time, that PYGO2 is overexpressed in 1q21+ MM patients and that the PYGO2-MDR1 axis can be involved in CFZ resistance in MM cells, suggesting that PYGO2 could be a potential drug target for MM patients with 1q21+.

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Alternative Splicing and Non-Homologous End Joining Pathways Are Vulnerabilities Associated With Loss of The Tumor Suppressor TENT5C in Myeloma

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Introduction: Loss of the tumor suppressor gene TENT5C through mutation or deletion occurs in more than 20% of newly diagnosed MM patients and is associated with poor progression-free and overall survival. Here we sought to identify synthetic lethal targets related to the loss of TENT5C in MM cells. **Methods:** We generated knock-out (ko), knock-in (oe), and ko-rescue of TENT5C in MM cell lines. Modified cell lines were compared to their original counterparts. Targeted and high-throughput drug screens (HTS) were performed to identify vulnerabilities related to TENT5C loss. **Results:** Cell growth analysis showed that TENT5C-null cells had a higher growth rate than TENT5C-positive cells (Day 4, KMS11ko 6.7x105cell/mL vs. 5.1x105cell/mL KMS11wt, p< 0.001). Cell cycle analysis indicated that TENT5C-null cells had an increased G2/M population compared to TENT5C-positive cells (H929 TENT5C-/- 8.22% vs. TENT5Coe 1.18%, p< 0.001). Consistent with TENT5C tumor suppressor function, loss of TENT5C induced an enhanced cell proliferation and cell cycle progression. Given our prior data indicating an increase in alternative splicing (AS) abnormalities and non-homologous end joining (NHEJ) activation in TENT5C-/- patient samples, growth inhibition assays were performed. The AS inhibitors pladienolide B and isoginkgetin affected TENT5Cko cells at lower concentrations than TENT5Cwt cells (U266 TENT5Cko GI50=0.5 vs. TENT5Cwt GI50=1.4 nM, U266 TENT5Cko GI50=7.0 vs. TENT5Cwt GI50=13.7 µM, p< 0.001, respectively), as did NHEJ inhibitors STL127705 and NU7441 (U266 TENT5Cko GI50=22.5 vs. TENT5Cwt GI50=62.5 µM, U266 TENT5Cko GI50=9.5 vs. TENT5Cwt GI50=16.6 µM, p< 0.01). In parallel, when the same drug targets (SF3B1 and KU70) were individually silenced using targeting siRNA-pools, TENT5Cko cells had a higher growth inhibition than TENT5Cwt cells (KMS11 TENT5Cwt 3.8 vs. TENT5Cko 13.8%, KMS11 TENT5Cwt 9.7 vs. TENT5Cko 24.9%, p< 0.001, respectively). Moreover, AS analysis of RNAseq data identified on average 37% more events in TENT5Cko vs TENT5Cwt compared to TENT5Coe vs TENT5Cwt cells. Particularly, more intron retention events (dPSI >0) in TENT5Cko vs TENT5Cwt (N=628, Log2FC=1.3, p=0.1) were observed indicating the enhanced intron retention activity in TENT5C-null cells. Furthermore, GSEA of proteomic data showed decreased AS and cell cycle progression and increased DNA damage checkpoint signaling in TENT5Crescued compared to TENT5CKO cells. In addition, a HTS using the LOPAC1280 library identified several hits specifically affecting TENT5Cnull cells. We found that the top enriched hits in LOPAC1280 drug classes targeted cell proliferation (57.14 %) followed by DDR pathway targets (45.16%). The same trend observed in all results was validated in the other modified cells to ensure TENT5C specificity. **Conclusions:** Our results indicate a tumor suppressor role of TENT5C in MM, with antiproliferative properties and susceptibility to AS and NHEJ inhibitors.

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YM155 Exerts Anti-Myeloma Effects via Myc/BBC3 Signaling Pathway in Vitro

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Introduction: Our previous studies have demonstrated a strong link between Myc rearrangement (Myc-R) and poor prognosis in

newly diagnosed multiple myeloma (NDMM). Survivin inhibitor YM155, a novel small molecule, is currently under clinical investigation in aggressive B cell lymphomas with Myc translocation. However, its effects on myeloma cells remain unclear. This study aims to explore the anti-myeloma mechanisms of YM155 in vitro through cell-based experiments. **Methods:** In vitro, six MM cell lines (AMO-1, MM.1S, RPMI-8226, NCI-H929, U266, and KMS-11) were treated with YM155 to determine IC50 using CCK8 method. Cell apoptosis was detected by flow cytometry. RNA sequencing was performed on MM.1S and RPMI-8226 cells treated with YM155 to identify relevant regulatory pathways. Protein-protein interaction and transcription factor target prediction analyses were conducted to predict interactions between proteins and the binding sites of Myc and target genes. The identified regulatory pathways were validated with qPCR and Western blot (WB). **Results:** The IC50 of YM155 in various MM cell lines ranged from 2.5 to 15 nM, which was similar to that of bortezomib. YM155 demonstrated a time- and dose-dependent inhibition of cell proliferation and apoptosis, significantly downregulating Myc mRNA expression and protein levels. The combination of YM155 and bortezomib showed superior cell-killing effects compared to single-agent, suggesting a synergistic effect. RNA sequencing indicated that Myc expression was suppressed and P53 signaling pathway was activated after YM155 treatment. This was confirmed by RT-qPCR and WB, which showed activation of pro-apoptotic protein BBC3 and inhibition of anti-apoptotic protein BCL2. JASPAR bioinformatic analysis predicted that Myc might inhibit BBC3 expression by binding to its promoter region, thereby activating the P53 pathway. Additionally, the IC50 of YM155 in bortezomib-resistant cells was similar to that in non-resistant cells. **Conclusions:** YM155 exhibits in vitro anti-myeloma activity in a concentration- and time-dependent manner and has a synergistic anti-tumor effect with bortezomib, reversing resistance to some extent. YM155 exerts its anti-myeloma effects by inhibiting Myc and upregulating BBC3 expression, which activates the P53 pathway. This provides a potential evidence for the treatment of high-risk/relapsed refractory MM.

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Dual Targeting of the RAS-MAPK Pathway as a Personized Medicine Approach in RASMut Multiple Myeloma

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Introduction: Targeting RAS mutations has proven to be a successful treatment strategy in various cancers. In multiple myeloma (MM), RASMut are common but have not been targeted. Previous research has identified MAP4K2 as a potential therapeutic target in RASMut MM (Li et al., Blood 2021). Inhibition of MAP4K2 (MAP4K2i) has been shown to slow down cell growth and reduce critical transcription factors such as IKZF1/3, BCL-6, and c-Myc. Another target in the RAS-MAPK pathway is MEK, and its inhibition (MEKi), has shown effectiveness in patients with BRAFV600E mutated MM, when used with a BRAF inhibitor (Giesen et al., Blood 2023). The potential of simultaneously targeting MAP4K2 and MEK to enhance anti-MM effects and counteract resistance mechanisms is a promising avenue for further exploration. **Methods:** The combined effects of dual kinase inhibition were studied using an inducible knockdown system, tet-on sh-MAP4K2 lentivirus transduced in RASMut MM1.S cells. After doxycycline-induced MAP4K2 knockdown, cells were treated with various concentrations of MEKi trametinib for five days and then analyzed for proliferation, apoptosis, and cell cycle. Additionally, RASMut H929 cells were treated with a combination of trametinib and different MAP4K2i (TL4-12, NG25 and BAY61-3606), followed by proliferation, apoptosis, and cell cycle assays. The effects on the downregulation of target proteins were assessed via western blot assay for combination of trametinib with either shMAP4K2 or MAP4K2i. **Results:** The data showed that cell proliferation significantly decreased when MAP4K2 silencing was combined with MEKi (MEKi alone vs. with shMAP4K2: 32% vs. 10%, $p< 0.01$) and apoptosis increased (MEKi alone vs. with shMAP4K2: 8.1% vs. 80.8%, $p< 0.01$). The cell cycle assay demonstrated that MEKi induced G1 arrest in RASMut MM cells (MEKi alone: 76% vs. control: 54%, $p< 0.01$) and was further increased by combination with shMAP4K2 (92%). Western blot assay confirmed significantly enhanced IKZF1, c-Myc, and IRF4 downregulation by dual inhibition compared to either kinase inhibition alone. The enhanced anti-MM effects could also be demonstrated for various MAP4K2i. Drug combination of MEKi with either TL4-12 or NG25 led to decreased viability (MEKi vs. combination: 70.7% vs. 36.8%) of H929 cells as well decreased proliferation rate (MEKi vs. combination: 89.0% vs. 18.9%, $p< 0.01$). Additionally, western blot assay showed increased downregulation of target proteins ERK1/2 and MEK1/2 and their phosphorylation and transcription factors IKZF1/3 and c-Myc when H929 cells were treated with MEKi in combination with MAP4K2i. **Conclusions:** Our data lay the foundation for personalized treatment of RASMut MM patients, particularly relevant for patients who have failed immunotherapy. The synergistic treatment approach of targeting MAP4K2 and MEK in RASMut MM warrants further investigation in an in vivo setting to validate our findings and potentially translate them into clinical practice.

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Inhibition of Telomerase and the Alternative Lengthening Telomere Pathway Induces Cell Death in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is an incurable blood cancer with a complex and diverse genetic makeup. It involves numerous genetic changes such as mutations, structural

rearrangements, and variations in the number of copies of genes. These genetic alterations can be detected at different stages, from the pre-malignant conditions of monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) to clinically overt MM. Telomeres, the protective caps at the ends of chromosomes, are regulated by an enzyme called telomerase. In MM, telomerase activity is present in 90% of newly diagnosed and relapsed patients. Patients with MM have dysfunctional short telomeres at diagnosis and during disease progression, along with high levels of telomerase activity. These data indicate that telomerase or the alternative lengthening of telomeres (ALT) may safeguard critically short telomeric DNA in MM patients. **Methods:** Understanding the importance of telomere maintenance in MM, we investigated the impact of inhibiting telomerase and ALT on MM cell viability. The MM cell line RPMI 8226 (CRM-CCL-155™) was treated with the telomerase inhibitor BIBR 1532 (200 μM) and the ALT inhibitor Trabectedin (4nM) to evaluate whether telomerase and ALT inhibition lead to cell death in MM. The inhibitors were administered individually, simultaneously, and consecutively (BIBR followed by Trabectedin and Trabectedin followed by BIBR). Cell viability was monitored every 24 hours using a trypan blue exclusion assay over 144 hours. **Results:** The findings indicate that telomerase inhibition with BIBR 1532 resulted in a rapid decline in cell viability in RPMI 8226 after 24 hours. This effect intensified over time and reached its peak at 144 hours post-treatment, with cell viability dropping to below 5%. Inhibition of ALT using Trabectedin alone led to a gradual decrease in cell viability, indicating a time-dependent mechanism of action. The maximum inhibition of cell viability was observed 96 hours after treatment, with less than 5% viable cells remaining. Simultaneous treatment with BIBR 1532 and Trabectedin showed a rapid decrease in cell viability after 24 hours, similar to BIBR 1532 alone. Maximum inhibition was reached 72 hours after treatment (below 5% cell viability). Consecutive inhibition of telomerase and ALT (72 hrs of BIBR + 72 hours of Trabectedin) showed a gradual decrease in cell viability. Maximum cell viability inhibition reached 144 hours after treatment (below 5% viable cells). Remarkably, every drug combination decreases cell viability to about ~5% after 144 hours, indicating that MM is highly sensitive to telomerase and ALT inhibition. **Conclusions:** The results suggest that the MM cell line RPMI 8226 is most susceptible to the simultaneous inhibition of telomerase and ALT. This research represents a new opportunity for the future treatment of MM.

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Activation of the FOXO3/GSDME Axis to Overcome Bortezomib Resistance for the Treatment of Myeloma via Pyroptosis

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Introduction: Proteasome inhibitors including bortezomib are the major drugs in the treatment of multiple myeloma (MM) but its resistance is frequently seen in MM patients owing to mutations or overexpression of the target genes mainly including PSMB5. Overcoming such resistance is urgent. Pyroptosis is a novel form of programmed cell death different from apoptosis. Induction of pyroptosis has been proposed as a novel strategy to overcome chemoresistance or sensitize cancer cells to certain treatments. However, it is not well known in MM. **Methods:** Bioinformatical analysis was used to find significant genes altered in MM and patient outcomes; Luciferase assays and ChIP was used to identified transcription factor; Luciferase-based drug screen was performed to identify specific activators of GSDME. Xenografts in nude mice was used to evaluate in vivo efficacies. RNA sequencing was performed to identify latered genes in FOXO or corylin treated MM cells. **Results:** GSDME, a major executor of pyroptosis, is strikingly downregulated in MM cells and its low expression predicts poor prognosis of patients with MM. Moreover, we find that FOXO3 is a putative transcription factor of GSDME. By binding to the recognition elements (PREs) in the promoter region of GSDME, FOXO3 promotes GSDME transcription. Similar to GSDME, FOXO3 is also downregulated in MM cells. Enforced expression of FOXO3 activates GSDME via caspase-3 therefore promoting MM cell pyroptosis and suppressing myeloma tumor growth in mice. Furthermore, by screening a library of natural products, we found corylin, a flavonoid derived from Psoralea Fructus, activates the transcription of both FOXO3 and GSDME. As expected, corylin prefers to induce pyroptosis of MM cells expressing GSDME. Corylin displays potent anti-MM activity in association with pyroptosis by upregulating FOXO3 and GSDME in nude mice without overt toxicity. Moreover, RNA sequencing revealed that overexpression of FOXO3 and corylin treatment led to striking downregulation of the subunit proteins in the proteasomes, including PSMB1, PSMB2, and PSMB5, responsible for proteolysis in proteasomes. Furthermore, pretreatment with a low concentration of corylin markedly sensitized K562, a resistant cell line with a high level expression of PSMB5, to bortezomib, in association with pyroptosis. **Conclusions:** Loss of FOXO3 and GSDME is unfavorable for MM and activation of the FOXO3/GSDME axis could be a promising novel strategy for the treatment of MM and sensitization of resistant cells to bortezomib.

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Targeting HVEM Using a Monoclonal Antibody Shows Therapeutic Promise in Multiple Myeloma

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Introduction: Identifying novel targetable molecules in relapsing patients is an unmet clinical need in multiple myeloma (MM). We previously reported that the oncolytic herpes simplex virus 1 (HSV-1) can infect and kill MM cells via binding to HVEM

(TNFRSF14) expressed on MM cells. HVEM is also present on different immune cells and, along with several other ligands, mainly, B- and T-lymphocyte attenuator (BTLA), plays a pivotal immunomodulatory role by regulating T cell activation. We also showed that the expression of HVEM increased on the T cells of multi-relapsing patients and that silencing HVEM in MM cell lines decreased their growth. Building on these findings, we decided to therapeutically target HVEM in MM. **Methods:** Human MM cell lines and MM patient samples were studied for their HVEM expression using flow cytometry and gene expressing profiling of datasets that include large cohorts of newly diagnosed MM patients (MMRF CoMMpass Study). Different unique anti-human HVEM monoclonal antibodies (mAbs) were generated and based on their sequence, some were selected to produce murine-human chimeric mAbs. In vitro and in vivo functional studies led us to the selection of a final candidate (aHVEM17), which was fully humanized for subsequent experiments. The tissue specificity of aHVEM17 was studied in healthy and tumor human tissues using imaging mass cytometry (IMC). The anti-MM effect of aHVEM17 was then studied both in vitro and in vivo. **Results:** While MM cell lines showed varying levels of expression, HVEM was consistently highly expressed on CD138+ cells of all the studied MM samples without showing any genetic gain and loss. Among the anti-HVEM mAbs generated, aHVEM17 had a high binding affinity (KD= 1.30E-08 M). aHVEM17 binding was specific to BM as evidenced by IMC. In vitro ADCC experiments using MM.1S showed potent ADCC activity of aHVEM17 (10 µg/mL) against healthy donor (HD) NK cells (p=0.0046), which was comparable to that of the standard-of-care Daratumumab (Dara) (p=0.0024). In vivo experiments in nude mice (locally engrafted) and NSG mice (intravenously engrafted) with MM.1S cells showed that the i.v. injection (b.i.w.) of aHVEM17 (5 mg/kg) was able to significantly increase the median survival time from 15 days to 22 days in nude mice (p=0.0147) and from 31 days to 49 days (p< 0.0001) in NSG mice, compared to control IgG. aHVEM17 showed an advantage over Dara as evidenced by significantly less fratricide in NK cells at 24 and 48 h of treatment (10 mg/mL) (p< 0.0001 and p=0.0016, respectively). Furthermore, a HVEM: BTLA inhibitor screening assay revealed that aHVEM17 can block such interaction in a concentration-dependent manner. **Conclusions:** aHVEM17 is the first humanized mAb against HVEM capable of inducing potent anti-MM effects thorough NK-mediated ADCC. We are currently evaluating the activity of HVEM, alone or in combination with CAR-T cells, as a possible checkpoint inhibitor for the treatment of MM, the results of which will be presented at the meeting.

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Vaccinating Against Mutated RAS in Multiple Myeloma: The Phase I/II TG01 Study

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Introduction: RAS mutations are found in approximately 50% of newly diagnosed multiple myeloma (MM) patients with increasing prevalence as the disease progresses. RAS mutations are also present at the smoldering stage and may be one of the key drivers of the disease. TG01 is an injectable cancer immunotherapy consisting of a mixture of seven different synthetic peptides that mimic fragments of mutant forms of the human RAS protein. The peptides that make up TG01 are identical to peptides derived from single-base substitutions on codon 12 or 13 commonly found in MM patients. TG01 has previously been tested in phase I/II studies in patients with pancreatic cancer with a very tolerable safety profile and high levels of immunological responses. TG01 can be administered with QS-21 as an adjuvant. **Methods:** The TG01-study is an academic, single-arm, open-label, phase I/II study evaluating vaccination with TG01/QS-21 as single agent in patients with KRAS or NRAS codon 12/13 mutation and either MM with measurable disease following at least one previous line of therapy or high risk smoldering MM (HR SMM). The primary endpoint is safety and tolerability of TG01/QS-21. Secondary endpoints include response according to IMWG criteria, immunological response to the vaccine defined by the TG01-spesific cytokine production as well as the size of the RAS-mutated clone before and after completing study treatment and/or at progression. 20 patients will be included an receive TG01/QS-21 0,7 mg SC Q2W for the first 12 weeks followed by Q2M until week 52 for a total of 12 doses. Patients will be screened for RAS mutations and only included if they have one of the seven mutations that are targeted by the TG01 vaccine. **Results:** As of May 7, 2024, 37 patients have been screened and 9 patients have been included from the time of study initiation May 31, 2023. The first 7 patients were included in a safety cohort and followed for a minimum of 30 days from treatment initiation before enrollment could continue. 3/9 patients have HR SMM and 6/9 patients have MM. No patients have developed > 3 adverse events (AEs). A total of 3 patients have had an AE considered definitely related to the study medication, including local skin reaction (n=2) or pain in arm (n=1) around the site of vaccine administration, all grade 1. One patient developed chills considered possibly related to study medication, also grade 1. No other AEs have been considered related to the study medication. There has been no objective response to the vaccine and 6/9 patients have progressed with a median time to progression of 2 months. 3 patients are still on study and have stable disease with a median of 5 treatment cycles started (range 4-9). **Conclusions:** Preliminary data suggest that TG01/QS-21 has a very tolerable safety profile. No objective responses have so far been observed, but 3/9 subjects remain on treatment with stable disease and enrollment is continuing. The first analyses of the immunological responses are being performed in Q2 2024.

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Impact of Novel Therapies on the Overall Survival of Patients With Multiple Myeloma Over the Past Two Decades: A Real-Life Single-Center Study

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Introduction: The gradual introduction of numerous therapeutic advancements over the last two decades in the treatment of patients with multiple myeloma (MM) has contributed to a significant improvement in overall survival (OS), although it remains an incurable disease. This study aims to analyze the evolution of OS in MM patients treated at our hospital from 2000 to the present and the impact following the incorporation of various drugs into induction treatment regimens. **Methods:** We conducted a single-center retrospective observational study, including all MM patients treated at the University Hospital of Jerez de la Frontera (Spain), diagnosed between January 1st, 2000, and December 31th, 2022. Patients were divided into three calendar periods (2000-2007, 2008-2015, 2016-2022). We analyze the incorporation of proteasome inhibitors (Pis), immunomodulators (IMIDs) and anti-CD38 monoclonal antibodies to the first line of therapy either as single agents or in combination. The corresponding approval from the ethics committee has been obtained. For the statistical analysis, the R statistical software (v4.3.3; R Core Team 2021) was used. **Results:** 420 myeloma patients were included in the study, with a median age of 64 years. Median survival steadily improved from 50.72 months (33.88 – 73.22; 95% CI) in 2000-2007 to 72.46 months (57.5 – 98.2; 95% CI) in 2008-2015, and has not yet been reached in the 2016-2022 cohort (p= 0.008). If we compare the group of patients who received chemotherapy to those who did not receive it (and therefore received other treatments), the median overall survival was 64.60 months (52.07 - 75.75; 95% CI) and 99.53 months (72.46 - 139.34; 95% CI), respectively (p=0.011). All incorporated drug families increased that survival. The introduction of Pis improved the OS to 78.84 months (68.84 - 113.32; 95% CI) (p=0.049). The median OS of the patients treated with IMIDs or antiCD38 has not been achieved yet (p< 0.0001 and p=0.011, respectively). The improve in the OS was more dramatic in the trasplant elegibily patients. The group of patients who underwent autologous transplantation had a median overall survival of 132.66 months (113.32 - 150.98; 95% CI) compared to 38.81 months (31.57 - 51.61; 95% CI) in the non-transplanted patients. **Conclusions:** In our patient cohort, an increase in overall survival is observed in each time period. The incorporation of both proteasome inhibitors, immunomodulators, and anti-CD38 showed significant differences in terms of overall survival. Additionally, autologous hematopoietic stem cell transplantation continues to be the main consolidation therapy, with very significant differences between the groups of patients who underwent this procedure and those who did not.

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Brazilian Relapsed Refractory Multiple Myeloma Patients Treated with Teclistamab Outside of Clinical Trials as an Expanded Access Program

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Introduction: Teclistamab (TEC) was the first BCMA-targeting bispecific antibody approved in Brazil in March 2023. Between November 2022 and February 2023 triple-class relapsed / refractory myeloma (RRMM) patients had access to TEC through Expanded Access Program (EAP). Herein we described efficacy and safety of TEC for Brazilian RRMM outside of clinical trials in the EAP. **Methods:** Participants must have been triple-class exposed/ refractory (PI, IMiD and anti-CD38 therapies) and have received at least one dose of TEC. We collected retrospective data about demographics, previous therapies and refractoriness, as well as disease characteristics. Prospectively, data were focused on response, safety and adverse events of interest, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity (ICANS), use of tocilizumab and immunoglobulin (IVIG), and infections. **Results:** We included 27 RRMM patients (pts) from 6 states in Brazil, covering three of five regions in the country. Patients were mostly male (60%) with a median age of 59 years (39-77y) and had a median of 4 (2-8) previous treatments with 87% of patients being refractory to their last line of therapy. All pts were triple-class exposed and over 80% triple-class refractory. Patients not represented in Majestec-1 were included, such as dialysis-dependent patients. Regarding high-risk cytogenetics, 82% of patients did not have cytogenetics by FISH immediately prior to TEC. Only 12% of pts had been previously treated with another BCMA-targeted therapy (2 cases with belantamab mafodotin and another one with CAR-T ide-cel). Regarding response, the overall response rate was 48% (11% complete responses and 34% very good partial responses) and the median overall survival was 14.2 months. CRS occurred in 69% of pts, mostly grade 1 (54%), with 15% of grade 2 CRS and tocilizumab prescription. ICANS was rare, reported as grade 2 just in only 1 patient (4%). Infections occurred in 73% of pts (15% grade 3 or higher), especially during the first 6 months of therapy. Two pts died because of severe bacterial infections during the first months of TEC. IVIG was supplemented for most cases, covering 55% of patients between zero and 3mo and achieving 90% at 6mo of TEC. The most common cause of death was disease progression (13 pts), most of them without any subsequent treatment (7/13). Subsequent therapies of the remaining 6 pts included recycling agents (IMiD, PI and/or anti-CD38; 3 pts) talquetamab (1 pt) or pomalidomide-based regimens (2 pts). **Conclusions:** Our study is the first analysis of any BsAb treatment for Brazilian RRMM patients outside of

clinical trials. We included pts not represented in Majestec-1 study, such as dialysis-dependent patients, reinforcing the efficacy and safety of this therapy even for this difficult to treat population. A broader collection of data from real-world cases in Latin America is eagerly needed, as well as longer follow-up times for responders.

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Targeting Tryptophan Metabolism in Multiple Myeloma Offers Novel Therapeutic Approach

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Introduction: Multiple myeloma(MM) cells are critically dependent on the bone marrow microenvironment(BME) for survival. We have previously shown that a key pro-survival interaction is MM engagement with the dendritic cells(DCs) in the BME, leading to the production of the highly immunosuppressive enzyme indoleamine 2,3-dioxygenase 1(IDO1) by DCs. IDO1 catabolizes tryptophan (TRP) ⇒ kynurenine (KYN), and this depletion of TRP in the ME suppresses T cell activation. KYN is a ligand for transcription factor aryl hydrocarbon receptor(AHR) that induces essential pro-survival programs in MM. Below we have made the novel observation that MM cells can catabolize TRP⇒KYN independently through upregulation of tryptophan 2,3 dioxygenase(TDO). High TDO expression was correlated with poor clinical outcomes in MM patients; direct TDO inhibition caused MM cell death. These findings suggest that understanding how MM cells metabolize TRP could identify novel treatment targets that may also abrogate the immunosuppressive ME. **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⇒KYN enzymes with western blot and qPCR. 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. Viability was measured through flow cytometry. AHR activation was measured through qPCR of its downstream target CYP1a1. KYN production was measured by ELISA. **Results:** MM cells produce KYN in monoculture, indicating they produce TRP⇒KYN enzymes directly. MM cells do not express IDO1, but three of our four cell lines (8226, MM1S and KMS11) expressed the tryptophan metabolizing enzyme TDO. CoMMpass patients with the highest quartile of TDO expression have significantly lower rates of progression-free and overall survival. In vitro pharmacological inhibition or shRNA knockdown of TDO led to reduced cell viability and growth in all TDO+ cell lines but not the TDO- cell line U266. TDO inhibition led to reduced production of KYN and reduced expression of AHR downstream target CYP1a1. Co-culture with dendritic cells was only able to partially protect MM cell viability and restore KYN production from TDO inhibition. **Conclusions:** TRP metabolism has a central role in MM cell survival and we have made the novel observation that MM cells can metabolize TRP independently through the expression of TDO. TDO expression is linked to patient survival. We predict that the depletion of TRP could repress anti-MM T cell activity and production of KYN could directly support MM survival through AHR activation. TDO upregulation may be one mechanism by which MM cells become independent of the BME, which clinically heralds highly treatment-refractory disease. Understanding the pro-MM survival roles of the TRP metabolizing enzymes could lead to novel therapies that directly target the MM cell and reverse the immunosuppressive ME, leading to better responses to immunotherapy.

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Elucidating the Kinase-Independent Autoregulatory Loop of PIM2 in Multiple Myeloma

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Introduction: PIM2, an oncogenic serine/threonine kinase, is significantly overexpressed in multiple myeloma (MM), correlating with disease progression and poor prognosis. Our laboratory has identified a novel kinase-independent (Ki) function of PIM2 that may play a crucial role in maintaining its own expression and promoting MM cell survival. Preliminary data suggest that PIM2 can autoregulate its expression through a feedback loop involving the transcription factor MYC, a mechanism potentially critical for MM pathogenesis and resistance to existing therapies. **Methods:** To investigate the potential mechanism of PIM2 Ki autoregulation in MM cell lines, we utilized luciferase reporter assays, chromatin immunoprecipitation (ChIP), and pharmacological inhibition of PIM2. Luciferase assays were performed using the full-length PIM2 promoter to assess transcriptional activity in response to PIM2 Ki inhibitors (JP1 and JP2) and a PIM2 kinase-dependent (Kdep) inhibitor (AZD1208). Sequential promoter truncation luciferase assays identified the minimal promoter region for PIM2 expression. Site-directed mutagenesis was used to identify critical cis-regulatory elements (CREs) regulating PIM2 kinase-independent expression. ChIP-qPCR was employed to evaluate MYC occupancy at the PIM2 promoter under different PIM2 inhibitor treatments. **Results:** Luciferase assays revealed a significant decrease in PIM2 promoter activity upon treatment with the PIM2 Ki inhibitor JP1, but not with the Kdep inhibitor AZD1208. Sequential promoter truncation luciferase studies identified a region of approximately 2000 base pairs regulating PIM2 expression. Single base pair mutation using site-directed mutagenesis revealed a single SP1 binding site regulating PIM2 kinase-independent autoregulation. ChIP-qPCR demonstrated enrichment of MYC at the PIM2 promoter, which was disrupted by JP1 treatment and increased by AZD1208 treatment. Furthermore, pharmacological inhibition of MYC using the small molecule inhibitor 10058-F4 resulted in decreased PIM2 protein levels, similar to the effects of JP1 and JP2. These findings suggest that MYC may directly bind to the PIM2 promoter and complex with SP1, facilitating a PIM2 Ki autoregulatory loop that maintains aberrant PIM2 overexpression in MM cells. **Conclusions:** Our

preliminary data support the hypothesis of a novel PIM2 kinase-independent autoregulatory mechanism involving MYC and SP1 in MM. Disruption of this potential PIM2 Ki autoregulatory loop using selective inhibitors (JP1 and JP2) decreases PIM2 expression and promoter activity, suggesting it as a potential therapeutic target. Further investigation into the specific cis-regulatory elements and binding sites governing PIM2 Ki autoregulation may uncover new vulnerabilities to exploit in MM treatment.

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Novel Whole-Genome DNA-Damage Functional Screen Identifies Drivers of DNA Damage in Multiple Myeloma

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Introduction: DNA breaks are one of the most deleterious lesions caused by various genotoxic mechanisms. If DNA breaks are not accurately repaired before mitosis, they can lead to genomic rearrangements and instability. We hypothesized that genes contributing to increased DNA breaks can drive genomic instability and clonal evolution in myeloma (MM). To identify such genes, we developed a genome-wide screen to investigate the impact of gene modulation on expression of γ-H2AX (a marker for DNA breaks). **Methods:** We used a whole genome lentiviral expression library from Broad Institute containing 17,255 ORFs representing 12,728 genes. MM cell lines (U266 and JIM3) were transduced (in triplicate), selected in puromycin, cultured, fixed and stained using a fluorescent γ-H2AX antibody. Cells with high levels of DNA breaks were sorted via FACS and DNA sequenced to identify which ORFs induced DNA breaks. **Results:** Overexpression of 226 ORFs significantly associated with increased DNA breaks in both MM cell lines. The enriched ORFs were predominantly involved in one of the 6 different functions: 1) Serine/threonine-protein kinases including calcium/calmodulin-dependent protein kinases; 2) Cell cycle cyclin-dependent kinases and phosphatases; 3) Cytoskeleton, chromosome maintenance and mitosis/cytokinesis related proteins; 4) DNA repair and recombination proteins; 5) RNA helicases, and proteins involved in RNA processing, splicing and degradation; 6) Monooxygenases involved in metabolic detoxification of xenobiotics. In a clinical dataset (GSE24080; n=559), high expression of 20 of these genes correlated with poor OS, 23 with poor EFS and 12 with both poor OS and EFS. In IFM70 (n=170) dataset, high expression of 14 of these genes correlated with poor OS, 8 with poor EFS and 6 with both poor OS and EFS. High expression of 3 genes significantly correlated with both poor OS and EFS in both MM datasets. These included: 1) a kinase (DTYMK; deoxythymidylate kinase), which regulates nucleotide biosynthesis and contributes to DNA replication and repair; 2) a phosphatase (CDC25A; cell division cycle 25A), which is required for G1/S progression and whose degradation in response to DNA damage is essential to prevent cells with chromosomal abnormalities from progressing through cell division; and 3) a nuclease (EXO1; exonuclease 1) with roles in DNA repair and replication. We further validated the role of EXO1 whose expression and activity are elevated in MM. Both gain and loss-of function studies showed that EXO1 contributes to increased DNA replication/proliferation and spontaneous and chemotherapy-induced DNA breaks and genomic instability. We also developed a novel inhibitor of EXO1 that decreases genomic instability and growth of MM cells. **Conclusions:** We have identified genes/pathways driving DNA damage in MM. Some of these genes, separately or together, have potential to serve as novel and promising targets to make cancer cells genomically static and are thus currently being further investigated.

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Evaluation of the Safety and Efficacy of Denosumab in Patients With Multiple Myeloma and Severe Renal Impairment

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Introduction: Multiple myeloma (MM) patients often develop bone disease, predisposing them to skeletal-related events (SREs). Renal impairment (RI), a cardinal feature of MM, further complicates treatment strategies. Denosumab, a bone-directed agent, has demonstrated non-inferiority to zoledronic acid but its efficacy and safety in patients with severe RI remains underexplored. **Methods:** IMWG Bone Subcommittee scheduled a retrospective study to evaluate denosumab efficacy and safety in MM patients with severe RI (eGFR based on CKD-EPI < 30 ml/min/1.73m2). A multi-institutional chart review was performed and data from patients diagnosed with symptomatic MM and RI, under active treatment and denosumab, were analyzed. **Results:** This analysis included 96 MM patients: 49 (51%) with newly-diagnosed (NDMM) and 47 (49%) with relapsed/refractory MM (RRMM; median lines of prior treatment: 5); median age 69 years (IRQ 58.0–77.0); 49 (51.0%) patients were females. All patients had bone disease at the time of denosumab initiation and all RRMM patients had been given zoledronic acid previously. Median eGFR was 24.0 (16.1-28.0) ml/min/1.73m2. Nineteen patients (19.7%) were on dialysis. RI was due to underlying MM in 71 (73.9%) patients; concomitant hypercalcemia was present in 14 (14.5%) patients. The median follow-up was 12.1 (3.3-17.5) months. Eighty-four (87.5%) patients received denosumab at a dose of 120 mg monthly, while 12 (12.5%) at a dose of 60mg monthly. Best response to MM treatment for the whole cohort was as follows: 7 (7.2%) patients achieved ≥CR, 35 (36.4%) vgPR and 24 (25%) PR; median time to response was

42 (28-90) days. Regarding best renal response, 9 (9.3%) patients achieved CRrenal, 12 (12.5%) PRrenal and 30 (31.2%) MRrenal; median time to renal response was 30 (20-42) days. At the time of this report, 43 patients (44.8%) are still receiving denosumab, while 53 (55.2%) have discontinued. Reasons for treatment discontinuation included mainly disease progression (58.3%), side-effects (mainly hypocalcemia) (19.7%) and death. There were 41 recorded deaths (42.7%), mostly attributed to disease progression (87.8%). Fifty (52.0%) patients in our cohort developed hypocalcemia; almost four times higher than the reported incidence for patients with normal renal function or mild/moderate RI. Lower baseline calcium levels (Point-Biserial, coeff.=-0.43, p< 0.001) and higher denosumab dose (120 vs. 60 mg; Fisher's, p=0.016) were associated with hypocalcemia. There were 3 (3.1%) cases of osteonecrosis of the jaw and no case of new SRE during the follow-up period. **Conclusions:** Overall, our findings suggest that denosumab is effective and safe for MM patients with severe RI, provided that proactive measures are taken to mitigate hypocalcemia. Possibly 60 mg, monthly, is sufficient for these patients to prevent both SREs and hypocalcemia. However, further prospective research with larger cohort and longer follow-up period will confirm these results and refine treatment guidelines.

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How To Effectively Administer Belantamab Mafodotin: Knowledge Gained From the Phase 1/2 BelaRd Study in Newly Diagnosed Transplant-Ineligible Patients With Multiple Myeloma

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Introduction: Ocular adverse events (OAEs; best corrected visual acuity [BCVA] change from baseline and keratopathy) are common with belantamab mafodotin (belamaf). We present insights on belamaf dosing from the BelaRd study evaluating belamaf plus lenalidomide/dexamethasone (Rd) in transplant-ineligible patients (pts) with newly diagnosed multiple myeloma. **Methods:** The ongoing phase 1/2 BelaRd study comprises 2 Parts. Part 1 (36 pts) evaluates the safety/tolerability of belamaf 2.5/1.9/1.4 mg/kg plus Rd and established the recommended phase 2 dose of 1.9 mg/kg Q8W/Q12W. Ocular exams are performed by an ophthalmologist, OAEs are graded with the Keratopathy Visual Acuity scale and belamaf dosing is permitted when OAEs are Gr0-1. Dry eye disease and vision-related functioning are assessed with the Ocular Surface Disease Index (OSDI). We present safety/efficacy results over an extensive follow-up period from Part 1 (cut-off date 29/03/24). **Results:** Most pts (32/36; 88.9%) were switched to the Q12W schedule due to OAEs. Following an infusion at Gr0/Gr1, Gr≥2 OAEs were observed in 29.7%/48.8% of the subsequent ocular exams, while the median between-dose interval was 10.4/13.0 weeks (wks). Dosing belamaf when Gr< 2 or Gr≥2 dry eye, blurred vision, or visual impairment was observed, resulted in subsequent Gr≥2 ocular symptoms in 33.5%/80.5% of assessments and a median dosing interval of 12.4/14.7 wks. Regarding keratopathy, the proportion of ocular exams with Gr≥2 findings without concurrent Gr≥2 BCVA change from baseline was only 2.5%. Most (31/36, 86%) pts had cataract at baseline. Of note, in exams with Gr1 keratopathy findings, a higher proportion of Gr≥2 BCVA decline was observed when Gr3-4 (81.6%) than Gr0-2 (46.7%) cataract was present. Among 875 OSDI exams across cohorts, 40-46% reported ocular symptoms for "all/most/half of the time", while the respective proportion for daily functioning impairment was only 5-10%. Over a median follow-up of 28.4 months, ≥CR and ≥VGPR was attained by 55.6% and 88.9% of pts; median time to response was ~1 month and only 1/36 (2.8%) pt had disease progression. **Conclusions:** Our analyses highlight the importance of dosing belamaf when all previous OAEs are resolved completely, to mitigate the risk of subsequent ocular toxicity. To reduce peak toxicities, manifesting even with the extended dosing interval, dose reduction should be considered. High-grade cataract should be treated early, as it is a common problem in these pts that confers an additional risk for visual acuity decline. Severe keratopathy is rare, with a limited role in guiding dosing, as a discordance between BCVA and keratopathy was seldom observed. Although ocular symptoms were often reported, only a minor impairment in eyesight-related functioning was observed. Finally, the triplet regimen demonstrated substantial clinical activity, with rapid and deep responses, despite the extension of belamaf dosing to Q8W/Q12W.

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Elevated Desmoglein-2 Surface Expression Is an Independent Predictor of Poor Outcome in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is the second most common haematological malignancy worldwide with >175,000 new cases diagnosed each year. The Revised International Staging System (R2-ISS) stratifies MM patients into four risk categories (I-IV), with poorer prognosis patients defined by elevated serum beta-2-microglobulin and/or lactate dehydrogenase, and/or high-risk cytogenetics. However, there is a lack of stratified treatments for these risk categories and despite recent advances in therapy, MM remains incurable. The 5-year progression-free survival (PFS) rate is

only 17% for high-risk IV patients and 55% for low-risk I patients, highlighting the need for improved upfront prognostication. We recently discovered that a subset of MM patients express the adhesion protein desmoglein-2 (DSG2) on the surface of their neoplastic plasma cells (PCs). DSG2 expression is significantly elevated in ~30% of MM patients and predicts an almost 4-fold increased risk of death. Importantly, the strong association between DSG2 expression and poor prognosis was independent of genomic subtype and routinely measured MM biomarkers, positioning DSG2 as a promising prognostic biomarker for MM. **Methods:** We have established a biobank that is comprised of peripheral blood and bone marrow samples collected from local newly diagnosed or relapsed MM patients. DSG2 expression was prospectively assessed on diagnostic MM bone marrow PCs by flow cytometry, and a Cochran-Mantel-Haenszel test was used to correlate DSG2 levels to patient PFS. The functional contribution of DSG2 was investigated by assessing tumour growth of a MM cell line with or without DSG2 knockdown in a flank xenograft model in NGS mice. DSG2 CRISPR knockout MM cell lines were developed and the functional impact of DSG2 on proliferation (clonogenic and MTT assays), alterations to additional adhesion markers and modulation of secreted cytokines (protein profiler array) were assessed. **Results:** High DSG2 surface expression was detected on PC in 24% of bone marrow biopsies from the 67 newly diagnosed MM patients in our cohort. High DSG2 expression was associated with an almost 3-fold risk of progression within 3 years of diagnosis (p=0.022). Preliminary Xenograft studies suggest that targeting DSG2 attenuates MM growth and disease progression (p< 0.05). In vitro CRISPR knock out of DSG2 in multiple MM cell lines does not alter short term proliferation and initial studies suggest alterations in secretion of cytokines including VEGF, IP-10, FLT3L IL-1a and Dkk-1. **Conclusions:** Our data suggests that MM patient outcomes could be improved by rapidly identifying poor prognosis DSG2-high patients by flow cytometry who may benefit from early treatment intervention. Targeting DSG2 may also attenuate MM progression and we are now investigating the functional roles of DSG2 in MM and the efficacy of DSG2 inhibition to determine whether DGS2-targeting immunotherapies may improve outcomes for this high-risk subset of MM patients.

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Identifying Anti-Viral Drugs to Sensitize and Re-Sensitize MM Cells to Chemotherapy

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Introduction: Chemotherapy remains the most used systemic treatment for multiple myeloma (MM). However, despite significant improvement in chemotherapy agents, chemoresistance remains the major problem in MM management. Drug resistance has been reported for all clinically used chemotherapy agents, including traditional chemotherapeutics such as melphalan (Mel) and dexamethasone (Dex), and novel agents such as carfilzomib (Cfz). As a result, most, if not all, MM patients experience relapse after treatment and die from the disease. Therefore, overcoming chemoresistance represents a critically unmet clinical need in MM treatment. **Methods:** We screened 1855 FDA-approved drugs in human MM cell lines for their ability to sensitize MM cells to chemotherapy drugs. Mechanistic studies were then performed to investigate the target molecules in MM cells and to elucidate the underlying mechanisms. **Results:** Our results showed that the selective inhibitors of hepatitis virus replication complex such as EV and DV, an analog of EV, may be used to sensitize and re-sensitize MM cells to chemo-drugs. We found that EV was among the top drugs that significantly sensitized MM cells to Cfz, Dex, and Mel. EV and DV could also re-sensitize Cfz- or Dex-resistant MM cells to Cfz or Dex, respectively. Moreover, in the presence of EV or DV, lower doses of chemo-drugs were required to induce similar MM cell death compared to chemotherapy drugs alone at higher doses. We observed that EV and DV significantly enhanced drug retention in MM cells by inhibiting drug efflux through proteins of ATP-binding cassette (ABC) transporter superfamily. The potential binding proteins were categorized according to their functions. Interestingly, we identified that ATP9B (ATPase phospholipid transporting 9B) and ABCF3 (ATP binding cassette subfamily F member 3), which have transporter activity, in top 20 hits list, were promising targets. We further verified that DV bound to ATP9B and ABCF3 using pull down assay in ARP-1 cells. Depletion of ATP9B or ABCF3 expression sensitized MM cells to chemotherapies. By analyzing published data in Oncomine, ATP9B and ABCF3 were found to be highly expressed in MM cells compared to normal plasma cells, and their expressions in MM cells were negatively associated with treatment outcome in patients. Finally, EV and DV significantly improved the therapeutic efficacy of chemotherapies in MM in vivo without increased toxicity to normal tissues. **Conclusions:** These observations strongly suggest that EV and DV, which alone are non-toxic to MM or normal cells have a broad effect in sensitizing MM cells to different chemo-drugs, re-sensitize chemo-refractory MM cells to chemotherapies; and can reduce the doses of chemo-drugs to minimize the side effects of chemotherapy in patients. Our results provide the justification and tools for developing novel and effective strategies for targeting both MM drug efflux to improve the therapeutic efficacy of chemotherapy.

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Indirubin-3'-monoxime Improves Immune Cell Mediated Cytotoxicity via Fatty Acid Metabolism Reprogramming in Multiple Myeloma

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Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy. Despite recent advancements in immunotherapies including chimeric antigen receptor T (CAR-T) cell therapy and daratumumab(DARA), their efficacy remains unsatisfied. The efficacy of immunotherapy is limited to a great extent by immunosuppressive mechanisms within the tumor microenvironment. Our previous study reports that I3MO (Indirubin-3'-monoxime) acts as proteasome inhibitor and represents a promising therapeutic strategy to improve patient outcome in MM (eBioMedicine 2021). Herein we elaborated the mechanisms underlying of low-dose I3MO treatment restore immune cell function and improve immune cell mediated cytotoxicity against MM. **Methods:** Evaluation of the therapeutic effect of I3MO was performed by in vitro coculture system with MM cell line and human Natural Killer (NK) cell and in vivo NK-humanized murine model. I3MO induced transcriptional and lipid profile changes were investigated to determine the key signaling cascades in MM cells. **Results:** Besides the direct cytotoxicity against MM cells, we found that low-dose I3MO notably enhances NK cell activity and improves DARA-mediated NK cell cytotoxicity to MM in vitro and in vivo. However, I3MO treatment was not identified to affect the gene expression of CD38 or immune checkpoint. Therefore, we hypothesized that I3MO treatment would improve the immunocytotoxicity sensitivity to NK cell in MM. Of note, RNA-seq data demonstrates that I3MO induced the FAO metabolism reprogramming in MM cells. The phenotype of inhibition of fatty acid intake and oxidation (FAO) was confirmed in MM cells by Lipidomics, BODIPY™ FL C16, and Seahorse assays. Further study identified that PIM1 kinase, the downstream target of STAT3, was down-regulated in the treatment of I3MO. SM Pull down analysis further indicated that I3MO directly bound to STAT3 and suppressed the phosphorylation of STAT3 (y705 and y727), which caused the transcription suppression of PIM1. PIM1 kinase has been reported to play critical roles in driving fatty acid metabolic reprogramming in diverse tumor cells, and changes of lipid packing in tumors affect the tolerance of granzyme B. Here, our data demonstrated I3MO treatment significantly suppressed in the fatty acid oxidation via downregulation of PIM1 kinase in MM cells, which improved the sensitivity of MM cells in NK cells engaged treatment. Next, immunoprecipitation and mass spectrometry assay further identified that PIM1 bound to PARP1 protein and regulated PPARγ activities, which were involved in regulation of several FAO related genes in MM cells. **Conclusions:** Our results suggest that low-dose I3MO treatment improves the immunotherapy sensitivity of MM cells by suppressing the STAT3/PIM1/PARP1 signaling pathway that induced the Fatty acid reprogramming in MM cells. This study clarifies the immunomodulatory activity enhancement of low doses of I3MO in MM treatment and provides the rational for clinical practice.

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Hypoalbuminemia, a New Risk Factor for Progression in Patients With Monoclonal Gammopathy of Uncertain Significance?

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Introduction: Mayo Clinic and MGUS-like phenotype models are two scales commonly used to stratify the risk of progression in patients with monoclonal gammopathy of uncertain significance (MGUS). A proinflammatory environment of the bone marrow has been described to contribute to the progression of MGUS. The albumin is an inflammatory biomarker widely used in staging systems in multiple myeloma. However, its implication in the prognosis of MGUS patients is not well known. Aim: To validate Mayo Clinic and MGUS-like phenotype models. To investigate whether hypoalbuminemia is a prognostic factor for progression in patients with MGUS. **Methods:** An observational and retrospective study was designed including 927 patients with MGUS referred to the hematologist between 1990 and 2022. Albumin was determined by spectrophotometry and hypoalbuminemia was defined as an albumin ≤3.5 g/dL. Patients were stratified according to Mayo Clinic and MGUS-like phenotype risk models. **Results:** With a median follow-up of 6.3 years, the median time to progression (TTP) was 31.5 years. Mayo Clinic risk model was applied in 703 (75.8%) patients. Considering low-risk group as reference group (N=288; TTP not reached), low-intermediate (N=283; TTP not reached; P=0.012), high-intermediate (N=127; TTP not reached; P=0.001) and high risk (N=5; TTP 5.1 years; P< 0.001) had significantly higher risk of progression. Phenotypic model was applied in 430 (46.1%) patients: intermediate phenotype (N=122) was significantly associated with increased risk of progression as compared to MGUS-like phenotype (N=308; TTP 19 vs. 31.5 years; P< 0.001). Seventy-four (8%) patients presented with hypoalbuminemia at the diagnosis of MGUS. Hypoalbuminemia was more frequent in older patients (≥70 years: 75.5% vs. 57.7%; P=0.003), men (63.5% vs. 37.0%; P=0.023) and IgA isotype (32.4% vs. 19.2%; P=0.008). Patients with hypoalbuminemia presented lower hemoglobin levels (11.9 ± 1.9 vs. 13.8 ± 1.8 g/dL; P< 0.001) and higher creatinine values (1.4 ± 0.9 vs. 1.0 ± 0.4 mg/dL; P< 0.001). The median TTP in patients with hypoalbuminemia was inferior to patients with normal serum albumin levels (13.1 vs. 31.5 years; P< 0.001). Within the high-intermediate risk group of the Mayo Clinic, patients with hypoalbuminemia had a 7.5-fold increased risk of progression (7.2 years vs. not reached; P=0.006). Within the intermediate phenotype group, patients with hypoalbuminemia had a higher risk of progressions compared with those with normal serum albumin levels (9.7 years vs. not reached; P=0.040). **Conclusions:** Mayo Clinic and MGUS-like phenotype models were validated in our series. Hypoalbuminemia significantly increased the risk of progression in MGUS patients, especially in high-intermediate patients of the Mayo Clinic model and in the intermediate group of MGUS-like phenotype model. Although it must be confirmed in large independent studies, hypoalbuminemia could become a new risk factor for progression in patients with MGUS.

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Impact of the Addition of Daratumumab to the Frontline Treatment of Patients With Al Amyloidosis

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Introduction: AL amyloidosis is an uncommon plasma cell dyscrasia with a heterogeneous prognosis, highlighting very poor survival of patients with stage III-IV revised 2012 Mayo Clinic. However, the arrival of proteasome inhibitors (PI), and especially anti-CD38 MoAb, daratumumab (dara), have represented a paradigm shift in the treatment of this disease. Aim: To investigate whether hematological (HR) and progression-free survival (PFS) improved in patients with AL amyloidosis according to induction therapies. **Methods:** An observational and retrospective study was designed including 92 patients with AL amyloidosis consecutively treated in Salamanca between 1999 and 2023. Induction treatments were grouped into chemotherapy (chemo), including patients who directly underwent to autologous stem cell transplantation, and new drug-based schemes (PI, immunomodulators [IMiD] or dara): PI/IMiD and dara+PI. **Results:** Median age at diagnosis was 64 years (range, 39-90), 53.7% were men. Fifteen (18.1%), 24 (28.9%), 19 (22.9%) and 25 (30.1%) patients presented revised 2012 Mayo Clinic stage I, II, III and IV, respectively. Twenty-one (22.8%) patients received dara+PI-based schemes; 46 (50.0%) patients PI/IMiD-based schemes and 25 (27.2%) patients chemo. Dara+PI-based schemes resulted in a rate of HR (≥ partial HR) of 100%, significantly higher compared to 78.3% in patients receiving PI/IMiD (P=0.021) and 60.9% with chemo (P=0.001). Likewise, 76.2% of patients treated with dara+PI achieved complete HR (cHR), compared to 37.0% with PI/IMiD (P=0.004) and 13.0% with chemo (P< 0.001). Notably, all the patients at stage III-IV treated with dara+PI achieved HR compared to 70.0% with PI/IMiD (P=0.029) and 55.6% with chemo (P=0.008). In addition, 84.6% of these patients receiving dara+PI achieved cHR compared to 45.0% in patients treated with PI/IMiD (P=0.032) and 11.1% with chemo (P=0.004). Time to HR was shorter in patients treated with dara+PI (28 days) compared to those treated with PI/IMiD (72 days; P< 0.001) and chemo (95 days; P< 0.001) as well as time to cHR (4 months vs. not reached vs. not reached; both P=0.002). This advantage was even noticeably at stage III-IV, both in time to HR (28 vs. 77 vs. 171 days; P=0.002 and 0.005, respectively) and time to cHR (2 vs. 9 months vs. not reached; P=0.090 and P=0.030, respectively). With a median follow-up of 51.5 months, PFS was prolonged in patients receiving dara+PI (not reached) compared to those treated with PI/IMiD (18.0 months; P=0.040) and chemo (6.0 months; P=0.009). This clinical benefit was more evident in patients at stage III-IV with PFS not reached in patients treated with dara+PI compared to 8.0 months for patients receiving PI/IMiD (P=0.025) and 6.0 months (P=0.009) for those receiving chemo. **Conclusions:** The addition of daratumumab to PI in the frontline treatment of AL amyloidosis improved HR and resulted into deeper and faster responses and, subsequently into a significant benefit in PFS for all patients, even those at stage III-IV.

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Outcomes of Incorporating IV Daratumumab for the Treatment of Al Amyloidosis in Real World Patients From a Multicenter Registry in Latin America

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Introduction: Daratumumab is an anti-CD38 monoclonal antibody that has demonstrated outstanding results in the treatment of AL amyloidosis. Nevertheless, patients with advanced cardiac disease have been usually excluded from clinical trials and data from real world patients in Latin America is lacking. Objective: Describe hematological (HR) and organ response, overall survival (OS) and event-free survival (EFS) of incorporating IV Daratumumab for the treatment of AL amyloidosis. **Methods:** Multicenter, retrospective cohort study of patients older than 18 years with a histopathological diagnosis of AL Amyloidosis and treated with at least one cycle in first-line (Group 1) or subsequent lines of treatment (Group 2) with Daratumumab IV, included in the registry of amyloidosis (RIA, NCT01347047) **Results:** Thirty-seven patients were included. Characteristics of the population are summarized in Table 1. Twenty-four patients (65%) had cardiac involvement, 25 (68%) renal involvement, and 14 (40%) both. Of the patients with cardiac involvement, 20 had cardiac stages Mayo 2012 III/IV. Group1 included 18 patients who received daratumumab (48%), 17 in combination with CyborD. Group2 included 19 patients (51%), 12 received Daratumumab in combination with dexamethasone, 5 with CyborD and 2 with lenalidomide. Thirty-three patients (90%) achieved HR, median time to best hematologic response was 2 months (IQR 1-9 months). Seventeen patients (59%) achieved CR (group1 n=8 Group2 n=9), 9 MBRP (group1 n=4 group2 n=5), 7 PR (group1 n= 5 group2 n=2). Of the 20 patients with Mayo stages III/IV, 18 achieved hematologic response and 9 cardiac response. Three patients had stable disease, all of them were relapsed. Three patients presented subsequent relapses. The Organ response rate was 59% (n=22, IC 45-75), 14 renal response, median time to response 8 months (IQ R4,6-14,1), 13 cardiac response, median time to response 6,4 months (IQR 6,4-6,4). Five patients had response of both organs. The median follow-up of the entire cohort was 18 months (CI 11-75). The median EFS at 1 year was 88% (CI 71-95)

and at 2 years 83% (CI 64-93). Median OS at 12 months was 91% (CI 75-97) and at 24 months 86% (CI 68-95). There were 7 deaths in the entire cohort, 5 were due to cardiac complications associated with amyloidosis. Five of the deceased patients achieved a HR. Eleven patients presented adverse events, mainly infectious complications, 5 of them grade 3 or 4. **Conclusions:** This study provides real-world evidence for Daratumumab IV treatment in patients with AL amyloidosis in the first line and at relapse, achieving fast and profound HR, which translated into a high organ response rate and improvement in OS and PFS. This study is relevant since it is a real life study, in which intravenous daratumumab was used since the subcutaneous formulation is not available in most Latin American countries and also included patients with advanced cardiaca stages. Treatment with Daratumumab should be considered a therapy of choice in AL amyloidosis.

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Ibrutinib Plus Rituximab Versus Ibrutinib Monotherapy in Patients With Waldenström Macroglobulinemia: A Pooled Analysis of Three Prospective Studies

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Introduction: Bruton tyrosine kinase (BTK) inhibitors are approved by the FDA and the EMA for treating Waldenström macroglobulinemia (WM). Ibrutinib (I) was the first-in-class BTK inhibitor and has been shown to be highly effective in WM. The INNOVATE study compared ibrutinib plus rituximab (I+R) versus placebo plus rituximab in WM and showed the combination was associated with superior outcomes. It is unclear if there is a benefit of I+R over I in WM, and this question will not be answered in prospective clinical trials. Therefore, we undertook a comparative pooled analysis of prospective studies to evaluate the response and survival outcomes of I+R versus I in WM patients. **Methods:** We collected demographic, response, and survival patient-level data from three prospective studies (NCT01614821, NCT02604511, and NCT02165397). Data from NCT02165397 was obtained through YODA (YODA #2022-4928). For this analysis, we divided the patients into two groups: I+R (n=75) and I (n=124) and excluded patients without MYD88 mutations. The final analytical cohort included 58 patients treated with I+R and 116 patients treated with I. Differences in demographic characteristics and response outcomes between the groups were assessed using the Chi-square test. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. P-values < 0.05 were considered statistically significant. **Results:** There was a higher proportion of women (75% vs. 59%; p=0.03) and a higher proportion of previously treated patients (73% vs. 47%; p=0.01) in the I versus the I+R group. There were no detectable differences in age >65, IgM ≥7000 mg/dl, hemoglobin < 11.5 g/dl, platelet count ≤100 k/l, beta-2-microglobulin >3 mg/l, albumin < 3.5 g/dl, IPSSWM score, or presence of CXCR4 mutations. Categorical responses for I versus I+R were ORR 93% vs. 100% (p=0.05), major response 82% vs. 90% (p=0.26), and VGPR 28% vs. 38% (p=0.21). There were no detectable differences in categorical responses between I and I+R in patients with (p=0.38) or without CXCR4 mutations (p=0.83), in TN (p=0.83) or RR patients (p=0.71), and in patients with low (p=0.82), intermediate (p=0.80) or high IPSSWM scores (p=0.32). The 30-month progression-free survival (PFS) rates for I versus I+R were 72% and 79%, respectively (p=0.22). The 30-month PFS rate was inferior for I versus I+R in patients with CXCR4 mutations (62% vs. 77%; p=0.03) and in patients with high IPSSWM scores (20% vs. 100%; p=0.03). There were no detectable differences between I and I+R groups in patients without CXCR4 mutations (p=0.85), TN (p=0.66), RR (p=0.48), or low (p=0.60), intermediate IPSSWM scores (p=0.52). **Conclusions:** Based on this pooled analysis of patient-level data from three prospective studies, the addition of rituximab to ibrutinib was associated with superior 30-month PFS rates in WM patients with CXCR4 mutations and in patients with high IPSSWM scores.

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Retrospective Review of Two Cases of Localized Iatrogenic Anakinra-Type Amyloidosis at the University of Texas MD Anderson Cancer Center

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Introduction: We present two cases of iatrogenic anakinra-type amyloidosis at MD Anderson Cancer Center. 82yr old F with Erdheim Chester disease treated with anakinra since 2015. In 2024, she reported an abdominal mass at the anakinra injection site. PETCT Imaging confirmed a non-FDG avid mass at the injection site. Biopsy findings of the mass confirmed AILRAP (anakinra)-type amyloidosis. Systemic amyloidosis work-up which included bone marrow biopsy and aspiration, serum protein electrophoresis with IFE, urine protein electrophoresis with IFE, free light chains, fat pad biopsy, echocardiogram, pulmonary functions tests were negative confirming this is a localized amyloid presentation. 66yr old M with Extranodal marginal zone lymphoma in remission and Schinizler's syndrome treated with anakinra who was found to have a left medial superior thigh lesion on imaging. Pathological findings were consistent with amorphous material positive for AILRAP (anakinra)-type amyloidosis. Further examination confirmed this lesion's location correlated with his usual anakinra injections delivery site. Systemic amyloidosis work-up which included serum protein electrophoresis with IFE, urine protein electrophoresis with IFE, free light chains, fat pad biopsy, echocardiogram, pulmonary functions tests were negative confirming this is a localized amyloid presentation. **Methods:** Retrospective review of the clinical history, serological analysis (serum protein electrophoresis with IFE, urine protein electrophoresis with IFE, free light chains), and histological evaluation of lesions, fat pad and bone marrow aspirations and

biopsies with Congo-red staining as well as mass spectrometry of two patients currently treated at MD Anderson Cancer Center in year. **Results:** Pathological analysis of the tissues (primary lesion reported, fat pad, bone marrow biopsy and aspiration) which included mass spectrometry demonstrated and confirmed that the amyloid deposits found on the primary lesions were of AILRAP (anakinra)-type amyloidosis. Fat pad and bone marrow aspiration analyses were negative for systemic amyloid disease. **Conclusions:** This is a case series reporting two patients with localized iatrogenic anakinra-type amyloidosis due to an injectable protein drug. The mechanism of iatrogenic amyloid disease due to anakinra has not been elucidated. Further studies, possibly including genetic analysis of tissue microenvironment may help elucidate the pathophysiology of the disease. Given the widespread use of anakinra in the management of cytokine release syndrome and immune effector cell associated neurotoxicity syndrome due to chimeric antigen receptor T-cell therapy and bispecific antibodies for hematologic malignancies, providers should be aware of this presentation.

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Clinical Characteristics and Prognostic Factors of Patients With Solitary Plasmacytoma: A Multicenter Retrospective Study

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Introduction: Solitary plasmacytoma (SP) represents an infrequent occurrence within plasmacytomas, which may persist or transform into multiple myeloma post therapeutic interventions. This investigation sought to evaluate the clinical attributes and prognostic indicators for individuals afflicted with SP. **Methods:** We retrospectively evaluated 49 patients diagnosed with SP at the First Affiliated Hospital of Nanjing Medical University, Affiliated Changzhou Second Hospital of Nanjing Medical University, Nanjing First Hospital between the years 2009 and 2024. Clinical features were compared utilizing the Fisher's exact test. The Kaplan-Meier curves were constructed to compare the survival outcomes. The independent risk factors were determined based on the Cox proportional hazards model. **Results:** In total, 49 cases were categorized as solitary bone plasmacytoma (SBP), comprising 30 patients (61.2%), or solitary extramedullary plasmacytoma (SEP), involving 19 cases (38.8%). Notably, SEPs were more common in the upper respiratory tracts (47.4%), whereas SBPs were predominantly located in spines (30.0%) and long bones (20.0%). The median age at diagnosis of patients with SP was 57 years (range 34-79). The distribution showed a slightly higher prevalence in those under 60 years, with males accounting for approximately 62.5% of the cases, reflecting a male-dominated patient population. Of these 49 patients, the majority of patients received radiation therapy alone (35.4%) or radiotherapy plus surgery (39.6%). The SBP cohort exhibited inferior progression-free survival (P=0.0002). While the difference in overall survival between the SBP group and SEP group was not statistically significant (P=0.1012). Radiotherapy in conjunction with surgery or chemotherapy did not substantially enhance the outcome of the patients with SP. SBP involvement (P=0.068, HR=0.068, 95%CI: 0.008-0.537) and elevated Ki67 expression (P=0.049, HR=4.545, 95%CI:1.005-20.542) exceeding 35% were independent risk factors of progression-free survival of patients with SP. **Conclusions:** The prognosis of patients with SBP was poorer than that with SEP. Patients with SBP exhibiting Ki67 expression exceeding 35% had the poorest outcome.

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Systemic Amyloidosis With Gastrointestinal Involvement: Low Suspicious Presentation, Late Treatment, Multiorgan Disfunction and Higher the Risk of Death After Autologous Stem Cell Transplant

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Introduction: Light chain amyloidosis (AL) is a heterogeneous and life-threatening disease caused by extracellular deposition of misfolded free light chains (FLC) that typically originate from small plasma cell clones. The majority of these patients have a significant impairment of vital organs, such as the heart, kidney, and liver. However gastrointestinal (GI) involvement is an uncommon manifestation of systemic amyloidosis. The most common clinical signs are nausea, vomiting, dysphagia, gastroparesis, gastro-esophageal reflux, loss of appetite, constipation, abdominal pain, bloating. The Gl bleeding may occur from any site of amyloid deposition and can be seen in up to 57% of patients. Few data are available, with the exception of some case reports. GI direct biopsy verification of the disease is needed to identify amyloid deposit. **Methods:** NA. **Case Report:** 49 years old, female, without previous comorbidities was admitted to an emergency unit hospital in January 2020 to investigate epigastric pain and postprandial fullness that started eight months before diagnosis. The blood count was normal, abdominal ultrasound showed hepatomegaly. Endoscopy showed infiltrative lesion, of entire anterior region of the gastric body, with enanthematic and friable mucosa. Biopsy was congo red positive. Bone marrow aspirate showed 2,4% of clonal plamocytes Lambda monoclonal light chain. Mass spectrometry detected lambda-type immunoglobulin light chain.. She had she left Cardiac ventricle fibrosis due to cardiac Amyloid deposition, New York Heart Association Scored 3 (NYHA 3), hepatomegaly, GI and renal involvement. August 2020 patient was treated with cyclophosphamide, bortezomib, and dexamethasone, 6 cycles. Daratumumab was added for 4 cycles to improve response. According to Mayo Clinic organ response criteria the patient improved cardiac function (NYHA2), decreased pro-BNP, presented hematological response (very good parcial response), but no of liver or kidney improvement. June 2022 She was submitted to an autologous stem cell transplant (ASCT), at

D+9 after ASCT she had a major GI bleeding, hypovolemic shock, progressing to organ failure and death. **Conclusions:** It is important to draw attention to GI symptoms in amyloidosis involvement and its nonspecific symptoms could delay diagnosis and favor advanced organ failure. The lack of a risk score to estimate massive bleeding in GI involvement makes the management of these patients more difficult. This case had a late diagnose of systemic amyloidosis with GI, cardiac, hepatic and renal involvement. Despite of Cardiac and hematologic response, she progressed with hepatic and renal disease increasing the risk of death after transplant.

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Smoldering Multiple Myeloma in Latin America

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Introduction: Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder with a prevalence of 0.5% in the >40 yrs population. Effort has been made to characterize these patients in the real world. There is scarce data about SMM in Latin America (LA) and we aimed to characterize SMM in this region. **Methods:** A consortium between the Brazilian and Latin America myeloma study groups (GBRAM-GELAMM) were stablished to conduct a retrospective cohort study of SMM cases diagnosed from 2015 to 2023. Data collected included demographics, diagnostic and prognostic tools. We also captured data of progression to MM and SMM management. Progression-free survival (PFS) and overall survival (OS) were calculated. **Results:** A total of 247 pts had been included, from 35 different institutions belonging to eight different countries. Ninety-five (38.5%) of pts were followed in the public health sector (PS). The median age at diagnosis was 64 (34-90) yrs and 158 (64%) patients were female. The immunoglobulin isotype were IgG, IgA and light chains in 158 (64%), 70 (28.3%) and 14 (5.7%), respectively. Regarding exams availability, 210 (85%) pts had FLC analysis, 111 (44.9%) pts had a total body MRI or PET-CT and 106 (42.9%) pts had low radiation total body CT. A total of 191 (77.3%) pts had all the 20-2-20 criteria available from whom 74 (38.7) were low risk, 61 (32.9%) were intermediate risk, 56 (29.3) were higk risk. From the total of patients included 59 (23.9%) progressed, from whom 10 (4%), 14 (5,7%),18 (7.3%) and 17 (28.9%) were low, intermediate, high risk and unknow data, respectively. Median time to progression was 34 (3-136) months, and 11 patients had progressed over 12 months from diagnosis. Chance to progression considering the risk factors from 20-2-20 criteria was identified but not significant (p=0.08). Thirteen (5%) pts died or lost follow-up. The median follow-up was 42.2 months. **Conclusions:** This is the first cohort with representation of patients with SMM in LA. Although the majority of MM patients in LA are followed in the public sector, only 40% of the SMM cases in the present study belong to this sector, reveling the access difficult to diagnosis tools for SMM cases in the public sector. The majority of pts did have access to CT, MRI, PET, FLC assay and bone marrow study, which we interpret as a correct identification of SMM criteria in our cases. The 20-2-20 criteria works for the study population stratification although no statistical difference was observed, possibly due to the number of cases and/or shot follow-up.

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A Unique Presentation of Light Chain Deposition Disease: Kidney Disease With No Proteinuria

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Introduction: Monoclonal gammopathy of renal significance (MGRS) is a group of disorders caused by a nonmalignant or premalignant B cell or plasma cell clone causing kidney injury through secretion of a monoclonal immunoglobulin. Patients with light chain deposition disease (LCDD) commonly present with acute, subacute or chronic kidney injury, and proteinuria, with or without hematuria. We present a unique case of LCDD with kidney injury but no proteinuria. **Methods:** 64-year-old fit male with no comorbidities presented with slowly declining renal function over 2 years with GFR 39 mL/min/1.73 m2, elevated blood urea nitrogen 28 mg/dL and serum creatinine 1.89 mg/dL. Serum protein electrophoresis and immunofixation did not reveal a monoclonal spike. He had elevated kappa free light chains (FLC) 140 mg/dL, elevated lambda FLC 33.5 mg/dL with a high kappa/lambda FLC ratio 4.2. Given patient's elevated FLC ratio in the setting of worsening renal function, a bone marrow biopsy was performed that showed atypical plasma cells with Dutcher bodies that constituted 5-10% of the total cells but were polytypic with no light chain restriction. Cytogenetic studies and Florescent in-situ Hybridization revealed the presence of CCND1/IGH fusion gene involving 8.6% of the cells, resulting from an unbalanced translocation involving chromosomes 11 and 14, t(11:14). Skeletal survey and FDG PET scan did not show any evidence of lytic lesions. Given the inconclusive bone marrow biopsy,

kidney biopsy was performed revealing kappa LCDD with linear staining of the renal basement membranes. **Results:** A diagnosis of LCDD was thus made and the patient was started on treatment with daratumumab, cyclophosphamide, bortezomib and dexamethasone followed by daratumumab maintenance. **Conclusions:** MGRS has been described by the International Kidney and Monoclonal Gammopathy Research Group (2012) as patients meeting criteria for monoclonal gammopathy of undetermined significance, with kidney injury being attributed to the underlying monoclonal protein. The kidney injury is primarily caused by the abnormal deposition or activity of monoclonal proteins in the kidney, including, light chains, heavy chains, or intact immunoglobulins, produced by small, nonmalignant or premalignant plasma cell or B cell clones. Patients with LCDD usually have abnormal FLC ratio, hematuria and proteinuria ≥1.5g/day. However, our patient with biopsy-proven LCDD presented with non-proteinuric kidney dysfunction, which has not been previously reported. Although LCDD is considered a nonmalignant or premalignant hematologic condition, patients with LCDD can develop progressive kidney disease and end-stage renal disease if not treated promptly. This case highlights the importance of having a high index of suspicion, in patients with monoclonal gammopathy and an unexplained decrease in renal function with or without proteinuria, to proceed with kidney biopsy, as improved renal outcomes have been associated with hematologic response from clone directed therapy.

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Autologous Stem Cell Transplantation for Light Chain Amyloidosis: A Single Center Report

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Introduction: Since the 1990s, high-dose intravenous melphalan followed by autologous hematopoietic stem cell transplantation (ASCT) has been a cornerstone in treating light chain (AL) amyloidosis. Patients who achieve a complete hematologic response after ASCT tend to have better overall survival (OS). However, transplant-related mortality (TRM) and clinical complications during ASCT remain significant challenges and major concerns. **Methods:** We reviewed patients with AL amyloidosis who underwent ASCT between 2016 and 2024 at Beneficência Portuguesa de São Paulo to assess the procedure's safety and long-term outcomes. Our analysis focused on patient baseline characteristics, progression-free survival (PFS), intensive care unit (ICU) admission rates, and overall survival (OS). **Results:** Twenty-seven patients met the criteria for this retrospective study. The median age was 60 years (95% CI, 38-70). Seventeen patients (63%) had an ECOG score of 0, and eleven (40%) had a Mayo Cardiac score of 1. Cardiac involvement was present in 11 patients, and renal involvement in 23. Among the cohort, 81% (95% CI, 61-92%) received ASCT as part of first-line therapy, while five patients (18%) received no therapy prior to ASCT. Twelve patients (44%) received a CyBorDex regimen, and nine (33%) received a Dara-based quadruplet regimen. The most commonly used conditioning regimen was Melphalan 200 mg/m^2 (55.6%), with the remaining patients receiving 140 mg/m^2. During hospitalization, 11 patients experienced congestive heart failure decompensation (4 profile 'B' and 7 profile 'C'), with a higher risk observed in patients with pre-existing cardiac dysfunction (OR = 5.2, 95% CI, 0.92-47, p = 0.06). None of the patients were on renal replacement therapy at baseline; however, 4 required hemodialysis during hospital follow-up. There were no in-hospital deaths in this cohort, although 33% of patients were admitted to the ICU within 30 days of follow-up (95% CI, 16-51%). The OS and PFS rates at 2 years, estimated by the Kaplan-Meier method, were 88% (95% CI, 73-100) and 89% (95% CI, 76-100) respectively, with no early deaths (within 100 days of ASCT). **Conclusions:** The present analysis reiterates the vital importance of careful patient selection for ASCT, as complications can occur and may be serious. Therefore, a center's experience is fundamental to guaranteeing the best outcomes. The vast majority of patients in our cohort remained alive, with no transplant-related deaths within the first 100 days.

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Monoclonal Gammopathy of Renal Significance: How Should We Evaluate Response? Experience in a Hospital Complex

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Introduction: The term monoclonal gammopathy of renal significance (MGRS) defines a clonal population of plasma cells or B lymphocytes that produces a nephrotoxic complete or partial immunoglobulin. However, this monoclonal gammopathy (MG) is not always detectable in serum or urine, which complicates the evaluation of the response. **Methods:** This observational and retrospective study includes 4 hospitals with the same pathological anatomy department. It includes every GMSR diagnosed between 01/2016 and 01/2024 through renal biopsy. The primary endpoint was to assess renal response according to proteinuria and glomerular filtration rate (GFR). The secondary endpoint was to analyze possible prognostic factors. Hematological response (RespH) was evaluated according to the categories proposed for AL amyloidosis in 2012. Renal response by GFR (RespGFR) was assessed according to the consensus of the international myeloma group in 2010. Regarding renal response according to proteinuria (RespPro), we considered complete response when proteinuria was < 200 mg/day,

very good partial response when proteinuria decreased >60%, partial response when it decreased 30-60%, stable disease when it decreased ≤ 30%, and progression when it increased ≥30% without significant deterioration of GFR. Renal stages were classified according to proteinuria >5g/day and GFR < 50mL/min/m2 (0 points Stage I, 1 Stage II, 2 Stage III). **Results:** This study includes 39 patients. Ten patients had AL amyloidosis, and 29 had other types of MGRS. There was no detectable MG in 12 cases (31%). Graphic 1 shows distribution according to type of MGRS and absence of MG. Table 1 describes clinical characteristics. Thirty-one percent of patients were stage I, 38% II, and 31% III. With a median follow-up of 32 months (IQR 10 - 57), 82% of patients received treatment. Table 2 describes treatment regimens and types of response. The median time to the first and best RespH was 2 (IQR 1.2 - 2.6) and 5 months (IQR 2.5 -6.3) respectively. RespPro was not assessable in 9% of patients due to proteinuria < 500 mg/day at diagnosis, while RespGFR was not assessable in 49% due to GFR > 50 mL/min/m2. The median time to the first and best RespPro was 4 (IQR 2.2 - 6.7) and 11 months (IQR 5.6 -23) respectively. The median time to the first and best RespFG was 2.6 (IQR 2 – 3.5) and 8 months (IQR 3 –9) respectively. There were 11 relapsed/refractory patients (28%) according to proteinuria, 12 (30%) to GFR, and 7 (18%) to both assessments. Eight patients (21%) required renal replacement therapy after a median time of 15 months (IQR 7 – 24). Fifty percent of patients with stage III, 21% with II, and 0% with I required renal replacement therapy. **Conclusions:** MGSR is a group of entities that require close follow-up by Nephrology and Hematology. Although advances in treatment allow the achievement of rapid and profound hematological responses, up to 30% of patients did not have renal improvement, and 21% required renal replacement therapy in our cohort.

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Monoclonal Gammopathy of Renal Significance: Diagnosis, Treatment and Prognosis in a Hospital Complex

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Introduction: The term monoclonal gammopathy of renal significance (MGRS) consists of a clonal population of plasma cells or B lymphocytes that produce a nephrotoxic complete or partial immunoglobulin. They constitute around 10% of monoclonal gammopathies of uncertain significance and their prevalence in people older than 50 years is 0.32%. **Methods:** This observational and retrospective study includes four hospitals in Madrid with the same pathological anatomy department. It includes every patient diagnosed with GMSR between 01/01/2016 and 04/01/2024 through renal biopsy. The primary endpoint was to describe what types of MGRS have been diagnosed in our hospital complex. The secondary endpoints were to analyze their clinical presentation, treatment, and prognosis. Hematological response was evaluated according to the response categories proposed for AL amyloidosis. **Results:** This study includes 39 patients, 64% men. Ten patients had AL amyloidosis, and 29 had other types of MGRS. The median age at diagnosis was 65 years (interquartile range (IQR) 53 – 71). Table 1 describes clinical characteristics at diagnosis. The median time between the first Nephrology consultation and diagnosis was 90 days (IQR 7 – 270). In 77% of the cases, Nephrology was the first medical appointment, and 38% of the patients did not have a consultation with Hematology before diagnosis. The most common MGRS was proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) followed by immunoglobulin-related amyloidosis and monoclonal immunoglobulin deposition disease (MIDD). Sixty percent of AL amyloidosis had extrarenal involvement. The median time between diagnosis and hematological treatment was 30 days (IQR 15 – 45). With a median follow-up of 32 months (IQR 10 - 57), 32 patients (82%) received hematological treatment. Table 2 describes treatment regimens and the degree of hematological response. The median duration of treatment was 4 months (IQR 3 – 9). The median number of induction cycles was 6 (IQR 3 – 6). Eight patients (21%) required renal replacement therapy after a median time of 15 months (IQR 7 – 24). One received a kidney transplant from a deceased donor two years after diagnosis. Graphic 1 illustrates distribution according to the type of MGRS at diagnosis and the beginning of renal replacement therapy. Treatment of hemopathy was not required for reasons other than MGRS. Six patients died. Three had AL amyloidosis, two had MIDD, and one had PGNMID. Eighty-three percent of patients died from causes related to their disease. **Conclusions:** Monoclonal gammopathy of renal significance is a rare entity, and population studies are very scarce. The results presented agree with the scarce published literature. Real-life studies are necessary to understand our population and improve its management.

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Health-Related Quality of Life in Patients With Mayo Stage IV Light Chain (AL) Amyloidosis Treated With Birtamimab Plus Standard of Care: Results From the VITAL Trial

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Introduction: Patients with AL amyloidosis have reduced health-related quality of life (HRQoL), particularly those with advanced cardiac involvement who have a high symptom burden and poor physical function. Here, we assessed longitudinal HRQoL changes in the VITAL trial among patients with Mayo Stage IV AL amyloidosis. **Methods:** In the Phase 3 VITAL trial, newly diagnosed treatment-naïve patients with AL amyloidosis received birtamimab + standard of care (SoC) or placebo + SoC. The Short Form-36 questionnaire, version 2 (SF-36v2) was completed at baseline and months 3, 6, and 9; lower scores indicate worse HRQoL. A mixed model for repeated measures was used to estimate least squares mean (LSM), standard error (SE), and 95% confidence interval for each treatment group and LSM difference between groups. **Results:** In patients with Mayo Stage IV AL amyloidosis, baseline values were similar between birtamimab (n=38) and placebo (n=39) arms for all eight SF-36v2 domains and component summary scores. The LSM difference between treatment groups for change from baseline to month 9 numerically favored birtamimab in all domains. There was a significant difference at month 9 between treatment arms for role physical, bodily pain, social functioning, and physical component summary (PCS) score (PCS score previously reported in Gertz et al. Blood 2023). LSM (SE) change from baseline to month 9 in birtamimab and placebo arms [LSM difference], respectively, was: −2.1 (3.8) vs −13.5 (3.4) [11.5; P=0.023] for role physical; −3.0 (5.5) vs −19.4 (5.0) [16.3; P=0.025] for bodily pain; −5.7 (5.5) vs −28.5 (5.1) [22.8; P=0.002] for social functioning; −0.8 (1.7) vs −5.4 (1.6) [4.7; P=0.046] for PCS score. **Conclusions:** Treatment with birtamimab + SoC in patients with Mayo Stage IV AL amyloidosis was associated with significantly less decline in HRQoL versus placebo + SoC in several SF-36v2 domains.

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Evaluating the Efficacy and Safety of Limiting Dexamethasone in Newly Diagnosed AL Amyloidosis Compared to Conventional Dosing

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Introduction: AL amyloidosis is caused by the deposition of misfolded monoclonal immunoglobulin light chains, called amyloid fibrils, that can lead to cardiac, renal, hepatic, and other organ damage. Standard treatment involves chemotherapy with high-dose dexamethasone to suppress light chain production. However, long-term corticosteroid therapy can lead to significant adverse events. This retrospective study evaluates the effects of limited dexamethasone exposure versus standard prolonged exposure in newly diagnosed AL amyloidosis, focusing on treatment response and common adverse events. We hypothesize that limited steroid exposure will not impact disease response and will reduce steroid-related complications. **Methods:** A retrospective chart review from January 1st, 2017 to January 1st, 2023 identified adult patients with newly diagnosed AL amyloidosis who received treatment at our institution. Baseline data included patient history, demographics, symptoms, markers of organ involvement (NTproBNP, 24-hour urine protein, alkaline phosphatase), and monoclonal labs. Treatment data included regimen, dexamethasone dose/duration, hematologic and organ responses at 6, 12, 18, and 24 months based on ISA criteria. Steroid-related toxicities included hospitalization, heart failure exacerbations, increased diuretics, diabetic complications, and others. Using Chi-Square and Fisher's Exact tests, the primary outcome was the comparison of hematologic and organ response rates between patients with early dexamethasone discontinuation (< 6 months) and conventional dexamethasone discontinuation (≥6 months). The secondary outcome assessed steroid-induced complications. **Results:** A total of 216 AL amyloidosis patients were included in the analysis, divided into quartiles based on the duration of dexamethasone use: < 4.0 months (n=56), 4.0-5.4 months (n=52), 5.5-13.4 months (n=54), and ≥13.5 months (n=54). Comparison across these quartiles showed no difference in hematologic response (VGPR or CR) or organ response at 24 months. We then analyzed two groups based on the quartiles: early discontinuation of steroids (< 6 months, n=117) compared to those with prolonged steroid exposure (≥6 months, n=99). Combined CR/VGPR rates at 24 months were comparable between the groups, 82.3% vs. 80.8% (p=0.78). Steroid toxicities increased significantly in the prolonged exposure group versus the early discontinuation group, with higher rates of hospitalizations (75.5% vs. 62.3%, p=0.041), heart failure exacerbations (41.4% vs. 27.4%, p=0.029), and increased diuretic use (82.8% vs. 62.4%, p< 0.001). **Conclusions:** Our findings indicate that limiting dexamethasone usage in newly diagnosed AL amyloidosis patients maintains effective hematologic and organ response rates compared to conventional duration while significantly reducing the risk of adverse events, including life-threatening toxicities. By updating guidelines to support early discontinuation of steroids, we can enhance patient safety without compromising treatment success.

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Evolving Disease in Smouldering Myeloma (SMM) Is Accompanied by Serial Change in Immune Marrow Composition

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Introduction: An evolving phenotype has long been associated with progression in SMM independently from current snapshot risk models. COSMOS is a prospective, multi-centre, UK, observational study examining tumour dynamics and immune function longitudinally. In this analysis, we characterise patients

with evolving disease in terms of immune function and outcome. **Methods:** Patients with previous history, newly diagnosed, or suspected SMM were enrolled and clinical, radiological and laboratory features recorded. On study entry, fresh marrow samples undergo flow cytometry for tumour and immune cell subsets. To date, 129 patients are evaluable at 12 months. Evolving disease was defined broadly per previously described criteria applied across all patients not only those at diagnosis. **Results:** Evolving disease was seen in 45 patients (34.8%). Of these 30 had evolving haemoglobin, 12 evolving paraprotein, 2 evolving light chains, and 1 multiple features. There were no differences in baseline demographics between evolvers and non-evolvers, including in time from diagnosis. Baseline paraprotein, light chains, and BMPC% were not significantly different between the groups. Those with evolving disease were more likely a higher Mayo risk score at entry(p=0.004) but there was no significant difference in presence of high-risk cytogenetics. At entry NK-cells were higher in those who went on to evolve compared with those who did not(p=0.023). Serial samples at entry and 12m were available for 13 patients with evolving disease and 17 patients with non-evolving disease. These show a significant decrease in NK CD56high cells was seen in both groups(p=0.01/p=0.002), however evolvers also show an increase in CD4+ T-cells(p=0.048) and NKT cells(p=0.006) with a trend to increased Tregs(p=0.08). To date, 17 patients have progressed on study (excluding at entry or within three months), at a median of 8m from entry and 13m from diagnosis. One patient had evidence of evolving disease prior. Bone disease was seen in 40% of patients at progression. Patients who progressed within 24m(n=16) were more likely to be enrolled closer to the time of diagnosis(p=0.046) and were enriched in higher-risk Mayo groups(p< 0.001) compared to non-progressors in the same period. At baseline, these patients had higher NKT cells(p=0.014). Serial samples at entry and progression were available for only 4 patients thus definitive conclusions regarding dynamics in progressors versus non-progressors are not yet possible. **Conclusions:** In our data, while routine clinical data did not reliably differentiate those who would evolve from those who would not, evolvers had higher baseline NK cells. Dynamically, there was a significant increase in frequency of CD4+ T-cells and NKT cells and a trend to an increase in Tregs seen in evolvers. NK CD56high cells decreased overtime in both groups. Evolving disease dynamics appear to correlate with different immune trajectories that could help early identification of high-risk cases in the clinic.

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Correlative Analysis Between the 20-2-20 Score and 3D Telomere Profiling in Stratifying Smouldering Myeloma Patients

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Introduction: Multiple myeloma (MM) is preceded by asymptomatic precursor conditions: MGUS and smoldering multiple myeloma (SMM). The presence of a precursor condition in cancer indications provides an opportunity for intervention to delay or avoid progression to the symptomatic stage of the disease. In the case of MM, the low rate of progression of MGUS does not present a burden in the clinic. However, the SMM stage, with a progression rate of 40% over the first 5 years post-diagnosis, manifests an ideal scenario for intervention. Especially with the advancement in MM treatment regimens, there is now a possibility to achieve a cure. To take advantage of treatment possibilities for SMM patients, it is critical to identify the subset of patients with the highest risk of progression, to avoid exposing stable patients to treatments they do not need. Over the past years, several methodologies have been developed to stratify SMM patients. However, these methodologies did not exhibit satisfactory sensitivity to avoid exposing stable patients to treatment. Of particular interest are the multiparametric models, the Mayo Clinic 20-2-20 model, and the Spanish group model. In a recent report, we showed that the 3D profiling of telomeres, assessing telomere dysfunction and dynamically informing on genomic instability in SMM patients achieved unprecedented sensitivity and specificity in stratifying SMM patients of 83% and 76%, respectively, with associated positive predictive value (PPV) and negative predictive value (NPV) of 85% and 71%, respectively. **Methods:** We interrogated the correlation between the 3D telomere profiling and Mayo 20-2-20 score in assessing the risk of progression of the same subset of SMM patients. We included a cohort of 160 patients with available clinical outcome, Mayo 20-2-20 scores, and the TeloView outcome. The cohort included 99 SMM patients with short progression, and 61 long progression SMM patients.The 20-2-20 score classifies patients into low/intermediate/high risk of progression categories, while the TeloView prediction provides a binary patient outcome of either high or low risk of progression. To this end, we explored 3 scenarios to conduct the analysis: 1- eliminate patients scored as intermediate risk from the analysis; 2- harmonize the intermediate risk group into low-risk across both patient groups; and 3- harmonize the intermediate risk group into high-risk across both patient groups. **Results:** The highest correlation was achieved upon eliminating the intermediate risk group patients. We report an overall correlation of 53% between the TeloView prediction and the Mayo 20-2-20 score in the 110 patients qualified for the analysis. 49% correlation in short progression patients and 59% correlation in long progression patients respectively. **Conclusions:** The results of this study encourages further data mining to explore integrating the Mayo 20-2-20 score and the TeloView prediction model to achieve superior sensitivity and specificity in stratifying SMM patients.

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Prevalence of Type I Gaucher Disease in Patients With Smouldering or Multiple Myeloma: Results From the Prospective, Observational CHAGAL Study

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Introduction: Type I Gaucher disease (GD1) is a lysosomal storage disease caused by genetic defect of the enzime beta-glucocerebrosidase (GBA), associated with increased cancer risk. Risk for multiple myeloma (MM) occurrence is 5.9 - 51.1 times greater in patients with GD1 compared to general population. No studies explored the concurrent GD1 in patients diagnosed with MM except a small retrospective study. **Methods:** Type I Gaucher disease (GD1) is a lysosomal storage disease caused by genetic defect of the enzime beta-glucocerebrosidase (GBA), associated with increased cancer risk. Risk for multiple myeloma (MM) occurrence is 5.9 - 51.1 times greater in patients with GD1 compared to general population. No studies explored the concurrent GD1 in patients diagnosed with MM except a small retrospective study. **Results:** A total of 1004 patients affected by Smouldering Myeloma (SMM) or MM were enrolled in 22 Italian haematology centres. Median age was 68 (range: 36-92) years, median haemoglobin value was 11.8 g/dl (range: 4.5-17.6), median platelet count was 195 x 103/mmc (range: 10-772). Of 891 patients, 54% had newly diagnosed (NDMM), 32% relapsed refractory MM (RRMM) and 3% SMM. The monoclonal component was mainly IgG kappa (369, 37%), followed by IgG lambda (197, 20%). Forty percent of patients had anaemia, 15% renal failure, 6% hypercalcemia, 56% bone disease. As for high risk cytogenetic features, 1q21 was reported in 13% of patients, del17p in 4%, t(14;16) in 1% and t(4;14) in 8%. Twenty-three percent had International Staging System (ISS) III, 9% Revised-ISS (R-ISS) III. We found 14 patients (1.3%) with a positive DBS test, one with a compound heterozygous mutation of GBA gene (prevalence: 0.09%; 95%CI: 0.022-0.36), one with a double heterozygous mutation and 12 with a single heterozygous mutation (prevalence of double/single heterozygous status: 1.3%). The most frequently identified mutation was N370S (3 patients), followed by L444P (2 patients) and others; the compound heterozygous GBA mutated patient had L444P and R170C mutations. In the 13 heterozygous patients, median value of GBA enzymatic activity was 2.8 nmol/h/ml (range: 2.4-3.9) and median LysoGb1 value was 2.8 ng/ml (range: 1.7-5.4); 30.7% had a lower range GBA enzymatic activity with no abnormal LysoGb1 value. **Conclusions:** In our study the prevalence was 1 every 1004 MM/SMM patients - lower than hypothesized 0.5%- therefore the primary endpoint was not met. However, we found a 5.3 times higher prevalence in our study than that reported in Italy (0.09 vs 0.017/1000), closer to that in the Ashkenazi Jewish population (0,14/1000); as a similar study also found in MGUS. Therefore, it was demonstrated that GD1 should be considered an associated disease with plasma cell dyscrasias and patients with MGUS/SMM/MM and any signs of GD1 should be screened for the disease.

P-304

Impact of Pesticide Exposure on the Prevalence of Monoclonal Gammopathy of Undetermined Significance (MGUS) Among Residents of Western Paraná State: An Epidemiological Case-Control Study

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Introduction: Monoclonal Gammopathy of Undetermined Significance (MGUS) is marked by the asymptomatic proliferation of monoclonal plasma cells, which precedes Multiple Myeloma (MM), a bone marrow malignancy primarily affecting individuals over 50 years old and accounting for 10% of hematological cancers globally. While the etiology of MGUS remains largely unclear, evidence suggests that pesticide exposure may contribute to the development of this condition, especially among rural workers, due to their constant exposure to such substances. **Methods:** This study is an epidemiological, observational, case-control investigation designed to assess the prevalence of MGUS among residents of the western macro-region of Paraná State, Brazil. The study population includes men over 50, divided into two groups: the case group, consisting of individuals with a history of occupational pesticide exposure (pesticide applicators), and the control group, representing the general population. The study aims to enroll 480 participants, with 240 in each group. Ethical approval was granted by the Human Research Ethics Committee (opinion number 5.794.378), and Libbs Pharmaceutical financially supports the research through the institution's "Research Incentive Program." **Results:** Preliminary Results Data were collected from 158 participants between September and December 2023, with an average age of 63 years, predominantly residing in urban areas (68.99%). Of these, 92 participants were pesticide applicators, with 55.43% reporting prior pesticide use. The most common exposure method was backpacking spraying (50%). Soybeans were identified as the crop with the highest pesticide use (20.45%), with glyphosate being the most frequently used pesticide (23%), followed by 2,4-D (14%) and Paraquat (12%). Pesticide preparation for application was identified as the period of highest exposure (29%). Personal protective equipment was used by only 49% of participants, with 15% reporting occasional use. MGUS was

diagnosed in 5.7% (n=9) of the participants, with five cases from the applicator group and four from the non-applicator group. No statistically significant differences were observed between the groups, and no correlation was established between pesticide use and MGUS (p=0.730). However, logistic regression analysis indicated that age is a significant risk factor for MGUS (p=0.007, OR 2.70, CI 1.03-1.22). **Conclusions:** To date, no correlation has been identified between pesticide exposure and MGUS. Nevertheless, the study is ongoing, and future data will offer deeper insights into this subject, potentially aiding in formulating public health policies to safeguard the health of rural workers and the general population against the adverse effects of pesticide exposure.

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The Journey to Diagnosis of Light Chain Amyloidosis: A Real-World Experience from a Single Center in Latin America

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Introduction: Light chain (AL) amyloidosis is a clonal plasma cell disorder that causes organ dysfunction, primarily affecting the heart and kidneys. Due to non-specific clinical manifestations, diagnosis is challenging, resulting in delayed treatment and extensive organ involvement at diagnosis, which implies a poor prognosis. There is limited real-world data from Latin America on time from symptom onset to diagnosis. This retrospective cohort study aimed to assess the diagnostic journey and outcomes of patients with AL amyloidosis treated in a medical care program in Argentina. **Methods:** AL amyloidosis patients were identified using a 12-year follow-up data (January 1, 2010 to December 31, 2022) from the Institutional Registry of Amyloidosis. Diagnosis of AL amyloidosis was confirmed by tissue biopsy staining positive with Congo red, the demonstration of a monoclonal plasma cell proliferative disorder, and the presence of amyloid-related systemic syndrome. Symptoms and signs associated with amyloidosis, medical consultations and healthcare resource utilization data were collected from electronic medical records. Statistical analyses were performed using Stata version 13.0. Continuous variables were presented as median and interquartile range (IQR) and categorical variables as absolute frequencies and percentages. Survival rates were estimated by Kaplan-Meier. **Results:** From 181,807 community patients included in the comprehensive health care program, 28 were diagnosed with AL amyloidosis. The median age at diagnosis was 73 years (IQR, 66.5-80.5), with 64% (n=18) being female. Heart and kidney were the most frequently affected organs. The median time from the first sign and/or symptom to diagnosis was 15.9 months (IQR, 8.8-38.2). Only 4 patients (14%) were diagnosed within the first six months of symptom onset. The median number of symptoms/signs before diagnosis was 4 (IQR, 3.5-7). The median number of medical consultations prior to diagnosis was 3 (IQR, 1-5). The most consulted specialties were internal medicine (n=24, 86%), cardiology (n=14, 50%), and nephrology (n=10, 36%). Twelve patients (43%) were hospitalized at least once before diagnosis. Fifty-seven percent (n=16) had cardiac involvement, mostly in advanced stages. Of 23 patients treated, 22 received bortezomib-based regimens in first line; 3 in combination with anti-CD38. The median overall survival was 21 months (IQR, 4.6-49.8). The one-year overall survival rate after diagnosis was 55% (95% CI 34-71). The one-year overall survival rate for patients diagnosed within 12 months of symptom onset was 70% (95% CI 32-89), while for those diagnosed after 12 months, it was 45% (95% CI 20-67). **Conclusions:** This study provides real-world evidence about the diagnostic journey of AL amyloidosis patients in Latin America and supports that early diagnosis of AL amyloidosis remains an unmet need.

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Open-Label Phase 1b Study to Evaluate the Safety and Efficacy of ABBV-383 Monotherapy in Patients With Relapsed or Refractory Light Chain Amyloidosis

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Introduction: Trial in progress. Light chain (AL) amyloidosis is the most common form of systemic amyloidosis, and there is a high unmet need for new therapies for patients. Due to shared pathologic pathways, including expression of membrane-bound B-cell maturation antigen (BCMA) on clonal plasma cells, therapeutic approaches for AL amyloidosis have long followed multiple myeloma (MM). The innovative BCMA x CD3 bispecific antibody ABBV-383 features a unique design with a bivalent BCMA-binding domain with high avidity, a low-affinity CD3-binding domain that reduces the risk for cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life that allows for dosing convenience. Data from the phase 1 study of ABBV-383 monotherapy in patients with relapsed/refractory MM (NCT03933735) showed encouraging efficacy and a favorable safety profile. Among patients receiving 60 mg ABBV-383 monotherapy once every 4 weeks, the overall response rate was 65%, the complete response rate was 30%, and median time to first complete response was 4.2 months (range: 3.1–10.2 months). The incidence of CRS in this cohort was 43% (38% grade 1, 5% grade 2) (Rodriguez et al. J Clin Oncol. 2024;42[suppl 16]:7531). This study will evaluate the safety and efficacy of ABBV-383 monotherapy in patients with previously treated AL amyloidosis. **Methods:** This open-label, phase 1b study (NCT06158854) will enroll approximately 76 patients across

multiple sites globally. Eligible patients (≥18 years) have a diagnosis of systemic AL amyloidosis and have received prior treatment with a proteasome inhibitor and anti-CD38 monoclonal antibody. Additional eligibility criteria are ECOG performance status ≤2, at least 1 organ impacted by AL amyloidosis, and AL amyloidosis risk stage of 1, 2, or 3a. Intravenous ABBV-383 will be administered for a fixed duration or until hematologic progression, unacceptable toxicity, or other discontinuation criteria are met. The first dose of ABBV-383 will be administered in a hospital, where patients will be monitored for ≥24 hours for CRS. The study consists of 2 stages: dose escalation and safety expansion. Three different dose levels of ABBV-383 will be evaluated during the dose-escalation phase, which will be guided by Bayesian optimal interval design. After completion of dose escalation, 2 dose levels will be selected for safety expansion. Approximately 40 patients will be randomized 1:1 to the selected dose levels. The primary objectives of the study are to characterize the safety and toxicity profiles of ABBV-383 monotherapy and to determine the recommended dose. Secondary objectives include evaluation of hematologic and organ activity, pharmacokinetics, and immunogenicity of ABBV-383. Study enrollment started in the second quarter of 2024. **Results:** n/a. **Conclusions:** n/a.

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Waldenstrom's Macroglobulinemia: Clinical Presentation and Treatment Outcome From a Tertiary Care Centre From India

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Introduction: Waldenstrom's macroglobulinemia (WM) is a low grade, B-cell lymphoma characterized by the infiltration of the bone marrow by clonal lymphoplasmacytic cells that secrete monoclonal IgM immunoglobulin. This is a rare B NHL, which has an indolent course but remains incurable. It is characterized by MYD88 mutation, which is seen in 90% of patients. CXCR4 is the second most common mutation seen in 40% of patients. Since this is a rare malignancy, there is not much published literature in Indian settings. We herein present baseline characteristics and treatment outcomes of patients with Waldenstrom macroglobulinemia from a tertiary care center in north India. **Methods:** We retrospectively collected the data from Hospital information system (HIS) & Radiology department for patients of Waldenstrom macroglobulinemia from Jan 2016 to January 2024. **Results:** We had a total of 46 patients diagnosed with WM. The median age was 65 years with male preponderance (82.6%). Lymphadenopathy was seen in 18 patients (39.1%), splenomegaly in 11 patients (23.9%) and hepatomegaly in 7 patients (15.2%). One patient had presented with features of hyper viscosity. Mean Hb was 7.6g/dl and mean platelet count was 1.31L/dl. Mean M band on SPEP was 2.7. On IFE, majority were IgM kappa (89.1%). MYD88 mutation status was seen in 25 patients. 23 out of these 25 patients (92%) had positive MYD88. The patients were further stratified according to R IPSSWM. 2(4.3%) patients belonged to low risk, 8 (17.4%) had intermediate risk, 21 (45.7%) had high risk and 15 (32.6%) had very high risk. 29 out of the 46 patients underwent therapy at our institute. The commonly used regimens were Bortezomib, Dexa and Rituximab (BDR), Rituximab Bendamustine and Rituximab Cyclophosphamide Dexa (RCD). 5 patients were lost to follow up after initiation of therapy and hence their response could not be assessed. Out of the remaining patients, CR was observed in 2 patients, VGPR in 1 patient, PR in 9 patients and MR in 6 patients. ORR was 75%. 4 patients had stable disease and 2 patients had progressive disease. 7 patients had relapsed after frontline therapy. 3 patients received R Benda and 2 patients received BDR as 2nd line therapy. 1 patient expired and 1 patient was lost to follow up after relapse. 1 patient, who had received R Benda as 2nd line relapsed and was started on Acalabrutinib. A total of 4 patients died. 2 patients died due to disease complications in the form of hyper viscosity and sepsis with DIC. 1 patient died at relapse due to sepsis. 1 patient, in 2nd remission, died to road traffic accident. **Conclusions:** In this study, we report the presenting features as well as the treatment outcomes of Waldenstrom macroglobulinemia. The response rates were lower when compared to Western literature. However, this is one of the few Indian studies, till date, to report on the characteristics of the disease.

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Epidemiology of POEMS Syndrome: Experience of the Grupo Argentino de Mieloma Múltiple (GAMM)

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Introduction: POEMS syndrome is a paraneoplastic syndrome caused by an underlying plasma cell neoplasm. There are major and minor criteria to diagnose this syndrome. The actual incidence is unknown. It is often underdiagnosed because the clinical manifestations are complex and involve multiple systems. Treatment should be aimed at eliminating the plasma cell clone and controlling symptoms. Its low prevalence makes it a difficult syndrome to suspect. Reports of this disease are scarce and there is no precise data on this pathology in Argentina. **Methods:** A retrospective multicenter cohort study. Inclusion criteria: Patients over 18 years of age diagnosed with POEMS syndrome between 2013 and 2023, according to the criteria of Dispenzieri et al. Exclusion criteria: Patients with Castleman disease variant of POEMS syndrome. Statistical analysis was performed using descriptive statistics. The Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). Stata 13 software was used. **Results:** Twenty patients were included. The median age at diagnosis was 48 years (range, 29-74), with 70% male patients. The median time to

diagnosis was 6 months (IQR 3-18 months). The main symptoms were fatigue, weight loss, polyneuropathy, and extravascular volume overload. All patients met the main criteria of polyneuropathy and monoclonal gammopathy, most frequently IgA lambda in 9/20 patients (45%) and IgG lambda in 7/20 (35%). VEGF levels were measured at diagnosis in only 3/20 patients (15%), all elevated; 5/20 patients (25%) had Castleman disease and 7/14 (60%) had sclerotic bone lesions. Among the minor criteria, 14/20 (70%) had organomegaly, 12/20 (40%) extravascular volume overload, 18/20 (90%) endocrinopathy, 15/20 (75%) skin changes, 4/20 (20%) polycythemia, and 10/20 (50%) thrombocytosis. The median number of treatment lines was 1 (range, 1-2). Nine patients (45%) received radiotherapy. Common regimens were VCD in 8/20 patients (40%), RD in 4/20 (20%), and RVD in 3/20 (15%). The median number of cycles was 4 (range, 1-10). Hematologic response was complete in 9/20 patients (45%), very good partial in 6/20 (30%), and partial in 4/20 (20%). Ten patients (50%) underwent autologous stem cell transplantation. Symptomatic improvement was observed in 18/20 patients (85%). At analysis, only 1 patient had relapsed and all were alive. After a median follow-up of 27 months (IQR 17-77), median PFS (95% CI, 31-NR) and median OS (NR-NR) were not reached. **Conclusions:** POEMS syndrome is a rare disease, often unrecognized or underdiagnosed. Sixty percent of patients had a time to diagnosis of more than 6 months from the onset of symptoms. Its etiology is uncertain, although VEGF appears to contribute significantly to the appearance of many symptoms. Its measurement continues to be difficult in our environment. Differential diagnosis and prompt recognition of symptoms remain crucial, as treatment should be started as soon as possible to prevent its progression.

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Diagnostic Challenges in Systemic Amyloidosis: Exploring the Impact of Mass Spectrometry in a Middle-Income Country Cohort

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Introduction: Systemic amyloidosis is often underdiagnosed in low and middle-income countries due to limited awareness and access to diagnostic methods, resulting in prolonged journeys and delayed diagnoses. Identifying the precursor protein accurately is a crucial but challenging aspect of patient care. In this study, we aimed to perform mass spectrometry (MS) to subtype amyloid and assess the diagnostic performance of a clinical-laboratory model for amyloid typing in the absence of the gold standard method. **Methods:** This is a retrospective, observational and unicentric study. Biopsies were randomly selected from a cohort of 127 patients diagnosed with systemic amyloidosis at a Brazilian university public hospital between 2009 and 2018. Previous diagnoses and medical records were reviewed. The clinical-laboratory model determined the amyloid subtype based on various factors such as clinical presentation, monoclonal component, pyrophosphate scintigraphy, immunological methods for amyloid typing, and genetic mutations. If precise subtype criteria couldn´t be defined, subtyping diagnosis relied on available data and clinical judgment. **Results:** Fifty biopsies were included from 11 different organs (kidney 31%, heart 20%, subcutaneous fat 12%, gastrointestinal tract 10%, nerve 8%, lung 8%, lymph node, bone marrow, liver, salivary gland and tongue 2% each). MS identified the following subtypes: AL (58%, n=29), ATTR (24%, n=12), AA (6%, n=3) and AFib (2%, n=1). Five cases were inconclusive. The clinical-laboratory model correctly subtyped amyloid in 100% of AL, AA and AFib, and 75% of ATTR cases. Three patients with ATTR were misdiagnosed as AL. **Conclusions:** Despite the satisfactory performance of the clinical-laboratory model in typing amyloid in our study, MS remains the gold standard. It can be performed on routinely collected or previously stored paraffin embedded tissue samples, identifying known amyloid proteins and describing new ones without requiring multiple antibodies for each subtype. Its implementation minimizes misdiagnosis, avoiding potential harm from misdiagnosis and incorrect treatment.

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Clinicopathological Characteristics of Patients with POEMS Syndrome – Analysis from the UCLH POEMS Centre Registry

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Introduction: POEMS syndrome is a rare multisystem paraneoplastic plasma cell disorder. The mandatory features of a monoclonal plasma cell disorder and peripheral neuropathy are well established, but additional clinical features are increasingly described. We describe the clinical characteristics, beyond neuropathy, of patients with POEMS syndrome seen in our specialist service. **Methods:** We undertook a retrospective cohort analysis of all patients in the UCLH POEMS Centre Registry. **Results:** POEMS syndrome was present in 156 patients; 142 had prerequisite data recorded and were included. Years of diagnosis were 1998-2024. The median age at diagnosis was 54 years (range 26-84), and 103 (72.5%) patients were male. Median time from symptom onset to diagnosis was 10 months (range 2-178m). At diagnosis, 30 were mobilising unaided, 100 with aids (35 stick, 30 wheelchair. 23 frame, 12 orthotics) and 12 bedbound. Skin changes were present in 97 (68.3%) and fluid overload in 94 (66.2%). Venous thrombotic complications occurred in 21 (14.8%) and stroke in 13 (9.2%). Thrombocytosis was present in 45 (31.7%) and polycythaemia in 19/142 (13.4%) patients. Median serum VEGF was 3807pg/mL (range 200-30,101) and elevated in 138/142 (97.2%) patients, with four normal values in patients on steroids. Renal impairment was present in 22 and

18 patients had albumin < 35g/L. A relevant endocrinopathy, as per established diagnostic criteria, was present in 79/142 (55.6%). CSF protein was elevated in 69 of 72 tested patients (95.8%), at a median of 1.2g/L (range 0.35-4.8). Paraprotein was detected in 117 (82.4%) at median concentration of 4 g/L (range TFTQ-17). The heavy chain was IgA in 59 (50.4%), IgG in 58 (49.8%), and IgM in 1 (0.8%). Biclonal paraproteins were present in 8 (6.8%). Four cases (3.4%) were light chain only. All 142 cases were lambda light chain restricted, although an additional kappa paraprotein was detected in five cases. Median serum free lambda light chains 39.5 (range 10.1-561) and kappa 31mg/L (7.8-220), with ratio 1.2 (0.17-56). Bone lesions were present on imaging in 112/142 (78.9%) patients, 61 sclerotic, 24 lytic and 27 mixed, and 62 (43.7%) had organomegaly. A systemic plasma cell disorder was present in 104/142 (73.4%) patients. Bone marrow examination demonstrated clonal plasma cells in 73 (51.4%), with a median marrow burden of 7.5% (range 2-30%). Castleman disease was present in 18/142 (12.7%) patients. A solitary plasmacytoma was present in 38/142 (26.7%). **Conclusions:** POEMS syndrome is a heterogenous condition with a median age at diagnosis of 54 years. Only 21% were mobilising unaided by time of diagnosis. All had a lambda-light chain restricted plasma cell dyscrasia and elevated VEGF, apart from those already on steroids. Negative immunofixation but biopsy-proven plasma cell dyscrasia was observed in 17.6% cases. A quarter of cases are due to a solitary plasmacytoma. Serum free light chain assays typically demonstrate a mild polyclonal increase, with preserved ratio.

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Systemic Treatment Outcomes in Relapsed or Refractory POEMS Syndrome – Analysis from the UCLH POEMS Centre Registry Spanning 25 Years

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Introduction: Treatment options for relapsed or refractory (R/R) POEMS syndrome typically mirrors that of multiple myeloma (MM). However, there is a paucity of data regarding outcomes in this relatively rare plasma cell disorder. We describe the outcomes of patients at our specialist centre. **Methods:** We retrospectively reviewed the treatment and outcomes of patients with R/R POEMS in the UCLH POEMS Registry from 1998-2024. **Results:** Of 142 patients with complete data, 44 patients (31%) with R/R POEMS were identified. Second line (2L) chemoimmunotherapy was delivered in 36 (82%) cases, following previous upfront melphalan autologous transplant (ASCT) (n=21), lenalidomide-dexamethasone (Rd) (n=10), cyclophosphamide-d (Cd) (n=2), bortezomib-d (Vd) (n=2) and oral melphalan (n=1). Median age was 55 years (range 37-85) and median follow up (f/u) time from start of 2L was 39 months (1-158m). Twelve (27%) patients were primary refractory and all received 2L treatment: 6 daratumumab-Vd (DVd), 2 Rd, 2 Vd, 1 ixazomib-Rd (IRd), carfilzomib-d (Kd). 4/12 patients remained refractory. Best VEGF complete response (CRV) was seen in 6/12 (50%), partial response (PRV) 1 (8%) and no response (NRV) in 5 (42%); haematological PR 7/12 (58%) and NRH in 5 (42%). 2L 1- and 3-year overall survival (OS) was 100% and 80% (95% CI 52-100%), and 1- and 3-year progression free survival (PFS) both 51% (27-93%). 3L therapy was required in 2 cases; both received Cd; 1 CRV and 1 NRV; 1PRH and 1 NRH. 4L pomalidomide-d (Pd) was used in 1 case, to PRV and PRH. Relapsed disease was seen in 24 patients; 14 received Rd, 3 Cd, 3 DVd, 2KRd, 1 oral melphalan-d, and one proceeded directly to 2L ASCT. 1- and 3-year OS were both 95% (87-100%); 1- and 3-year PFS were 81% (66-100%) and 70% (53-93.6%). CRV was seen in 15/21 (71%) assessable cases, PRV 3 (14%) and NRV in 3 (14%); CRH in 1 (5%), PRH in 12 (57%) and NRH in 8/21 (38%). 3L therapy was given in 6 relapsed cases; Cd in 2, Vd in 2, DVd 1 and DRd 1, with 1- and 3 year OS both 83% (58-100%); 1- and 3 year PFS both 51% (8%-NR). Only 2 relapsed cases required 4L therapy; both received isatuximab-Pd (IPd) with 1-year OS and PFS both 100%. For all 2L R/R DVd, 1- and 3-year PFS was 71% (45-100%); 1- and 3-year OS 100%; CRV in 4 (44%), PRv 3 (33%) and NRV in 2/9(22%); PRH 4(44%) and 5/9 (56%) NRH. For 2L R/R Kd/KRd all 3 patients responded with 1- and 3-year OS and PFS 100%. CRV seen in 100%; 1/3 (33%) CRH and 2/3 PRH (67%). ASCT was performed 2L in 7/36 patients, including 2nd ASCT in 4, with CRV in 7/7 (100%); PRH in 4/7 (57%), and NRH in 3/7 (43%). Only 1/7(14%) subsequently relapsed. 1- and 3-year OS both 100%; 1- and 3-year PFS was 100% and 67% (30-100%). **Conclusions:** A third of patients with systemic POEMS in our cohort required 2L therapy. Therapies used for R/R MM are efficacious. 2L line ASCT resulted in deep and durable responses. However, attainment of CRH is relatively rare. A third of primary refractory cases did not respond 2L. Further study on treatment for R/R POEMS is required.

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Systemic AA Amyloidosis; As Idiopathic Multicentric Castleman's Disease Complication With Emergent Monoclonal Plasma Cell Escape As POEMS

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Introduction: Idiopathic multicentric Castleman disease (iMCD) is a subtype of MCD characterized by a chronic inflammatory process involving polyclonal lymphoproliferation and is negative for HHV-8. While the exact etiology of iMCD is not clear yet, dysregulated IL-6 expression with high circulating IL-6 concentration seems to be a major contributor. iMCD is also a part of POEMS syndrome. The differential diagnosis between POEMS and iMCD can be quite challenging due to their identical histology, and overlapping symptoms such as organomegaly, anasarca, and constitutional symptoms. Clarity in diagnosis is crucial for treatment planning. Persistent inflammatory response may be complicated by

systemic AA amyloidosis. In AA amyloidosis amyloid fibrils are derived from an acute phase reactant protein serum amyloid A (SAA) protein. IL-6 is one of the major stimulants of SAA. We here report a patient with POEMS-associated CD disease who stayed a long time without treatment and came to attention with emergent AA amyloidosis-related symptoms. **Methods:** A 48-year-old male patient was referred as having treatment-refractory iMCD with multiple mediastinal lymph nodes, emerging monoclonal gammopathy, and massive proteinuria. In the past, he had been evaluated for infertility, diagnosed as having primary hypogonadism, and was found to be with a normal karyotype and no inherited disorders. He was exhausted, dyspneic, striking skinny, and lost 20 kg in the last three months. Based on the laboratory results as anemia, high serum CRP, serum creatinine level, hypoalbuminemia, and massive proteinuria; a kidney biopsy was decided. He had monoclonal gammopathy as IgM lambda and IgG kappa type and 0,46 g/dL M protein on serum protein electrophoresis. Abdominal fat aspiration was found to be amyloid negative. Kidney histology was consistent with AA amyloidosis. Severe iMCD-associated AA amyloidosis was diagnosed. Based on blocking the downstream effects of IL-6, an anti-IL-6 receptor monoclonal antibody tocilizumab which was available in the country, was chosen for treatment. Three courses of tocilizumab led to significant improvement but proteinuria and serum creatinine levels continued. **Results:** He gradually developed polyneuropathy affected sensory and motor nerves when receiving tocilizumab 3rd course. Upon re-evaluation following the onset of new polyneuropathy symptoms, it was determined that the patient fulfilled the criteria for POEMS syndrome. The treatment plan was revised to include immunomodulatory agents lenalidomide and an anti-CD38 monoclonal antibody, daratumumab. **Conclusions:** AA amyloidosis is a rare systemic complication caused commonly by chronic inflammation in MCD. POEMS-associated MCD is a clinical subtype of iMCD. Approximately 15-20 percent of patients with POEMS syndrome also have iMCD. We have chosen first to control inflammation with anti-IL-6 but changed the management when monoclonal escape as POEMS emerged. A more targeted therapy was given to control monoclonal plasma cell disorder.

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Plasmacytoma-like Posttransplant Lymphoproliferative Disorder in a Young Kidney Transplant Recipient

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is a group of lymphoid or plasmacytic proliferations that can occur in transplant recipients as a result of immunosuppression, often driven by the Epstein Barr virus (EBV). While PTLD usually originates from B-cells and resembles B-cell lymphomas, it can exceptionally present as a plasmacytic process resembling multiple myeloma. This report describes a rare case of plasmacytoma-like PTLD in a young kidney transplant recipient. **Methods:** Case report **Results:** A 23-year-old man who received a kidney transplant in 2003 for perinatal asphyxia complicated by cortical necrosis, was on chronic immunosuppression with methylprednisolone, tacrolimus and azathioprine. He presented diarrhea for several months. Following an episode of acute allograft dysfunction, a urinary tract ultrasound revealed numerous mesenteric and retroperitoneal enlarged lymph node with compression of the left iliac vein. A PET scan confirmed the multiple mesenteric adenomegalia and the presence of hypermetabolic adenopathies in the right cervical region. Further investigations demonstrated a positive blood PCR for EBV (>3,000 copies/mL), elevated kappa free light chain M-protein (924 mg/l) with an abnormal kappa/lambda ratio (55), with 5-10% abnormal plasma cells in the bone marrow biopsy. A cervical lymph node biopsy showed a plasmacytoma-like PTLD with kappa monotypia. Epstein-Barr encoding region (EBER) in situ hybridization was negative. A colonoscopy was performed due to diarrhea, and colonic biopsies confirmed the presence of the plasmacytoma-like PTLD also in the colon. Treatment included reduction of immunosuppression by discontinuing azathioprine, followed by 8 cycles of bortezomib – dexamethasone and 9 cycles of rituximab, based on CD20-positive cells as part of the population, resulting in complete hematologic and metabolic remission on PET scan, with diarrhea resolution. Notably, we did not use daratumumab as it is not reimbursed in Belgium for this indication. Intensive chemotherapy with melphalan followed by autologous hematopoietic stem cell transplantation was initially planned based on the rare cases reported in the literature, but had to be postponed due to severe myocarditis, likely related to COVID-19 infectious complications. After a follow-up of 21 months, the patient is still in complete metabolic response. **Conclusions:** This case highlights a rare occurrence of plasmacytoma-like PTLD in a young renal transplant recipient. Treatment recommendations are based on a limited number of case series. Effective management has included reduction of immunosuppression and targeted chemotherapy. Despite advances in the treatment of multiple myeloma with immunomodulatory agents and proteasome inhibitors, there is minimal data on their use in PTLD, leaving clinicians with limited guidance on prognosis and treatment. This case highlights the critical need for continued vigilance and personalized care strategies to manage rare post-transplant complications.

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Daratumumab for Refractory Proliferative Glomerulonephritis With Monoclonal Immunoglobulin G Deposits and Severe Chronic Kidney Disease

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare immune-mediated kidney disorder most often associated with IgG3 kappa deposition in glomeruli. PGNMID poses major challenges to clinicians as it frequently progresses towards kidney failure and recurs after transplantation. In addition, there is no consensus about the appropriate treatment in patients with PGNMID, especially in the absence of a plasma or B cell clone. **Methods:** Here we report the presentation and outcome of a patient with PGNMID refractory to rituximab and complicated by severe chronic kidney disease treated with daratumumab. **Results:** A 54-year-old White patient with no relevant medical history was referred for nephrotic syndrome, heavy proteinuria (urine protein to creatinine ratio 9 g/g), hematuria and progressive decline in glomerular filtration rate (GFR). A kidney biopsy showed mesangioproliferative glomerulonephritis, with bright (3+) IgG3 kappa and complement C3 deposition on immunofluorescence, and the absence of organized deposits on ultrastructural analysis, consistent with the diagnosis of PGNMID. Interstitial fibrosis and tubular atrophy score was 2, involving 25-50% of the renal cortex. A complete workup, including serum and electrophoresis and immunofixation, serum free light chains assay, bone marrow aspiration, positron emission tomography and flow cytometry showed no evidence of plasma or B cell clone. Despite renin angiotensin system inhibition, dapagliflozin, and four weekly doses of rituximab (375 mg/m2), proteinuria and hematuria persisted and the CKD-EPI estimated GFR declined from 55 mL/min to 16 mL/min/1.73 m2 over a 12-month period. The patient was then referred to discuss alternative treatment options. Based on a recent case series from the Mayo Clinic, suggesting that daratumumab may lead to remission in cases of PGNMID refractory to rituximab (Zand, JASN 2021), the patient was treated with subcutaneous daratumumab (1800 mg) weekly for 8 weeks, then every other week for 8 additional doses. Daratumumab was well tolerated, i.e. with no infection. After 6 months, proteinuria decreased to 4 g/g, serum albumin increased from 29 to 37 g/L and eGFR stabilized at 19-21 mL/min/1.73 m2, in contrast to the >35 ml/min decline over the 12 months preceding initiation of the anti-CD38 monoclonal antibody (see graph). Because of the risk of relapse and the low eGFR, daratumumab was further continued once a month for at least 6 additional consolidation cycles. **Conclusions:** Daratumumab may delay progression to kidney failure in patients with PGNMID refractory to rituximab and severe chronic kidney disease. Daratumumab appears to be effective and well tolerated, and deserves further evaluation in both treatment-naïve and treatment-resistant PGNMID.

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Safety and Efficacy of Elranatamab in Patients with Relapsed or Refractory AL Amyloidosis: A Retrospective Case Series

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Introduction: Elranatamab (Elra) is a bispecific T-cell engager targeting B-cell maturation antigen expressed on plasma cells, which has demonstrated a high rate of deep and sustained hematological responses in multiple myeloma. AL amyloidosis is a related plasma cell disorder with limited treatment options despite its similar treatment paradigm. Characterized by tissue deposition of amyloid free light chain (FLC) fibrils, effective plasma cell therapy to achieve a deep and rapid hematological response is critical to halt amyloid production, maximize organ function, and prolong survival. There are currently no published data regarding the safety and efficacy of Elra in patients with AL amyloidosis. **Methods:** 3 adult pts with relapsed/refractory AL amyloidosis were treated with Elra between 2/2024 – 5/2024. The revised 2004 Mayo Clinic criteria with European modifications were used for cardiac staging. Demographics, response rates, and adverse events were evaluated, and pts were assessed for hematological and organ response. **Results:** The median age was 64 (range 46-68), 2 were female, and all had multiorgan amyloid involvement (range 3-4), including 3 cardiac (2 stage 3A, 1 stage 3B), renal (2), soft tissue (2), and autonomic (2). No pts met criteria for multiple myeloma, but 2 pts had a FLC ratio >100. Pts received a median of 2 lines of prior therapy (range 1-2). All had prior exposure to CD38 antibodies, bortezomib (2), ixazomib (1), pomalidomide (1), and venetoclax (1). 2 pts had primary refractory disease to frontline DaraCyBorD or Dara-Dex. 2 were refractory to their immediate prior line of treatment. All were transplant ineligible and BCMA-naïve. The ORR was 100% with hematologic complete remission (hCR) in all pts. Median time to hCR was 14 days (range 11-14). 1 pt achieved a cardiac response at 30 days. All pts were still alive and continued in hCR at the time of report with a median follow up of 81 days (range 80-118) and median of 5 doses (range 2-15). 2/3 pts developed cytokine release syndrome (CRS), both grade 2 within 24 hours of 1st priming dose, which lasted 2 days, required a delay in the 2nd priming dose, and improved after tocilizumab and glucocorticoids. There were no subsequent CRS events and no ICANS present. 2 pts developed cytopenias during the 1st cycle, 1 with grade 2 neutropenia requiring growth factor and 1 for grade 1 thrombocytopenia, however neither required transfusion. No pts required ICU level of care. **Conclusions:** In this series of relapsed/ refractory AL amyloidosis, including daratumumab primary refractory pts, Elra showed outstanding depth and rapidity of hematological response with all pts achieving hCR and a stringent difference in FLC (dFLC < 10 mg/L) within the 1st cycle and organ response in 1 pt. Elra was well-tolerated with a manageable side effect profile. Elranatamab shows promise in treating pts with relapsed/ refractory AL amyloidosis. Larger prospective studies are needed to determine long-term outcomes and safety in this high-risk population.

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A Retrospective Analysis of the Efficacy and Safety of a Single-Center Daltuzumab-Based Treatment for Light Chain Amyloidosis

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Introduction: 192/ 5000 Light chain amyloidosis (AL) is a disease caused by amyloid deposition in tissues and organs due to misfolding of immunoglobulin light chains. The prognosis of AL is poor, and although Daratumumab has shown significant efficacy in patients with AL in several clinical trials, patients with poor underlying conditions were excluded due to strict selection criteria. This study explores the efficacy and safety of Daratumumab-based treatment in patients with poor basic conditions under non-strict screening, and provides clinical treatment options and references. **Methods:** Patients with AL who attended Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology from May 2021 to May 2024 and received ≥ 3 courses of Daratumumab were included. Patients received different combinations of Daratumumab combination regimens, including Daratumumab lenalidomide dexamethasone, Daratumumab bortezomib dexamethasone, Daratumumab pomalidomide dexamethasone, Daratumumab serinexol dexamethasone, Daratumumab isazomib dexamethasone, Daratumumab carfizomib dexamethasone. **Results:** This retrospective analysis included 38 patients, 28 newly diagnosed and 10 relapsed/refractory, with a median age of 59 years (38 to 75 years). Mayo staging III to IV was observed in 52.6% of patients. 29 patients (76%) had cardiac involvement and 20 patients (52%) had renal involvement. The median NT-proBNP was 2375 (14-54883) ng/L, the median 24-hour urinary protein quantification was 0.683 (0.123-15.094) g, and the median eGFR was 71.1 (4.1-118.7) ml/min/1. 73m2. The median dFLC was 132.05 (6.4 -11328.63) mg/L. In terms of hematological response, the objective response rate (ORR) of all patients at the first month after treatment was 52.6% (20/38), of which 16 patients had ≥ VGPR; ORR was 72.2% (26/36) at 6 months, ≥ VGPR was 22 cases; ORR was 90.9% (10/11) and ≥ VGPR in 9 cases at 12 months. In terms of organ response, the response rate in patients with cardiac involvement was 42% after 3 months of treatment, 78% after 6 months, and reached 85% after 12 months. Of the patients with renal involvement, 9 (45%) developed an organ response 12 months after treatment. In terms of safety, the most frequent adverse effects were neutropenia and anemia in 12 cases (31.5%); Infusion reaction occurred in 8 cases (21%), all of which were grade 1-2. **Conclusions:** This study reviews the real-world data of Daratumumab in the treatment of AL patients, confirming that Daratumumab rapidly induces hematological and organ responses, with an ORR of 90.9% at the 12th month, which is comparable to the current data of Daratumumab in the treatment of AL with an ORR of more than 80%., achieved a similar level of efficacy. At the same time, the adverse reactions were slightly controllable. It shows that Daratumumab is an effective treatment option for AL patients, which provides an important treatment reference and basis for clinicians when facing AL patients with poor basic conditions.

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Daratumumab Combined With Carfilzomib and Dexamethasone as an Induction Regimen Results in Rapid Response in Newly Diagnosed POEMS Syndrome

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Introduction: POEMS syndrome is a rare plasma cell disease, mainly characterized by multiple peripheral neuropathies and proliferation of monoclonal plasma cells. Current treatment regimens are based on anti-plasma cell therapy. **Methods:** This study retrospectively analyzed 50 patients with newly diagnosed POEMS syndrome diagnosed in the Department of Hematology of the First Affiliated Hospital of Sun Yat-sen University from June 1, 2013 to August 31, 2023. **Results:** The median age of the 50 patients with newly diagnosed POEMS syndrome was 55 years, 100% of the patients combined with neurologic symptoms, 80% of the patients with organomegaly, and 72% of the patients with endocrine axis abnormalities. 52% of patients with POEMS syndrome had skin changes, and 58% had monoclonal plasma cells. Overall Response Rate (ORR) in hematology reached 56.3% at the end of 2cycles and 56.6% at the end of 4 cycles, and 42.3% of patients who obtained a VEGF ORR at the end of 2cycles, and at the end of 4cycles, patients with POEMS syndrome had a VEGF ORR of 73.9%, and VEGF levels were significantly lower than before treatment (p=0.005). Patients in the Dara+KD group had an ORR of 100% at the end of 4 treatments for either hematology or VEGF. Transplantation significantly improved patient outcomes, with an increased percentage of patients with hematology CR (16.7% vs. 63.6%). Meanwhile, VEGF response was significantly higher in post-transplantation (CR 41.6% vs. 90.9%), and VEGF levels were significantly lower than pre-transplantation (p=0.012). **Conclusions:** Anti-plasma cell-based regimen and ASCT to treat POEMS syndrome can achieve good response, Dara +KD can result in rapid response.

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A Real-World Comparison of First-Line Regimens in Transplant Ineligible Patients with Multiple Myeloma

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Introduction: The management of transplant-ineligible (TI) patients with newly diagnosed multiple myeloma (MM) is challenging given wide variability in treatment tolerance. At this time, lenalidomide(R)/dexamethasone(Rd), bortezomib/Rd(VRd), and daratumumab/Rd(DRd) are used in TI patients. Data on treatment outcomes is derived from clinical trials which are not representative of the real-world population. In addition, real-world

data on DRD is limited. We conducted a retrospective population-based study to compare outcomes between the 3 regimens in the first year of diagnosis. **Methods:** We used data from the Institute for Clinical Evaluative Sciences (ICES), an administrative database capturing all health records in Ontario, Canada. We identified adult patients with MM from 2017-2023 who are TI, had 1st-line treatment with Rd, VRd, or DRd, and ≥1 year follow-up. We evaluated patient demographics, treatment details, health care utilization, early mortality, and 1-year overall survival (OS). We also captured patient-reported symptoms using the Edmonton Symptom Assessment System (ESAS) score which evaluates 9 common symptoms with a score of 7-10 considered to be severe. **Results:** During the study period, 765, 547, and 73 patients received Rd, VRd, and DRd, respectively. This is consistent with approval dates: DRd was approved recently in September 2022. Median age at start was 80, 77, and 73 years, respectively. The most common dose for R was 10-15 mg both at treatment start (60%, 67%, and 56% for Rd, VRd, and DRd, respectively), and at 1 year (54%, 58%, and 49%, respectively); < 25% started at 20-25 mg. By 1 year, only 16%, 9%, and 14% of patients in the 3 groups, respectively, were using 20-25 mg. The 1-year mortality rate was 25% for Rd,19% for VRd, and 22% for DRd with 1-year OS being 75% (95%CI: 72-78), 81% (95%CI: 78-85), and 78% (95%CI: 69-88), respectively. Health care utilization was high across all 3 regimens, with >50% of patient experiencing at least one hospitalization within 1 year following regimen start. Post-treatment cytopenias were highest for the DRd group compared to other regimens with 42% experiencing at least one episode of grade 3+ anemia (Hb< 8g/dL), 23% thrombocytopenia (< 50 x 10^3/μL), and 52% neutropenia (< 1.0 x 10^3/μL) within year 1. For all regimens, there was a high symptom burden with 32%, 22%, and 25% of patients on Rd, VRd, and DRd, respectively reporting ≥1 severe ESAS score within the year 1 post treatment. **Conclusions:** Our study is one of the first to highlight the ongoing high rate of early mortality, health care utilization, and symptom burden in TI MM patients with novel combinations including DRd, in the real-world. This highlights the need for better supportive care strategies. For all regimens, real world R dosing is lower compared to the clinical trial setting. Despite this, DRd is still associated with a high rates of neutropenia. One-year mortality appears similarly high for DRd and VRd, but further follow-up is needed for longer term outcomes.

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First-Line Treatment Landscape in Multiple Myeloma: Analysis of Stem Cell Transplantation and Drug Utilization in Brazil and Argentina from the TOTEMM-A and TOTEMM-B Real-World Studies

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Introduction: Real-world data on patients with multiple myeloma (MM) are scarce in Latin America; consequently, the treatment landscape remains poorly understood. The TOTEMM study was conducted to describe real-world treatment patterns and clinical outcomes of patients with MM in Brazil (TOTEMM-B) and Argentina (TOTEMM-A). Here, we describe treatment characteristics in patients with MM in both countries. **Methods:** Both studies comprised a retrospective database analysis. TOTEMM-A used a database of electronic private medical records from Hospital Italiano between Jan 2010 and Dec 2021, and TOTEMM-B used administrative claims data from patients with private insurance plans from Orizon between Jan 2015 and Jun 2021. Index was defined as a proxy of diagnosis and could be the first MM-related health term/ICD-10 code, or any related procedure, exam, or treatment for MM. Adults (≥18 years) with ≥1 MM-related health term/ICD-10 code and ≥12 months of follow-up after index were included. Frequencies of stem cell transplant (SCT) or antineoplastic drug (AD) use for incident cases (treatment naïve for ≥1 year before MM index) were described. **Results:** In TOTEMM-A and -B, 134 and 736 patients with MM, respectively, from the incident cohort were included. In TOTEMM-A, 6.0% were diagnosed at <50 years old, whereas in TOTEMM-B this was 14.1%. Mean (standard deviation [SD]) age was 70.6 (11.7) years in TOTEMM-A and 61.9 (11.3) years in TOTEMM-B. Mean (SD) follow-up in TOTEMM-A was 58.9 (32.6) and in TOTEMM-B was 30.6 (14.3) months. In TOTEMM-A, mean (SD) weight was 74.7 (17.8) kg and 71.0% had a body mass index of ≥25 kg/m2 (no data for TOTEMM-B). Median (interquartile range [IQR]) time from index until first treatment was 1.1 (4.4) months in TOTEMM-A and 0.9 (1.5) months in TOTEMM-B. Around one-fifth underwent SCT in TOTEMM-A (17.9%) and one-quarter in TOTEMM-B (23.2%) during follow-up. In TOTEMM-A, two patients underwent SCT in 1L therapy, and the time from index until SCT was 17.0 months. In TOTEMM-B, 9.6% (n=57) underwent SCT in 1L therapy, and the median (IQR) time from index to SCT was 6.0 (3.3) months. Among those who received ADs in 1L, 69.4% (n=93) received triple therapy and 2.2% (n=3) received quadruple therapy in TOTEMM-A, whereas in TOTEMM-B, 58.2% (n=424) received triple and 8.4% (n=61) quadruple therapy. Median (IQR) number of lines of therapy for the incident cases in TOTEMM-A was 3 (3) and in TOTEMM-B was 3 (2). More than 80% of both populations received ≥2 LOTs: in TOTEMM-A, 82.1% (n=110); and in TOTEMM-B, 82.1% (n=604). **Conclusions:** In Argentina and Brazil, less than two-fifths of treated patients with MM underwent SCT contrasting with studies in Europe and the USA that have a higher rate of SCT. Even in countries within Latin America, there are differences in demography and practices that could further impact patient outcomes. Efforts to better understand the prognostic factors reported here are crucial to support improvements for patients.

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Real-World Evidence of Proteasome Inhibitors, Immunomodulatory Drugs and Anti-CD38 in Patients with Multiple Myeloma Treated in Brazil: TOTEMM-B Study Insights

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Introduction: Patients with multiple myeloma (MM) are exposed to different treatment regimens; however, the frequency with which standard care agents are used and the combinations used in clinical practice for MM in Latin America are unknown. The TOTEMM-B study is a real-world data study conducted to describe the treatment patterns and clinical outcomes of patients with MM in Brazil. Here, the proportion of patients exposed to first-line (1L) monotherapy or combination therapy with a proteasome inhibitor (PI), immunomodulatory drug (IMiD), or anti-CD38 agent (monoclonal antibody) is described. **Methods:** Retrospective analysis was performed using administrative claims data from Orizon (January 2015–June 2021). Index was a proxy of diagnosis and could be the first ICD-10 (C.90) procedure, exam, or treatment for MM. Adults aged ≥18 years with ≥1 MM ICD-10 health term and treatment (stem cell transplant [SCT] and/or antineoplastic drug [AD]) and ≥12 months of follow-up after index were included. Incident cases included patients who were treatment naïve for ≥1 year before MM index (after January 1, 2016). The frequency of monotherapy or combination therapy with a PI, IMiD, or anti-CD38 at 1L and the most used AD in each therapeutic class were described. **Results:** In total, 736 patients with MM from the incident cohort were included. Mean (standard deviation) age was 61.9 (11.3) years. Around one-third of patients were treated with SCT (n=237; 32.3%); 728 patients received ≥1 AD. Among these, 83.5% received PI (n=608), 14.4% received anti-CD38 (n=105), and 7.6% received IMiD (n=55). The most used AD in each class was bortezomib, daratumumab, and lenalidomide, respectively. Monotherapy was received by 10.7% (n=78) of patients, with 39.7% of patients receiving a PI (n=31). Almost one-quarter (n=165; 22.7%) received dual therapy; PI + chemotherapy was most used, received by 33.3% (n=55) of patients, with bortezomib + cyclophosphamide/zoledronic acid the most common combination. Approximately, two-thirds (n=424; 58.2%) received triple therapy, with a majority receiving PI + chemotherapy + steroids (n=360; 84.9%), and 8.0% receiving anti-CD38 + PI + steroids (n=96; 19.0%); bortezomib + cyclophosphamide/zoledronic acid + dexamethasone, and daratumumab + bortezomib + dexamethasone were the most used combinations, respectively. Quadruple therapy was received by 8.4% (n=61) of patients, and among them, 72.1% (n=44) received anti-CD38 + PI + chemotherapy + steroids; a majority received daratumumab + bortezomib + zoledronic acid + dexamethasone. **Conclusions:** Bortezomib, daratumumab, and lenalidomide were the most used ADs in 1L treatment for MM in the Brazilian private care setting, in line with most global guidelines. However, use of lenalidomide was slightly lower compared with use in developed countries, probably due to later (2017) regulatory approval and barriers to reimbursement in Brazil. A similar pattern was observed for the use of daratumumab as 1L therapy.

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Daratumumab-Based Maintenance in Patients with Relapsed Multiple Myeloma after Salvage Autologous Hematopoietic Stem Cell Transplantation

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Introduction: Maintenance therapy is standard of care after upfront autologous hematopoietic stem cell transplantation (auto-HCT) for patients with newly diagnosed multiple myeloma (MM). There is paucity of data on maintenance after a first or second salvage auto-HCT for these patients. **Methods:** In this phase II clinical trial, relapsed MM patients who underwent salvage auto-HCT received maintenance with daratumumab (dara), with the addition of pomalidomide (pom) in a later amendment. The primary end point was PFS. Patients with prior exposure to dara or pom were included, those refractory to either drug were excluded. Patients received dara SQ weekly for weeks 1–8, every 2 weeks for weeks 9–24, and monthly from week 25 until progression. Pom was given at 2 mg PO from day 1–21 every 28 days. **Results:** The trial was terminated due to poor accrual after 13/56 patients were enrolled between May 2019 and August 2022. Median age at salvage auto-HCT was 64 (range: 43–76) years. Median prior lines of treatment was 2 (range: 2–4). Six patients (46%) had a prior auto-HCT. Median time from diagnosis to salvage auto-HCT was 58.3 (range 7.6-132) months. Five patients (38%) had high-risk cytogenetic abnormalities (1q+ in all 5). Eight (61%) patients received melphalan alone, 4 (31%) received busulfan/melphalan, and 1 (8%) received gemcitabine/busulfan/melphalan/panobinostat as their conditioning regimen. Three patients (23%) started maintenance with dara alone, while the remaining 10 (77%) patients received dara + pom. At study entry, 6 patients (46%) had a complete response (CR), 4 (31%) had a very good partial response (VGPR), 2 (15%) had partial response (PR), and 1 (8%) had stable disease (SD). At day 100 post maintenance, 9 (69%) were in CR, while 1 (8%) each had VGPR, PR, SD and progressive disease (PD), respectively. For the 12 patients that did not progress at day 100, best response to dara +/- pom maintenance was CR in 10 (83%), and VGPR and SD in 1 (8%) each. With a median follow up of 32.4 months (range: 20.1–43.5) from the start of maintenance, five patients progressed one of whom died. Median

PFS from the date of auto-HCT, and from start of maintenance were not reached. Two- year PFS rate from start of maintenance was 82% (95%CI: 59%-100%). Most common adverse events were neutropenia (n=11, 84%; n=5, 38% grade >3), grade 1-2 fatigue (n=6, 36%), grade ≤3 viral infection (n=6, 46%), and grade ≤3 bacterial infection, grade 1-2 diarrhea and grade 1 thrombocytopenia (n=5, 38% each). **Conclusions:** Maintenance therapy with dara, +/- pom, is safe and feasible after a salvage auto-HCT, with 83% achieving a CR. After a median follow up exceeding 2 years, median PFS from the date of auto-HCT and from the start of maintenance was not reached.

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Non-Cryopreserved Stem Cell Transplantation in Multiple Myeloma (MM) Patients: A Case Series Report

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Introduction: Despite numerous recent advancements in therapies for multiple myeloma, stem cell transplantation remains an effective and critical treatment. Recent studies indicate that the use of non-cryopreserved cells is both safe and effective, and could simplify the transplantation process, especially in resource-limited settings by eliminating the need for cell freezing. This approach may also reduce treatment-related complications while preserving cell functionality. This study aims to evaluate the outcomes of non-cryopreserved stem cell transplant, focusing on the procedural feasibility and initial clinical outcomes in a retrospective cohort of MM patients. **Methods:** We analyzed data from multiple myeloma (MM) patients who underwent autologous stem cell transplantation (ASCT) between January 2022 and July 2023. Patients were mobilized using G-CSF, and stem cell collection was planned on the fourth day, guided by peripheral CD34+ cell counts. In cases of mobilization failure, plerixafor was administered according to institutional protocols. Collected cells were preserved for up to 48 hours at a controlled temperature of 4°C (±2°C) and were infused 24 hours after a single-dose 200 mg/m^2 melphalan infusion. **Results:** Thirty-five patients were treated between April 2021 and July 2023. The median age was 59 years (range: 44-69). The male-to-female ratio was 1.3:1. Procedural adherence was achieved in all cases, with no patient requiring cryopreservation of the cells. The average number of collected and infused stem cells was 5.02 x 10^6 cells/kg (range: 2.92-10). All patients demonstrated successful marrow engraftment, except for one 63-year-old female who experienced sudden cardiovascular death on day +9 post-transplant. All other patients were alive at day +100 post-transplant. The median number of days to neutrophil engraftment was 10 (range: 9-12), with a typical hospital stay of 19 days (range: 14-26). **Conclusions:** This case series demonstrates that non-cryopreserved stem cell transplantation is a viable and effective option for multiple myeloma patients, with engraftment and hospitalization durations comparable to traditional methods. The successful implementation of this technique in a resource-limited setting, without the need for cryopreservation, underscores its potential to simplify the transplantation process while maintaining safety and efficacy standards.

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VRd Dosing and Outcomes in Indian Patients with Newly diagnosed Multiple Myeloma: Report from a Propsepctive Clinical Study

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Introduction: Bortezomib lenalidomide, dexamethasone (VRd) is a highly efficacious & commonly used regimen for newly diagnosed multiple myeloma (NDMM). Delivery of such a regime requires careful attention to doses, tolerance & appropriate modification. Conflicting findings have been reported in few studies from non-caucasian patient population & there is limited data in the Indian context where tolerance is often perceived to be poor. In this analysis we evaluate prospectively the tolerance and efficacy of VRd with respect to dosing in Indian NDMM patients. **Methods:** We are enrolling NDMM patients in a prospective study evaluating the utility of MRD guided therapy (CTRI regd no: CTRI/2021/11/037702). Patients remaining MRD positive after consolidation are being randomised to maintenance versus further therapy with VRd or VPd till MRD negativity for a maximum of 1 year. The current analysis focuses on pre-randomisation therapy with VRd for patients not planned for upfront autologous stem cell transplant. Here we included patients receiving VRd for at least 8 cycles. Baseline characteristics, dose modifications & reasons for the same were collected & impact of VRd dosing on overall response rates (ORR) at end of cycle 8, MRD negativity & progression was analysed. **Results:** Total of 116 patients were included in this analysis. Ninety six had received VRd from the start of therapy while the remaining 20 (17.2%) received VCd and were changed to VRd after 1-2 cycles. Median age of the cohort is 55 (range, 32 to 75 years). R-ISS stage distribution is R-ISS 1 in 12 (10.3%), II in 57 (49.1%) & III 31 (26.7%). Starting dose reductions were done in 60 (51.7%) patients, mainly due to renal dysfunction in 26 (22.4%), age/poor performance status in10 (8.6%) patients, pre-existing neuropathy in 2 (1.7%) & cytopenias in 10 (8.6%). Sixty five (56%) required further dose reduction after starting therapy. The causes were peripheral neuropathy in 34 (29.3%), myelosuppression in 9 (7.8%), allergic skin reaction in 10 (8.6%), infections & diarrhoea in 2 (1.7%) each. Hematological adverse events were as follows: Grade 3 or more anemia & thrombocytopenia in 2 (1.7%) each & neutropenia in 3 (2.6%). In the landmark analysis of patients

receiving all 8 cycles, the ORR of this cohort is higher at 92.2% and 92 (79.3%) have achieved VGPR or better. At a median follow-up of 13 months with only one death, the PFS and OS data is not mature and at 12 months time point 91% patients are progression free. The ORR, response rates VGPR or better & MRD negativity rates did not differ between patients who received reduced VRd doses versus others. **Conclusions:** Dose modifications were commonly required in our study cohort, however the majority of patients tolerated VRd with appropriate dose modifications. Dose modification did not adversely affect the myeloma outcomes at an early time point however a longer follow up is needed. This analysis suggests considering appropriate dose modification in Indian patients for optimal outcomes.

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Incidence, Timing, and Management of Infections in Patients Receiving Daratumumab for the Treatment of Newly Diagnosed Transplant-Ineligible Multiple Myeloma in the MAIA Study

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Introduction: Multiple myeloma (MM)-associated infections are a significant cause of morbidity and death in patients (pts) with MM due to impaired immunity. In the primary analysis of the phase 3 MAIA study (NCT02252172), daratumumab plus lenalidomide/dexamethasone (D-Rd) resulted in significant PFS benefit vs Rd (HR 0.56 [95% CI 0.43-0.73]; P< 0.001) but grade 3/4 infections were more common with D-Rd vs Rd (32.1% vs 23.3%). In 2022 (after MAIA was fully enrolled), IMWG issued guidelines for infection prophylaxis. Here, we explore infection incidence, timing, and management in MAIA. **Methods:** Pts with newly diagnosed MM (NDMM) who were transplant ineligible due to age ≥65 yr or comorbidities were randomized 1:1 to receive D-Rd or Rd. Pts received 28-day cycles of Rd (R: 25 mg PO on Days 1-21; d: 40 mg PO QW) ± daratumumab (16 kg/mg IV QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W thereafter) until disease progression or unacceptable toxicity. Pts were frequently monitored for infection; prophylaxis/management were per institutional guidelines. In the protocol, prophylaxis was considered for pneumocystis pneumonia and recommended for herpes zoster reactivation during therapy. **Results:** A total of 364 and 365 pts received ≥1 dose of D-Rd or Rd, respectively. At a median follow-up of 64.5 mo, in the D-Rd and Rd groups, 90.1% vs 78.1% of pts had ≥1 treatment-emergent infection and 42.6% vs 29.6% had ≥1 grade 3/4 infection (pneumonia 19.5%/10.7%, influenza 3.8%/2.5%, sepsis 3.6%/3.0%, urinary tract infection 3.6%/2.5%). Median time to first onset of any grade infections was 3.5 vs 3.8 mo and of grade ≥3 infections was 10.7 vs 8.7 mo. In the D-Rd and Rd groups, 64.8% vs 29.9% of pts had postbaseline IgG < 400mg/dL; median time to onset was 4.9 vs 3.8 mo; 11.5% vs 1.9% of pts with hypogammaglobulinemia AEs or postbaseline IgG < 400 mg/dL received IVIg. In the D-Rd and Rd groups, grade 3/4 neutropenia/febrile neutropenia occurred in 54.7% vs 37.3% of pts; median time to onset was 1.0 vs 3.4 mo. In the D-Rd and Rd groups, 95.3% vs 89.6% of pts received antibiotic treatment (TMP/SMX 47.3%/41.1%, amoxicillin 42.6%/34.8%); 61.8% vs 56.2% received antibiotic prophylaxis (TMP/SMX 42.0%/37.3%). 28.3% vs 23.0% of pts in the D-Rd and Rd groups received antifungal treatment (metronidazole 13.2%/11.8%); 6.0% vs 3.0% received antifungal prophylaxis (fluconazole 3.8%/2.7%). 41.2% vs 22.5% of pts in the D-Rd and Rd groups received vaccines (influenza vaccine 21.7%/14.5%). Data on common types of infections will be presented, and treatment and prophylaxis for key infections will be discussed in relation to the IMWG guidelines. **Conclusions:** In MAIA, infections were common with D-Rd and Rd, typically occurred within the first months after treatment start and were generally manageable, consistent with historic observations in NDMM. Clinicians and pts should remain vigilant for infections throughout MM treatment and follow local/international recommendations for infection prevention.

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In-Class Transition From Parenteral Bortezomib (V) to Oral Ixazomib in Newly Diagnosed Multiple Myeloma (NDMM): Updated 3-Year PFS Analysis of US MM-6 Overall and by Patient (pt) Subgroups of Interest

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Introduction: US MM-6 is a prospective, community-based, phase 4 study of in-class transition (iCT) from parenteral V-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) in pts with NDMM (NCT03173092). We report an updated 3-year (yr) PFS analysis of US MM-6. **Methods:** Transplant-ineligible/delayed-transplant (≥24 months) NDMM pts with ≥stable disease after 3 cycles of V-based induction were enrolled at US community sites to receive IRd for ≤39 cycles or until progression/toxicity. For this 3-yr PFS analysis, efficacy and safety were assessed overall and by age (< 75 vs ≥75 yrs), frailty status (non-frail vs frail), and randomized controlled trial (RCT) eligibility status (eligible vs ineligible). **Results:** At time of data abstraction (Oct 2023), 140 pts had received IRd: 42% were aged ≥75 yrs, 61% were classified as frail, and 41% were RCT-ineligible. Overall median follow-up was 36 months (mos), and 8 pts (6%) were ongoing on study treatment. Among all pts, median duration of therapy (DOT) was 14 mos with all proteasome inhibitor (PI)-based therapy and 11 mos with IRd. The 3-yr PFS rate was 58% overall and median PFS was not reached (NR); 3-yr PFS rates were 65 vs 46% in pts aged < 75 vs ≥75 yrs, 62 vs 55% in non-frail vs frail pts, and 62 vs 52% in RCT-eligible vs -ineligible pts. For all pts, the 3-yr overall survival (OS) rate was 76% and median OS was NR; 3-yr OS rates were 81 vs 67% in pts aged < 75 vs ≥75 yrs, 77 vs 75% in non-frail vs frail pts, and 75 vs 77% in RCT-eligible vs -ineligible pts. Duration of response (DOR) rate was 62% overall and median DOR was NR; 3-yr DOR rates were 71 vs 47% in pts aged < 75 vs ≥75 yrs, 64 vs 60% in non-frail vs frail pts, and 66 vs 55% in RCT-eligible vs -ineligible pts. The overall response rate (ORR) increased from 62% at the end of V-based induction to 80% following iCT to IRd, with similar increases across subgroups (60 to 80% vs 64 to 80% in pts aged < 75 vs ≥75 yrs, 70 to 81% vs 57 to 79% in non-frail vs frail pts, and 64 to 80% vs 60 to 81% in RCT-eligible vs -ineligible pts; ≥VGPR rates increased from 32 to 64% overall. Of all 140 pts, 99% reported ≥1 TEAE, with similar rates across subgroups. Grade ≥ 3 TEAEs occurred in 70% overall, and in 70 vs 69% of pts aged < 75 vs ≥75 yrs, 61 vs 76% of non-frail vs frail pts, and 66 vs 75% of RCT-eligible vs -ineligible pts. **Conclusions:** In non-transplant pts with NDMM, iCT from V-based induction to all-oral IRd permits long-term PI-based treatment and improves depth of response while maintaining a tolerable safety profile. The expected decrement in outcomes associated with older, frail, and RCT-ineligible pts was observed; however, these results were not meaningfully different. Long-term triplet consolidation with IRd may provide an alternative approach to induction/maintenance for community-based NDMM pts who are not eligible for upfront transplantation, including those who are older, frail, and/or have comorbidities. This abstract was accepted and presented at the EHA 2024 Congress.

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Phase 1b/2 Trial of Iberdomide in Combination With Daratumumab, Dexamethasone +/- Carfilzomib To Eliminate MRD After Induction Therapy and ASCT in NDMM

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Introduction: MRD persistence after upfront treatment for NDMM is associated with higher risk of progression. Iberdomide (Iber) is a novel cereblon E3 ligase modulator (CELMoD™) with enhanced immune stimulatory and tumoricidal activity and amenable to combination with other anti-myeloma agents. We report for the first time results of Iber + daratumumab (dara) + dexamethasone (Iber-Dd) and Iber-Dd + carfilzomib (Iber-DKd) consolidation in MRD positive patients (pts) after ASCT. **Methods:** Eligible pts had NDMM, had received induction therapy with a proteasome inhibitor and IMiD +/- anti-CD38 mAb followed by ASCT, had no prior disease progression, obtained ≥PR from induction + ASCT and were 100-180 days from ASCT with MRD ≥ 10-5 by NGS (clonoSEQ®). On part 1 (dose finding) pts in Iber-Dd received Iber in consecutive cohorts at 1.0, 1.3 and 1.6 mg days 1-21 of 28-day cycles, with dara and dexamethasone. After 6 cycles, pts continued single agent Iber maintenance at 1.0 mg 21/28 days. Upon completion of Iber-Dd, part 1 and demonstration of safety, we enrolled subsequent pts in Iber-DKd, consistent of Iber-Dd + carfilzomib 56 mg/m2 (20 mg/m2 on first dose) on days 1,8,15 of cycles 1-6. In addition to conventional monitoring for safety and efficacy, pts underwent MRD assessment after 6 cycles and yearly thereafter. Both regimens are being explored in part 2 (dose expansion). **Results:** Median age of participants (N=21) was 66 (range 44-79), 7 had MM with high-risk chromosome abnormalities, and 9 had received induction containing anti-CD38 mAb. Median follow up is 9.5 months for Iber-Dd and 3.2 months for Iber-DKd. None of the pts enrolled in Iber-Dd, part 1 (N=9) developed dose-limiting toxicity (DLT) and all 3 dose levels were considered safe. We completed Iber-DKd, part 1 in the Iber 1.0 and 1.3 cohorts (N=6) with no patient developing DLT. Considering emerging data on Iber PK and PD, we did not

explore Iber 1.6 mg dose in Iber-DKd and expanded the 1.0 and 1.3 mg cohorts for both regimens in part 2 (dose expansion). Overall, 14 pts have been treated with Iber-Dd (9 in part 1, 5 in part 2) and 7 with Iber-DKd (6 in part 1, 1 in part 2). Most common adverse events were neutropenia (8/14, grade ≥3 in 6/14), thrombocytopenia (4/14, all grades 1-2) and infection (6/14, grade ≥ 3 in 2/14) in Iber-Dd and infection (3/7, grade ≥ 3 in 1/7) in Iber-DKd. Among pts who completed consolidation, 7/9 in Iber-Dd and 2/2 in Iber-DKd had reduction of MRD burden, 4/9 in Iber-Dd and 2/2 in Iber-DKd achieved MRD< 10-5 (primary endpoint), all also with MRD< 10-6. One participant with high-risk MM in Iber-Dd discontinued participation due to disease progression after 7 months of treatment. All other pts remain on treatment. **Conclusions:** Iber-Dd and Iber-DKd are safe combinations and able to eliminate MRD persistent after modern induction therapy and ASCT in NDMM. This study is ongoing, complete safety and efficacy results from part 1 and updated results from part 2 will be presented at the meeting.

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Real-World Data on the Daratumumab Plus Bortezomib, Thalidomide and Dexamethasone Followed by Lenalidomide Maintenance for Transplant-Eligible Newly Diagnosed Multiple Myeloma Patients

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Introduction: The standard approach to autologous stem cell transplantation (ASCT) in patients with newly diagnosed multiple myeloma (NDMM) included induction and maintenance until progression. The newest induction protocol that had included daratumumab (dara) in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) was approved in many countries worldwide. Nevertheless, only lenalidomide (lena) was approved as maintenance in the elegible setting. Real-world data (RWD) on patients from the Brazilian Multiple Myeloma Study Group (GBRAM) database platform were presented here. Aim- Present RWD on MM patients submitted to Dara-VTd induction followed by ASCT, Dara-VTd consolidation and lenalidomide as maintenance. **Methods:** Patients diagnosed with MM after January 1, 2018 have been included prospectively. The eligibility criteria were: intent-to-treat (ITT) MM patients submitted to Dara-VTd induction followed by ASCT, Dara-VTd consolidation and lenalidomide as maintenance, aged over 18 years. Analysis was performed with the JAMOVI project software v2.3. **Results:** A total of 2,212 pts were included, 106 (4.8%) of whom were treated with the described protocol. The results presented correspond to patients submitted to the Dara-VTd protocol. The median age of the patients at diagnosis was 60 (35 - 78) years old and 60 (56.6%) patients were male. The ECOG performance was 0 for 69 (73.4%), 1 for 18 (19.1%), 2 for 4 (4.3%) and >3 for 3 (3.2%) patients. The ISS 1, 2 and 3 scores were 37 (35.2%), 24 (22.9%) and 30 (28.6%), respectively, and those not available were 14 (13.3%). White and black race was self-declared by 62 (58.5%) and 20 (18%) of the patients, respectively. The MM IgG isotype was represented in 57 (53.8%) of the pts. The ASCT was performed in 72 (80.9%) of the patients until the present analysis. From the 17 (16%) who did not undergo the ASCT, three were because of comorbidities, 1 case presented progression, 1 refused, 1 had another type of cancer and 2 died. The median time between the start of induction and the ASCT and begin of maintenance was 157 (115-502) and 312 (195-745) days respectively. After a median follow- up of 47.4 months, in ITT analyses, the best overall response rate (> PR) was 73.7%. Better than VGPR and > nCR were 67.9% and 29.1%, respectively. The median PFS and OS were not reached. At 36 months, we observed a PFS of 84%. Ten patients died in this period, two of them due to progression. Fifty-four patients had started maintenance with lenalidomide. **Conclusions:** This study demonstrates RWD based on Dara-VTd and lenalidomide maintenance for NDMM-eligible pts. Response rates demonstrate clinical benefit, with a similar follow-up between the CASSIOPEIA trial and the present study, the PFS and OS data being similar, as well. A longer follow-up is necessary to demonstrate an advantage of lenalidomide maintenance in this setting.

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Long-term Survival of Multiple Myeloma Patients in Brazil

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Introduction: Multiple myeloma (MM) is a rare neoplasm. Its incidence in Brazil, in 2020, was 2.4/100,000 in males and 1.7/100,000 in females. Mortality ranged from 1.8 to 1.2/100,000. In Latin America, in patients eligible for autologous stem-cell transplantation (ASCT), overall survival (OS) was 56.0% in five years, whereas in non-transplant individuals it was 38.0%. **Methods:** Data were sourced from the São Paulo Oncocentro Foundation (FOSP) database, including MM cases from São Paulo state, between 2000 to 2018. OS was calculatedfrom the date of diagnosis until the date of death or last available information. OS curves were generated using the Kaplan-Meier method, compared

using the log-rank test, and prognostic factors determiated by Cox regression, hazard ratio (HR), a significance level of 5%, using the SPSS v.25. **Results:** The study cohort comprised MM patients with a median age of 63.5 years. Five- and ten-year OS rates were 43.8% and 26.1% (< 60 years) and 28.2% and 11.0% (≥60 years). Notably, patients with health insurance showed higher OS rates compared to those in the public system, the five- and ten-year OS for health insurance were 59.4% and 31.8%, versus 35.3% and 17.2% for public system. For those undergoing ASCT, five-year OS was similar in both sexes (62.9% males, 60.4% females); < 60 years age group had a 64.1% five year and 40.0% the ten-year OS. Non-ASCT patients showed lower rates 36.8% and 21.1% at five- and ten-years. Among non-ASCT patients over 60 years health insurance, five-year OS was 56.6%, versus26.1% for public healthcare, for ten-year OS was 24.3% versus 10.0%, respectively. Survival rates improved from 2010-2018, notably among transplant recipients:018 59.9% and 30.5% (five and ten years) vs 27.2% and 13.1%. **Conclusions:** MM survival in São Paulo has increased over five- and ten years, but disparities persist. Improved access to diagnosis and treatment is essential to reduce inequalities and enhance patient outcomes.

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Diagnostic Challenges Across the Multiple Myeloma Pathway: Perspectives of Primary Care Physicians and Orthopedic Specialists

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Introduction: Multiple myeloma (MM) is challenging to diagnose due to its non-specific symptoms. Patients often see multiple physicians before diagnosis, namely primary care physicians (PCPs), but also orthopedic specialists (OrS), nephrologists, rheumatologists and internal medicine physicians among others. One UK study reported that MM has the highest number of patients seeing >3 PCPs before specialist referral than any other reported cancer. The aim of this research is to better understand the barriers to rapid and accurate diagnosis of MM, to optimize the diagnostic pathway. **Methods:** Double-blind, virtual, 1-hour interviews were conducted in May 2024. Interviewees were required to have knowledge of MM and included 8 PCPs and 7 OrS from the US (9), France (2) and Australia (4). Interviews covered three themes: likelihood to suspect MM, diagnostic testing and referral patterns, and educational needs. Key words were used to identify concepts discussed and quantify the qualitative data. **Results:** All interviewees noted that MM is rare and is not front of mind for differential diagnoses. 100% of PCPs reported to rarely encounter MM, compared with 14% of OrS. Lower back pain, weight loss, and fatigue were identified as symptoms of MM by all interviewees. Clinical indicators that would raise suspicion of MM were anemia or renal function reported by PCPs (62% and 38% respectively); and atraumatic or multiple fractures reported by OrS (86% and 43% respectively). On suspicion of MM, 73% of interviewees reported conducting standard blood tests (complete blood count, kidney function and calcium levels) and all OrS reported conducting imaging (X-rays, MRIs, or CT scans). 73% of interviewees also reported to order electrophoresis alongside standard blood tests, however, only 13% ordered the guideline-based approach to MM diagnosis (electrophoresis and light chain assay tests). Further, 80% of interviewees reported discomfort with interpreting MM-specific blood test results, requiring input from hematologists. All interviewees reported receiving no MM-specific training outside of medical school. 57% of OrS gained familiarity of MM from fellowships and residency experience. OrS stated they were more likely to refer patients who ultimately received a MM diagnosis than PCPs. Referral criteria guidance and testing protocols were identified as potential tools to support education among 67% of interviewees. **Conclusions:** Disease rarity and a lack of local and national guidance makes the diagnosis of MM complex, both in suspicion and in confirmation. Targeted education on MM symptoms and testing guidance for non-MM specialists may improve the timely and accurate diagnosis of MM by supporting physicians to identify MM sooner in the diagnostic pathway. Tools to aid non-specialist diagnosis and referral of MM are in development, however, further research is needed to draw robust conclusions.

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Stem Cell Mobilization Strategy With Pegilgrastim for Stem Cell Transplantation for Multiple Myeloma: A Direct Cost Comparison

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Introduction: autologous stem cell transplantation is still standard of care among younger patients with multiple myeloma mainly in low-to-middle income countries. Strategies to improve availability of this procedure such as infusion of fresh stem cell graft are currently in place for this scenario. Here we report our experience with pegfilgrastim mobilization and fresh stem cell infusion for MM first autologous stem cell transplant. **Methods:** we conducted a direct cost comparison to estimate the mean cost per stem mobilization procedure among MM patients receiving either filgrastim (10 mcg/Kg/day for 4 days) or pegfilgrastim (single 6 mg dose) followed by plerixafor in a just-in-time approach. We reviewed data on 335 patients that received a mobilization to extract data on resource utilization. Costs for drugs were valued according to the CMED table added 18% taxation practiced at the state of São Paulo, costs for procedures were estimated using the AMB table and market research, all estimates in Brazilian currency (R$). We compared the mean difference for mobilization using bootstrapping, with 10.000 repetitions for each group. **Results:** efficacy results were largely overlapping between the two strategies, the mobilization failure rates were 0.6% for both groups (p value = 1), the yield of CD34 / Kg was also similar median 5.17 (95%CI 2.41-10.23) vs. 5.02 (95%CI 2.35-10.94) for filgrastim and peg respectively and

therefore we conducted a direct cost comparison. Use of plerixafor however was greater for peg, 57.3% vs. 23.2% ($p < 0.001$). Median cost per mobilization was lower for pegfilgrastim (Δ – R$ 3360,06 95%CI -30525,15 to + 18939,13). **Conclusions:** pegfilgrastim resulted in overall lower costs per mobilization strategy, given maximum expenditure per medication unit that is provided from the CMED table. This value difference might differ significantly over actual values practiced over large purchases, for example.

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ASCT: A Viable First-Line Treatment Option for Elderly Multiple Myeloma Patients Without Access to New Drugs

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Introduction: The standard first-line therapy for multiple myeloma (MM) involves induction therapy combined with autologous hematopoietic stem cell transplantation (ASCT). While no guidelines explicitly recommend against ASCT based on age, many centers typically set a cutoff at 65 years for this treatment. **Methods:** We conducted a retrospective analysis at Beneficência Portuguesa of São Paulo on patients with multiple myeloma (MM) who underwent autologous hematopoietic stem cell transplantation (ASCT) between 2016 and 2023. The study focused on patients over 65 and included a sub analysis of patients over 70. We analyzed progression-free survival (PFS) and overall survival (OS). **Results:** We included 136 patients aged 65 and older in our study, of whom 39 were over 70. The one-year, two-year, and three-year progression-free survival (PFS) rates were 80%, 67%, and 53%, respectively, with a median PFS of 3.3 years. In a subanalysis by conditioning regimen (melphalan 200mg/m^2, melphalan 140mg/m^2, melphalan 100mg/m^2 and BuMel), no significant differences in PFS were observed after two years. However, in one year, patients who received a Melphalan 200 mg/m2 conditioning regimen had a PFS of 83%, compared to 74% for those on a less intensive regimen Mel 140 mg/m2 and Mel 100mg/m^2. The median overall survival (OS) in proven population were 86.4% in the first year, 80.3% at the second year, and 74.1% at the third year. Our sub analysis revealed no significant differences in OS between patients under and over 70 years old regardless of conditioning regimen. **Conclusions:** This study provides a real-world perspective on the safety and survival benefits of ASCT in the elderly population. The overall survival (OS) and progression-free survival (PFS) rates observed are comparable to those in younger age groups studies. Currently, ASCT remains a viable treatment option for elderly patients and should be reevaluated in the future as newer therapies, such as CAR-T cells and bispecific drugs, become more established. This study provides a real-world perspective on the PFS and OS benefits of ASCT in the elderly population where the results are comparable modern protocols with combined drugs in young patients (MAIA and SWOG S0777). The ASCT in this population can be beneficent in first line therapy as new protocols are unavailable.

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Role of Consolidation Chemotherapy in the Real World for Multiple Myeloma Patients Undergoing Autologous Hematopoietic Cell Transplantation (auto-HCT)

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Introduction: Consolidation therapy is treatment given for a short duration typically with the same regimen used for induction therapy after auto-HCT. Consolidation is generally used for multiple myeloma patients who have not achieved an adequate response post transplant. It has, however, been incorporated as part of the standard treatment into many clinical trials recently that use Dara-VRD as induction regimens. To date, no studies have been conducted to assess progression free survival for patients who received Dara-VRd followed by consolidation versus no consolidation. Additionally, while most of the clinical trials are conducted with the addition of consolidation, in the real world, it is often not used. As there are no guidelines to advise which patients should receive consolidation therapy, often high-risk individuals are selected. This study aims to assess PFS in patients who were treated with induction Dara-VRd followed by consolidation compared to patients who received induction Dara-VRd without consolidation. **Methods:** This study included patients at Allegheny Health Network who were considered transplant eligible and received frontline treatment with Dara-VRd between January 1, 2019 and June 30, 2022. All patients were >18 years of age. Patients who received Dara-VRd in the noted time frame were evaluated to determine if they received consolidation therapy or not. The study also assessed the number of patients who received maintenance and their maintenance regimen. PFS was then analyzed comparing those that received consolidation and those without. **Results:** The total number of patients who underwent induction with Dara-VRd included in this study was 14 (12 males and 2 females). The average median age in the study was 60. The median follow-up time was 19.3 months. Of these 14 patients, 10 received maintenance alone and 4 out of the 14 patients received consolidation in addition to maintenance. Our analysis showed no statistically significant difference (p-value 0.68) in PFS in patients who received consolidation compared to those who received maintenance alone. It was also noted that often the patients that were chosen to receive consolidation were considered high risk secondary to poor response to frontline therapy. **Conclusions:** Most patients in the real world do not get consolidation unless considered high risk by their provider. No study exists to compare PFS in patients who receive induction with Dara-VRd followed by consolidation vs patients who don't. This study, while limited to a small population of patients, exhibits that the addition of consolidation may not provide a substantial benefit for PFS and may not significantly impact patient outcomes. Further research with a larger patient population needs to be conducted to draw stronger conclusions.

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Synchronic Occurrence of Multiple Myeloma, POEMS Syndrome and Prostate Adenocarcinoma – Is There a Role for Autologous Stem Cell Transplant?

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Introduction: The concomitant occurrence of multiple myeloma (MM) and prostate adenocarcinoma (PA) has been described, as well as the concomitant occurrence of POEMS syndrome and MM. However, our literature review did not verify previous reports of patients with the simultaneous diagnosis of the three entities, making the diagnostic and therapeutic approach of this case challenging. A 57y male, hypertensive, diabetic and dyslipidemic, also with motor sequelae due to a previous Guillain Barret, had been diagnosed with indolent PA (Gleason 7, normal PSA) in routine exams, following a watch and wait approach. Staging CT's which detected sclerotic lesions in the vertebrae and ischium. Hepatosplenomegaly and chronic portal vein thrombosis were also found, with a negative investigation for thrombophilia. A non-quantifiable IgA/lambda monoclonal peak was found. The patient did not have anemia, kidney damage or hypercalcemia. A bone marrow biopsy was performed finding 60% of clonal plasma cells (culminating in a diagnosis of MM with therapeutic indication) and a biopsy of one of the sclerotic lesions in the ischium has ruled out a metastatic prostate lesion. Karyotype 46,XY. FISH unavailable. ISS 2 and R-ISS scored at least 2. He arrived with high ACTH and normal cortisol values, and presented polyneuropathy. VEGF=5,055.4pg/mL. Thus, our patient also met criteria for POEMS. No skin changes or papilledema were detected. The patient refused CSF collection. Despite a high-risk HCT-CI score, the team figured he was a fairly fit patient for autologous stem cell transplant (ASCT). We opted for the DARA-VTD protocol. After the 4th cycle the patient was taken to ASCT (Mobilization GCSF 10mcg/kg per 5 days; 7.6 x10a6 cells collected, conditioning MEL 140, infusion: 2/3/24; engraftment: D+14). Currently, the patient is on D+131 of the transplant, with complete response (CR) to the MM treatment. VEGF on 3/13/24 was measured at 775.3 pg/mL, also indicating a reduction in inflammatory activity related to POEMS. Although there were no major changes in PET-SCAN in both prostate and sclerotic lesions uptake, the patient evolved with an increase in PSA levels (currently at 7) and was referred for radiotherapy for the treatment of the PA. He is currently in the 2nd cycle of maintenance treatment for MM with lenalidomide (now 5mg due to neutropenia and thrombocytopenia). **Methods:** n/a **Results:** n/a **Conclusions:** Synchronous occurrence of MM, POEMS and PA is uncommon in the literature. Our one-case experience was not able to detect a negative impact of the presence of indolent prostate adenocarcinoma at any stage of myeloma treatment, nor in ASCT. It is uncertain whether the treatment instituted for myeloma contributed to the enhancement of the PSA and whether it eventually contributed to the anticipation of therapeutic indication for prostate cancer. More studies are needed with patients with synchronous tumors to better evaluate such impacts. The patient remains under clinical follow-up and is in good general condition.

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Ixazomib-Based Maintenance Therapy in Multiple Myeloma Patients Eligible and Ineligible for Transplantation: A Real-World Study (INFINITE Study)

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Introduction: Ixazomib (IXA) is reported to improve the prognosis of multiple myeloma (MM) patients (pts) when used as maintenance therapy, with good safety profile. Due to limited real-world data in China, we aim to explore the effectiveness and safety of IXA maintenance therapy in MM pts eligible and ineligible for transplantation. **Methods:** This prospective, non-interventional, multi-center, ongoing study across 28 centers in China from May 2020 included MM pts who have received or were scheduled to be prescribed ≤1 dose of IXA-based treatment regimen, with IXA < 3 months (mo) from initial treatment. Primary endpoint: safety profile of IXA (adverse events [AEs]). Key secondary endpoints: effectiveness of IXA (overall response rate [ORR], duration of treatment [DOT], progression-free survival [PFS]. **Results:** As of 30 June 2023 (data cut-off), 419 pts were enrolled. Of them, 270 pts underwent IXA-based maintenance therapy. At a median follow-up of 16.6 mo, 153 pts discontinued IXA. Most common reasons for discontinuation were disease progression and AEs (11.8% each). Overall median age was 65 yrs [range 26-89]; Durie-Salmon stage III: 82.4% pts; International staging system (ISS) III: 44% pts; revised-ISS (R-ISS) III: 31% pts; high-risk by Stratification of Mayo mSMART: 49.3% pts. Common concomitant diseases before IXA treatment included hypertension (43.3%) and respiratory thoracic

and mediastinal disorders (28.1%, including emphysema, pleural effusion, asthma, bronchitis chronic, pneumonitis, interstitial lung disease). Of the 89 pts who underwent SCT, 66 underwent R-ISS staging (R-ISS stage II/III n=54). Of the 181 pts without SCT, 132 underwent R-ISS staging (R-ISS stage II/III n=110). At a median follow-up of 16.6 mo, overall median DOT was14.7 mo (95% CI: 11.3, 16.6). For transplant pts, median DOT was 19.5 mo (95% CI: 13.5, 19.8) [20.2 mo (95% CI:4.7, 21.2) for R-ISS stage I vs.19.3 mo (95% CI: 13.2, 19.8) for stage II/III pts]. For non-transplant pts, median DOT was 11.5 mo (95% CI: 8.2, 17.5) [13.2 mo (95% CI:4.2, 20.6) for R-ISS stage I vs.11.3 mo (95% CI: 8.2, 17.7) for stage II/III pts]. Overall, ORR before maintenance therapy was 88%, complete response (CR+sCR) rate was 30% which increased to 40% after maintenance therapy. For transplant pts, CR+sCR rate increased from 38% to 71% after maintenance therapy and from 27% to 41% in non-transplant pts. Treatment-emergent AEs (TEAEs) related to IXA were 44.1%. Most common hematologic TEAEs were platelet count decreased(all grades 19.3%, ≥G3 5.2%) and anemia (all grades 5.2%, ≥G3 0.7%). Most common non-hematologic TEAEs were diarrhea (all grades 6.7%, ≥G3 0.7%) and nausea (all grades 2.6%, ≥G3 0.0%). **Conclusions:** This real-world study demonstrated favourable DOT and effectiveness profile of IXA as maintenance therapy in transplant-eligible and -ineligible MM pts regardless of R-ISS staging. IXA-based continuous therapy can be a viable treatment option for MM pts in the real world.

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Iberdomide Is Immune Stimulatory and Induces Deep Anti-Myeloma Activity Across Doses in Combination With Daratumumab in Patients With TNE NDMM From the CC-220-MM-001 Study

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Introduction: Daratumumab (DARA) plus lenalidomide (LEN) and dexamethasone (DEX) is a current standard of care for transplant non-eligible (TNE) newly diagnosed multiple myeloma (NDMM). Iberdomide (IBER) is a novel oral CELMoD™ agent that enables more rapid substrate degradation than LEN, inducing greater myeloma cell death and immune stimulation. Preclinically, IBER has shown synergistic activity when paired with DARA, inducing deeper anti-myeloma cell activity than LEN + DARA; however, the activity of IBER + DARA + DEX (IberDd) in TNE NDMM has not been previously reported. Here we report first pharmacodynamic and biomarker results from the phase 1/2 CC-220-MM-001 (NCT02773030) dose-expansion cohort of IberDd in patients (pts) with TNE NDMM to support dose selection of IBER in this setting. **Methods:** Eligible pts had NDMM with no autologous stem cell transplant planned or were ineligible due to age or comorbidities. Oral IBER was given at 1.0 mg, 1.3 mg, and 1.6 mg on days (D) 1–21 of each 28-day cycle (C) with subcutaneous 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 oral DEX (40 mg; 20 mg of > 75 years of age). Analyses included immunohistochemistry (IHC) of CD138+ bone marrow (BM) samples for cereblon (CRBN), Aiolos, and Ikaros at screening and C2D15, flow cytometry of peripheral blood for changes in immune cell composition at C1D1 and C2D15, changes in involved serum-free light chains (sFLCs), and assessment of minimal residual disease (MRD) by Euroflow assay in pts achieving deep response (≥ very good partial response [VGPR]). **Results:** As of December 2023, 75 pts with TNE NDMM received IberDd (25 pts 1.0 mg; 25 pts 1.3 mg; 25 pts 1.6 mg). All pts with available samples showed CRBN expression in BM MM cells by IHC. Across all doses, substrate protein levels were significantly reduced by C2D15, with no dose-dependent trend. In the immune compartment, IberDd led to a > 4-fold increase in proliferating T and NK cells, > 2-fold increase in activated/effector memory T cells, and > 75% decrease in median absolute B cells, CD38+ T cells, and naïve T cells. Immune pharmacodynamics across doses were overlapping. Changes in involved sFLCs as a biomarker for tumor reduction also showed deep and overlapping decreases on treatment across all 3 doses with the nadir observed at around C3D1. In pts attaining ≥ VGPR and with available samples, MRD negativity at 10-5 was achieved in 10/17 (58.8%) pts at the 1.0-mg dose, 13/22 (59.1%) pts at the 1.3-mg dose, and 7/16 (43.8%) pts at the 1.6-mg dose. **Conclusions:** IberDd showed pharmacodynamic response across all 3 doses of IBER tested in pts with TNE NDMM. Notably, data showed significant overlap across doses suggesting all 3 doses of IBER tested are biologically active in combination with DARA + DEX. These data support the use of IBER at doses of 1.0 mg or higher in combination with DARA to achieve maximal pharmacodynamic effects. Previously presented at EHA 2024.

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Multiple Myeloma With High Cytogenetic Risk in Chile. Clinical and Cytogenetic Characteristics, First-Line Treatments and Response Rates

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Introduction: Multiple myeloma (MM) is a heterogeneous neoplasm in its biological behavior and prognosis. Survival has improved with an average of 10 years in transplant candidates, however, 15 to 20% have a poor prognosis with survivals of less than 3 years. The main factors that identify patients with high-risk MM (HMAR) are cytogenetics and response to treatment. The best strategy to combat them is to achieve deep and sustained responses, seeking negative residual disease with regimens based on corticosteroids, proteasome inhibitors, immunomodulators and autologous transplantation (ACT). The addition of daratumumab in

the first line is especially recommended as it increases rates, depth of response and progression-free survival (PFS) in MMAR. In Chile we do not have reports that specifically analyze patients with MMAR or the use of daratumumab in them. **Methods:** Retrospective analysis of patients with MMAR treated in national centers. The t(4;14), t(14;16), t(14;20), gan1q and del17p determined by FISH were considered high risk (cutoff value: more than 10% of plasma cells. More than 20% for del17p). Clinical and laboratory characteristics, first-line treatments, and response rates were recorded. **Results:** 47 patients diagnosed between June 2014 and January 2024 are included. The average age was 59 years, 53% women and 82% from public centers. The cytogenetic alterations were: del17p: 40%, gan1q: 72%, t(4;14): 48% and t(14;16): 9%. The average percentage of plasma cells with each alteration was 52, 55, 60 and 47%. Hypercalcemia, anemia, renal failure and lytic lesions were present in 23, 57, 21 and 83% respectively. 4% required dialysis. The R-ISS at diagnosis was II and III in 31 and 55%. First-line treatments were: CyBorD or VTD (34%), VRD (45%), VRD/VTD PACE (2%) and others (19%). The average number of treatment cycles was 4. 83% had a partial response (PR) or better and only 26% had a complete response (CR). Of 28 TAMO candidates, 50% receive it, with 67% achieving CR. Only 2 patients received daratumumab in the first line together with VRD, one achieving CR and the other presenting refractory disease. No grade 3 or 4 adverse reactions. The median overall survival of the entire cohort was 74 months. **Conclusions:** Patients with MMAR have a poor prognosis. They benefit from achieving and maintaining deep responses. In this analysis, CR rates were low compared to the literature and survival was suboptimal for a relatively young cohort of patients. Although the use of daratumumab in the first line was rare, TAMO remains an effective strategy in MMAR. It is important to seek the most effective treatment in the first line, especially in patients with adverse cytogenetics.

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Lower Utilisation of Autologous Stem Cell Transplant in Patients With Multiple Myeloma From Black Caribbean and Black African Ethnic Groups in the UK – a Single Center Experience

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Introduction: Multiple Myeloma (MM) occurs at a higher frequency and at a younger age among patients from Black ethnicity. Autologous stem cell transplant (ASCT) has been shown to improve survival in patients with MM from all ethnic backgrounds. However, studies from the United States of America (USA) showed lower utilisation of ASCT of Black patients. Our center covers the South-East London, a unique and diverse area in England, the United Kingdom (UK), that has a high density of Black Caribbean and Black African populations. We aim to investigate ASCT utilisation among patients from different ethnic backgrounds treated in our center. **Methods:** We included transplant-eligible patients (aged < 75 year old) who were diagnosed with MM (ICD Code 90.0) between January 2013 to December 2022 treated in our two hospitals: the King's College Hospital and the Princess Royal University Hospitals. Data was collected using automated platform and manual collection from the patient electronic patient records. Statistical analysis was performed using Stata 13.0. **Results:** We identified 332 patients. 30 patients (9.03%) had ethnicity label of 'Not Known' or 'Not stated'. The three biggest ethnicity groups were White British (45.48%), Black African (20.18%) and Black Caribbean (13.86%). As these three groups covered almost 80% of the study population, we grouped all the other ethnic groups, including 'Not Known' and 'Not Stated' as Others. The characteristics of these cases are shown in Table 1. We conducted a logistic regression analysis of ASCT utilisation in the different ethnic groups, taking into account patients' gender, age at presentation, and index of multiple deprivation tertile (a geographical measure of relative deprivation, 3–least deprived & 1-most deprived). Using White British as index ethnicity, we obtained the following Odds Ratios: Black African 0.511 (P = 0.069), Black Caribbean 0.325 (P=0.005), and Others 0.712 (P=0.305). **Conclusions:** We observed a lower ASCT utilisation among patients from Black Caribbean backgrounds, and a lower tendency among patients from Black African background, compared to White British patients. This was consistent with findings in the USA and despite younger age at presentation of Black patients. As ASCT is provided freely as part of standard of care for MM in England, this difference is neither due to the cost of treatment nor relative deprivation. Further study is required to validate these findings in the larger UK cohort, as well as finding the root cause of this difference. This study also differentiates Black Caribbean from Black African ethnic groups. This may reveal underlying biological and social differences in the Black ethnicities, an aspect that has not been previously explored.

Table 1 (abstract P-337) Characteristics of cases.

Parameters	White British	Black African	Black Caribbean	Others
Frequency	151	67	46	68
Mean age (range)	63.1 (39–74)	55.3 (30-74)	58.4 (38-74)	59.1 (36-73)
Female sex (%)	52 (34.4)	36 (53.7)	25 (54.3)	30 (44.1)
IMD tertile	2.2	1.4	1.5	1.8

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High Frequency of Electrolyte Derangement and Low Frequency of Transfusion Requirement Post Melphalan Autologous Bone Marrow Transplant – a Single Center Experience

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Introduction: Melphalan autologous stem cell transplant (ASCT) is an important consolidation therapy in Multiple Myeloma (MM). In our center, patients who are discharged after neutrophil engraftment are followed up in regular intervals to monitor their blood counts and electrolytes. The follow up (FU) intervals, including blood tests, are twice weekly for the first two weeks followed by weekly FUs until a clinical review. We conducted a retrospective audit to monitor the effectiveness of this practice. **Methods:** We included patients who underwent melphalan ASCT for MM between January to December 2022. Blood parameters (Full blood counts, magnesium, potassium, and calcium), blood product transfusions, and electrolyte replacements were collected electronically from the date of discharge for 12 weeks. **Results:** 50 patients were included in the analysis. 2.19% of Haemoglobin (Hb) values fall below our threshold of transfusion at 80 g/L. 7/50 (14%) patients required red cell blood (RBC) transfusion. Most transfusions were given at Hb values >= 70 g/L. 4/7 patients who were transfused had active infection at the time of infections. Most RBC transfusions occurred within the first two weeks post-discharge. One patient required RBC transfusion at week 5 associated with infection. Only one patient required 3 units of RBC transfusions, which was received between weeks 9 and 11 post discharge. This patient had COVID-19, and also received platelet transfusion. One other patient with COVID-19 infection and minor gum bleeding required platelet transfusion at week 12 post discharge. 4.29% of patients had neutrophil values below 0.5 x 109/L. We observed 5.87% of potassium values fall below 3.5 mmol/L. This led to potassium replacement in 64% of the patients. 5.83% of Calcium values were below 2.15 mmol/L. This led to calcium replacement in 68% of the patients. 11.2% of Magnesium values fell below 0.70. This led to magnesium replacement in 24% of the patients. Most of the electrolyte replacements were oral and done within the first week. **Conclusions:** A high proportion of RBC, and all of platelet transfusions, were related to active infections, especially COVID-19. We observed high rate of electrolyte replacements in our cohort. This is likely related to diarrhoea and poor nutrition that most patients continue to experience after discharge from hospital. Hypokalaemia around the time of neutrophil engraftment have previously been reported (genesis syndrome). The findings of this retrospective audit suggested that most patients after Melphalan ASCT do not require blood product support. They may be followed up less intensively in the absence of infection. Some patients may require G-CSF support at home. Furthermore, in view of high potassium and calcium replacement rates after discharge, these patients may benefit from prophylactic electrolyte replacements. This may allow a faster 'bleed and go' service that may reduce the time spent in hospital. Further work will be required to test these two hypotheses.

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Tandem Autologous Transplantation Can Overcome the Poor Prognosis of Double-Hit Multiple Myeloma Patients With 1q21 Gain/Amp and t(4; 14)

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Introduction: Novel drugs induction followed by autologous stem cell transplantation (ASCT) is the standard regimen for transplant-eligible patients with multiple myeloma (MM). However, approximately 20% of patients will have early relapse within 18 months after ASCT, which are defined as high-risk myeloma. Despite the fact that ASCT has become an important means to improve the prognosis of MM patients, further research is still needed to improve the outcome of high-risk patients, especially "double-hit" MM patients. Some studies suggest that tandem ASCT may overcome the poor prognosis of high-risk myeloma. But which type of high-risk MM patients may really benefit from tandem ASCT remains inconclusive. **Methods:** In this study, we enrolled 30 cytogenetic high-risk (including t(4;14), t(14;16), 17p- and 1q21 gain/amp) myeloma patients who underwent tandem ASCT. Another 53 cytogenetic high-risk patients who received single ASCT in the same period were enrolled as the control group. The differences in time-to-progression survival (TTP; primary endpoint) and overall survival (OS) between the two groups were estimated using the Kaplan-Meier method. This study is registered with the Chinese Clinical Trial Registry, number ChiCTR2100046510. **Results:** Kaplan-Meier estimates of TTP (not reach and 47.9 months, p=0.036) and OS (not reach and 62.5 months, p=0.039) were better in tandem ASCT group compared with single ASCT group. There was no significant difference in treatment-related mortality (TRM) between the two groups (p=0.64). Subgroup analysis showed that for patients with a single high-risk cytogenetic abnormality, there was no statistically significant difference in PFS (NR and 49.0 months, p=0.924) and OS (p=0.415) between those who received tandem transplantation and those who received single transplantation. Double-hit patients who underwent tandem transplantation had better PFS than those who underwent single transplantation (NR and 35.7 months, p=0.038), but there was no statistically significant difference in OS (p=0.881). Among them, patients with the double-hit of 1q21 gain/amp and t(4;14) who received tandem transplantation had better PFS (44.2 months and NR, p=0.924) than those who received single transplantation, while there was no statistically significant difference in PFS (27.5 months and 35.7 months, p=0.596) between patients receiving tandem or single transplantation for other double-hit MM patients. **Conclusions:** Tandem ASCT can overcome the poor prognosis of double-hit multiple myeloma patients, especially those with the double-hit of 1q21 gain/amp and t(4;14).

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Real-world Data on the Use of Subcutaneous Daratumumab Plus Bortezomib, Thalidomide, and Dexamethasone in Transplant-eligible Patients With Newly Diagnosed Multiple Myeloma

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Introduction: Subcutaneous daratumumab (DARA SC) + bortezomib/thalidomide/dexamethasone (VTd) is approved for the treatment of patients (pts) with newly diagnosed multiple myeloma (NDMM) eligible for autologous stem cell transplant (ASCT). However, there is a need for real-world (RW) data on DARA SC+VTd in routine clinical practice. Here we present RW data on the effectiveness and safety of DARA SC+VTd in ASCT-eligible pts with NDMM in Brazil. **Methods:** The MMY4046 non-interventional, multicenter, observational, post-authorization safety study enrolled treatment-naïve pts with NDMM who were eligible for ASCT (at start of DARA SC+VTd) and completed ≥1 cycle of DARA SC+VTd per local practice by Sep 30, 2022. Exclusions included contraindication to DARA SC, plans to change treatment, receipt of investigational drugs, and participation in interventional studies. Data were collected retrospectively from the start of DARA SC+VTd (baseline) to study inclusion using medical records and prospectively from the study inclusion visit to 30 days post-consolidation via electronic case report forms. Data on pt and disease characteristics, response, stem cell collection, ASCT outcomes, treatment-emergent adverse events (TEAEs), and DARA SC+VTd treatment were collected. **Results:** As of the data cutoff (Aug 8, 2023), 49 pts were included. Baseline median (range) age was 58 (38-73) yr, time since myeloma diagnosis was 0.7 (0-48.2) mo, and 93.8% pts had intent for consolidation therapy. Median (range) number of induction and consolidation cycles was 4 (1-6) and 2 (1-2), respectively; duration of treatment was 8.9 (1.0-15.7) mo. By the end of consolidation, 91.7% of pts achieved overall response (≥partial response), 89.6% achieved ≥very good partial response, and 25.0% achieved ≥complete response. Overall, 45 (91.8%) pts underwent stem cell mobilization (plerixafor given in 40.8%), with a median (range) stem cell yield of 5.7 (2.3-15.0)×106 CD34+ cells/kg; 44 (89.8%) pts underwent ASCT, of which 43/44 (97.7%) pts had a successful ASCT. TEAEs occurred in 44 (89.8%) pts, grade 3/4 TEAEs in 24 (49.0%) pts, and serious TEAEs in 14 (28.6%) pts. Grade 3/4 neutropenia/febrile neutropenia occurred in 16 (32.7%) pts, primarily the during ASCT phase (10 [22.2%]); serious events occurred in 2 (4.1%) pts (both febrile neutropenia during ASCT phase). Grade 3/4 infections occurred in 9 (18.4%) pts, primarily during induction (6 [12.2%]); serious infections occurred in 10 (20.4%) pts, the most common being COVID-19 (10.2%) and pneumonia (4.1%). As of the cutoff, 1 pt had discontinued treatment (thalidomide only) due to a TEAE (paresthesia), and 1 pt had died (due to post-ASCT septic shock 32 d after the last DARA SC+VTd dose). **Conclusions:** Results were consistent with the established profile of DARA SC+VTd, with no new safety concerns observed in RW practice. Notably, most pts achieved successful ASCT after DARA SC+VTd, supporting the frontline use of DARA SC+VTd in ASCT-eligible pts with NDMM.

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Response and Safety of Selinexor with VRD Regimen in Newly Diagnosed Multiple Myeloma (NDMM) with Extramedullary Disease (EMD): A Prospective, Open-Label, Multicenter, Phase 2 Study

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Introduction: Extramedullary disease (EMD) is rare in newly diagnosed multiple myeloma (NDMM) patients, associated with poorer prognosis and drug resistance. In this context, we present the preliminary findings from a prospective phase 2 study evaluating the safety and efficacy of selinexor in combination with VRd as a first-line treatment for NDMM patients with EMD(NCT05900882). **Methods:** The study enrolled NDMM patients under 75 years old who exhibited measurable extramedullary disease. Pts received selinexor (60 mg QW) in combination with VRd (SVRD) regimen as induction therapy for 4 cycles (28 days of each cycle). Following the induction phase, pts underwent two cycles of VRd consolidation therapy after autologous stem cell transplantation (ASCT), while those who did not undergo ASCT received another 4 cycles of SVRD consolidation therapy. All pts received bortezomib plus lenalidomide for maintenance for at least 24 months. The primary endpoint of the study was the best response rate during induction therapy, and secondary endpoints included complete response (CR) rate, duration of response (DOR), safety, and survival outcomes. **Results:** Between Oct 17, 2022 and May 17, 2024, a total of 19 NDMM pts with EMD were enrolled and received treatment. The median age was 58 years (range 43-70). Among them, 14 patients (73.7%) had ISS stage II/III disease. FISH was not available in 4 patients. 8 patients of the remaining 15 patients (53.3%) were classified as high risk based on the mSMART stratification, 5 patients (33.3%) was double-hit. 18 patients (94.8%) had EM-B (extramedullary bone-related plasmacytoma). 5 patients (26.3%) had EM-S (soft tissue-related plasmacytoma). 4 patients (21%) had both EM-B and EM-S. By the data cut-off, at a median treatment time of 12 months (range 0.3-19 months), 13 pts completed 4

cycles of SVRd inductive treatment, 7 pts underwent ASCT, 2 pts underwent CART, 2 pts had progressive disease during induction therapy. 1 pts had progressive disease after ASCT. Among the 19 evaluable pts for best serological response, 5 pts (26.3%)achieved serological CR/sCR, and 7 pts (36.8%) achieved VGPR. The depth of remission improved with the continuous treatment. Continuous extramedullary disease evaluation in 15 patients showed complete disappearance of extramedullary lesions in 8 patients (53.3%), PR in 6 patients (40%), and SD in 1 patient (6.6%). 14 (73.6%) pts experienced any grade AE. Grade 3 or 4 AEs were reported in 5 pts (6 events in total), with the most common being thrombocytopenia (4/19). Non-hematological AEs were mainly grade 1-2. 3 pts were required dose reductions to 40 mg. **Conclusions:** The combination of selinexor with VRd regimen demonstrated early, deep, and durable responses in NDMM patients with extramedullary disease, both in serological and extramedullary responses, with a manageable safety profile.

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Impact of Achieving <VGPR With Dara-RVD Induction Therapy in Newly Diagnosed Multiple Myeloma (NDMM) Patients

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Introduction: DRVd has been established as standard of care induction therapy following the randomized phase 3 PERSEUS study (Sonneveld et al, NEJM 2023). We previously presented data from our institutional dataset of 326 patients induced with DRVd demonstrating comparable depth of response and progression free survival (PFS) to the clinical trial experience (Joseph et al, ASH 2023). In aggregate, D-RVd induction yielded impressive very good partial response (VGPR) rates and these patients experienced prolonged PFS. The question of whether those that achieved < VGPR with DRVd experience similar outcomes is unknown. **Methods:** 1000 consecutive NDMM patients treated with RVd between 1/2007- 8/2016, and 326 NDMM patients treated with DRVd induction therapy from 4/2018 - 8/2022 were included in this analysis. Patient were treated with 4-6 cycles of induction therapy, followed by autologous stem cell transplant (ASCT) and risk-adapted maintenance therapy until disease progression. We evaluated the outcomes of patients achieving < VGPR compared to ≥VGPR post-induction and post-transplant in the RVd and DRVd cohorts. The primary outcome of interest is PFS. Demographic, clinical and outcomes data were obtained from our IRB-approved myeloma database. Responses were evaluated per IMWG Uniform Response Criteria. **Results:** The two cohorts are balanced: median age 62.1 vs 61.2 years, male 55.5% and 54.6%; black 41.7% vs 36.3%; most common isotype is IgG in 65.2% and 61.6% of patients in the D-RVd and RVd cohorts, respectively. High risk disease in 15.4 and 17.8%, ISS stage 3 in 20.2% vs 23.4% and R-ISS stage 3 in 6.1% and 11.5% of patients in the DRVd and RVd cohorts. Post-induction, the overall response rate (ORR) in the D-RVd cohort was 99.6% with 86.5%achieving ≥VGPR and 44 patients (13.5%) achieved < VGPR. This contrasts with the RVd group where 317 evaluable patients (32.4%) failed to achieve a VGPR. Post-transplant, of the 271 response evaluable patients, 95.6% achieved ≥VGPR and 4.4% achieved < VGPR. In the RVd group,129 (13.2%) failed to achieve a VGPR post-transplant.As shown in figure 1, the PFS among patients who achieved ≥VGPR both post-induction (panel A, p< 0.001)) and post-transplant (panel C, p< 0.001) with D-RVd induction experienced significantly improved PFS compared to the RVd cohort. However, patients who failed to achieve VGPR post-induction (panel B, p=0.994) and post-transplant (panel D, p=0.624) experienced similar PFS to the RVd cohort, suggesting a biologically aggressive group of patients prone for early relapse and inferior PFS. **Conclusions:** DRVd is a highly effective induction regimen with superior efficacy in terms of improved ≥VGPR rates and PFS compared to RVd. Using a quadruplet regimen, very few patients achieve < VGPR post-induction (13.5%) and/or post-transplant (4.4%). However, the outcomes of patients who fail to achieve a VGPR is no better than the RVD cohort, suggesting the need for a response-adapted approach to deepen response and improve long term outcomes.

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Safety and Efficacy of Dara-KAD induction followed with tandem ASCT and KP maintenance in Transplant-eligible, Ultra High-risk, Newly Diagnosed Multiple Myeloma and Primary Plasma Cell Leukemia

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Introduction: Patients with ultra-high-risk multiple myeloma (UHRMM), including "double-hit"or "triple-hit" MM, and primary plasma cell leukemia (pPCL), have a significantly poor prognosis with current therapeutic strategies. Circulating plasma cell is associated with poor outcome in NDMM. The addition of daratumumab (Dara) to induction improved response rate and PFS in TE-NDMM patients.Double transplant also improved outcome of HR TE NDMM patients.Dara-KRd with tandem transplant is feasible in patients with HR TE-NDMM and resulted in high response rates and PFS, but some patients discontinued the study due to stem cell collection failure(IFM2018-04). This study will assess the efficacy and safety of the combination of daratumumab, carfilzomib, liposomal doxorubicin, and dexamethasone induction followed with tandem ASCT and maintenance with carfilzomib and pomalidomide in patients with ultra high-risk TE NDMM and pPCL. **Methods:** This is a single-arm and prospective study. Key inclusion criteria were: 1.NDMM patients with ultra high-risk disease, as defined by one of the following: 1)"Double hit" or "Triple hit" (≥2 adverse markers: t(4;14), t(14;16), 1q21+, 1p32-, del(17p), BLPC≥ 1% ; 2.Newly-diagnosed pPCL; 3. Aged 18 years to 70 years. Treatment strategy includes Dara-KAD induction (4-6 cycles), tandem autologous stem cell transplantation (ASCT), carfilzomib-pomalidomide maintenance. The primary endpoint is PFS. Here,

we report efficacy and safety analysis of Dara-KAD induction. **Results:** Thirteen patients including 9 ultra-high risk NDMM and 4 pPCLwere included from Feb 2023 to May 2024. Median age was 56 (range 34-68) years old. ISS stage 3 and RISS stage 3 were present in 6 (46.2%) and 4(30.8%) patients. Based on inclusion criteria, all patients had HR cytogenetic, including 17p deletion (n=3, 23.1%), t(4;14) (n=3, 23.1%), t(14;16) (n=0,0.0%),and 1q21+ (n=11, 84.6%). Eleven(84.6%) patiens had circulating plasma cells. Six patients completed Dara-KAD induction, 4 patients completed stem cell collection, and 2 completed ASCT1. One patients discontinued treatment due to severe adverse event (neutropenic fever, n=1). Mobilization success rate was 100% in 4 patients and all CD34+ were ≥6*10^6/kg. Grade 3-4 treatment related adverse event were neutropenia (38.5%), thrombocytopenia (15.4%) and infection (23.1%). Rate of any TEAEs leading to definitive discontinuation was 10%, and rate of life-threatening TEAEs was 0%. Among 6/13 evaluable patients post induction, overall response rate of Dara-KAD induction was 100.0%, including 33.3% MRD (NGF, 10-5) negativity, 83.3 % ≥CR, and 100.0% ≥ VGPR. **Conclusions:** Dara-KAD as a pre-transplant induction therapy is safe and facilitates profound responses in patients with ultra-high risk TE NDMM and pPCL. The study is in progress, longer follow-up is needed to evaluate safety and efficacy of the comprehensive treatment approach with Dara-KAD induction, subsequent tandem ASCT, and KP maintenance in this subset of UHR patients.

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A Single-Arm Prospective Study of the Combination of KAPD Induction With or Without ASCT and KP Maintenance for Newly Diagnosed Extramedullary Multiple Myeloma

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Introduction: Extramedullary disease(EMD) is associated with poor outcome in newly diagnosed multiple myeloma(NDMM). Mainly derived from retrospective studies, intensive anti-myeloma/anti-lymphoma regimens, novel-agent combinations, and autologous stem cell transplantation(ASCT) are currently proposed as theoretical treatment options. The paucity of prospective studies makes it difficult to justify strong recommendations for any treatment approach for extramedullary MM(EMM). This study will assess the efficacy and safety of the combination of the combination of carfilzomib/liposomal adriamycin/pomalidomide/dexamethasone (KAPD) induction with or without ASCT and carfilzamib/pomalidomide maintenance for ND EMM. **Methods:** This is a single-arm prospective study. Key inclusion criteria were: (1) NDMM with EMD,as defined by one of the following: 1) the presence of extramedullary lesions in the paraskeletal areas or soft tissues/organs detected by MRI or PET-CT or CT imaging; 2) biopsy proved plasmacytoma of the extramedullary lesion; (2) Age: 18-70 years old; (3) A "measurable lesion": at least one extramedullary lesion ≥1.0 cm in length. Treatment strategy includes KAPD induction (4 cycles), tandem ASCT for transplantation eligible and another 4 cycles of KAPD for transplantation ineligible patients, followed with KP(carfilzomib-pomalidomide) maintenance. The primary endpoint is overall response rate. Here, we report the preliminary data of efficacy and safety analysis of KAPD induction. **Results:** extramedullary disease(EMB) were included from Dec 2023 to May 2024. Median age was 47(range 43-62). ISS stage 3 and RISS stage 3 were present in 2 (28.6%) and 0(0%) patients. High risk cytogenetics were presented in 4(57.1%) patients, including 17p deletion (n=1, 14.3%), 1p32 deletion (n=1, 14.3%), ,and 1q21+ (n=4, 57.1%). Three patients completed 4 cycles of KAPD induction, and 1 patients completed stem cell collection. One patients discontinued treatment due to severe adverse event (neutropenic fever, n=1). Grade 3-4 treatment related adverse event were neutropenia (28.6%), thrombocytopenia (14.3%) , neutropenic fever (14.3%), and drug fever (14.3%). Rate of any TEAEs leading to definitive discontinuation was 14.3%, and rate of life-threatening TEAEs was 0%. Among 4/7 evaluable patients post induction, overall response rate was 100.0%, including 25.0% MRD (NGF, 10-5) negativity, 25.0 % ≥CR, 75.0 % ≥VGPR, and 100.0% ≥PR. Among 3/7 EMD response evaluable patients post induction, overall EMD response rate of KAPD induction was 66.7%, including 2(66.7%) PR. **Conclusions:** KAPD as a induction regimen is safe and facilitates profound responses in patients with newly-diagnosed EMM. The study is ongoing, longer follow-up is needed to evaluate safety and efficacy of the comprehensive treatment approach with KAPD induction, with or without ASCT and carfilzamib/pomalidomide maintenance for newly diagnosed EMM.

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A Prospective Cohort Study of the Effect of Second-Line Induction Intensification in Suboptimal Responders to First-Line Induction in Newly Diagnosed Transplantation Eligible Multiple Myeloma

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Introduction: For multiple myeloma (MM) eligible for autologous stem cell transplantation(ASCT), 4-6 cycles of first-line induction followed by ASCT is the preferred recommendation by guidelines. Deeper pre-ASCT responses are associated with improved progression-free survival (PFS) after transplantation. It is still controversial whether sub-optimal responders to first-line induction should go to ASCT immediately or be switched to a second-line induction regimen to improve the level of response. This prospective cohort study will assess the effect of second-line induction on the response rates, progression free survival (PFS) and overall survival (OS) among patients achieving a suboptimal response (defined as less than complete response (CR)) to first-line induction of newly diagnosed transplantation eligible MM(ND TEMM). **Methods:** This is a non-randomized prospective cohort study. TENDMM achieving a suboptimal response (defined as less than CR) to first-line induction are included and was analyzed in two cohorts: those who received second-line induction after non-response to first line therapy and then proceeded to ASCT (cohort A) and those who had no additional induction chemotherapy but proceeded to

ASCT immediately (cohort B). This is an observational study, and the decision to intensify induction therapy or not is made by the clinician as well as the patient. The primary endpoints were PFS and OS from induction intensification. Secondary endpoints were response (including the proportion of conversions from ≤VGPR to CR in cohort B) and toxicity. Here, we report the preliminary data of response and safety analysis of second-line induction. **Results:** We identified 11 patients with MM who achieved less than a CR to first-line induction chemotherapy between Jan 2024 and May 2024, including two cohorts:cohort A (n=2) and cohort B (n=9). The regimens of first-line induction included VRD (boetezomib/lenalidomide/dexamethasone) and PAD (boetezomib/liposomal doxorubincin/dexamethasone). The regimen of second-line induction included Dara-KPD (daratumumab/carfilzomib/pomalidomide/dexamethasone). Among 7/9 evaluable patients in cohort B, second-line induction intensification resulted in deepening responses in 100.0% (CR in 57.1% and VGPR in 42.9%). Grade 3-4 treatment related adverse event were neutropenia (42.9%), Covid-19 infection (28.6%), pneumonia(14.3%) and rashes (28.6%). Rate of treatment related mortality was 0%. **Conclusions:** In conclusion, for patients achieving a less than VGPR to first-line induction therapy including with novel agent combinations, seconde-line induction intensification improved the depth of response. The study is ongoing, longer follow-up is needed to evaluate safety and efficacy of second-line treatment intensification in patients with sub-optimal pre-ASCT responses to first-line induction therapy.

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Cryoglobulinemic Vasculitis With Gangrene as an Initial Presentation of Multiple Myeloma

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Introduction: Type 1 Cryoglobulinemic vasculitis is a rare entity that can present with skin lesions and peripheral gangrene. Its association with lymphoproliferative disorders is well known. However cryoglobulinemia occuring in the context of newly diagnosed multiple myeloma is a rare entity. Here we describe the case of a 67 year old patient who presented with gangrene of all four limbs with renal dysfunction who was eventually diagnosed with multiple myeloma. **Methods:** 67 year old male patient with no prior co-morbidities presented with progressive gangrene of both fingers and toes of 2 weeks duration.He also had worsening renal dysfunction during this period with need for intermittent dialysis during this period.He was evaluated for renal dysfunction and his renal biopsy revealed membranoproliferative glomerulonephritis with IgG Kappa restriction on renal biopsy. His peripheral smear examination showed cryoglobulin deposits. His bone marrow examination showed 15% clonal plasma cells which were kappa restricted. There was evidence of cryoglobulin deposits in his bone marrow biospy specimen also. Serum immunofixation electrophoresis showed IgG kappa M spike with kappa/lamda light chain ratio of 30 on light chain assay. His autoimmune and infective work up was negative. **Results:** He was initiated on Plasma exchange for cryoglobulinemia and intermittent dialysis for renal dysfunction. Subcutaneous Daratumumab, Bortezomib, Cyclophosphamide and Dexamethasone was given as per standard protocol for the myeloma clone. He developed septic shock and worsening AKI. NDM Kleibsiella was isolated from Blood Biofire sample and he improved with appropriate anti microbial therapy. He had to undergo amputation of fingers and toes which had dry gangrene prior to initiation of treatement, however his renal function and blood parameters improved after 5 sessions of plasma exchange and Daratumumab based treatment of multiple myeloma. he was continued on standard myeloma therapy as per protocol and rehabilitation measures were initiated post amputation surgery. **Conclusions:** Our case highlights one of the rare presenting symptom of patient with Multiple myeloma and highlights the role of prompt intervention and multi disciplinary approach to salvage such patients who have a high risk of fatal complications.

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Renal Outcomes and Predictive Analysis of Progression in Newly Diagnosed Multiple Myeloma Patients

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Introduction: Up to 50% of patients with multiple myeloma present with renal impairment (defined as estimated glomerular filtration rate [eGFR] < 40 mL/min per 1.73 m2) at the time of diagnosis, and 2–4% require dialysis. Renal impairment has been linked to decreased overall survival, increased risk of early death and a greater relative risk of myeloma progression for people with multiple myeloma as compared to those without renal impairment. The objective of this research is to investigate renal impairments in newly diagnosed multiple myeloma patients and the risk factors associated with it. **Methods:** We conducted a retrospective analysis of 181 patients newly diagnosed with multiple myeloma at a tertiary medical center in India, from July 2022 to October 2023. Patients with baseline serum creatinine 2 mg/dl or eGFR < 40ml/min by MDRD equation were defined to have renal insufficiency. Responses in renal function with treatment were graded according to IMWG criteria. Prognostic markers like age, comorbidities, baseline GFR, dialysis requirement, R-ISS stage, serum free light chains and treatment regimen used were analyzed in relation to renal outcomes **Results:** A total of 181 patients were analyzed for the study among which 66.9% (N=121) were men and 31% (N=60) were female. The median age for the cohort was 55 years (range: 30-85). 27.15%

(N=45) of newly diagnosed multiple myeloma patients had renal impairment at baseline and 7.69% (N=14) required hemodialysis at baseline. 47.62% (N=21) among these patients had complete renal response, 4.76% (N=2) had partial response based on IMWG criteria. 14.29% (N=6) had minor response and 33.33% (N=15) had a further decline in renal function. Mortality at 1 year among patients with renal impairment was 79.17% (N=35) as compared to 20.83% (N=27) in patients without renal impairment at baseline. 39.63% (N=30) of patients with R-ISS III at presentation had renal impairment at baseline as compared to 5.88% (N=6) and 18.16% (N=9) patients with R-ISS I and II. 32.57% (N=32) and 10.81% (N=13) of patients with high risk and standard risk cytogenetics respectively had renal impairment at baseline. In our study using a Random Forest model to predict renal outcomes in multiple myeloma patients, we achieved an accuracy of 86.57% and an ROC-AUC score of 92.99%. The model identified the most critical predictors of renal outcomes as serum free light chain ratio, baseline serum creatinine, and changes in creatinine levels, highlighting their importance in assessing renal function deterioration in this patient population. **Conclusions:** Renal impairment was more prevalent in our cohort compared to previous studies and was associated with increased dialysis requirements. Additionally, mortality rates were higher among patients with more severe conditions. Treating these patients aggressively and early in the course of the disease is associated with better outcomes in terms of mortality and renal recovery.

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Time to Treatment Initiation Among Black and White Older Adults With Multiple Myeloma: A SEER-Medicare Analysis

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Introduction: Timely treatment initiation after diagnosis has been identified as an important component of quality cancer care. This study aims to describe time to treatment initiation for Black and White older adults with newly diagnosed multiple myeloma (MM), and to test the hypothesis that as treatments have become more effective over time, Black/White treatment initiation disparities will have increased. **Methods:** Black and White adults diagnosed with MM (2007-2017) were identified in the SEER-Medicare database. Individuals were required to have continuous Medicare Parts A and B 12 months before and after diagnosis (or until death), Part D 12 months after diagnosis (or until death) and not be enrolled in an HMO.We explored time to treatment initiation by race across three diagnosis time periods (2007-10, 11-14, 15-17) using Cox proportional hazard models to estimate hazard ratios with 95% confidence limits(CL), adjusted for age and sex using inverse probability weighting, accounting for death as a competing risk. We further estimated cumulative incidence of treatment initiation by race, at 3, 6 and 12 months after diagnosis across our three time periods. **Results:** White MM patients had a higher likelihood of initiating treatment than Black MM patients across all time periods. Hazard ratios (HR), varied only slightly over time, ranging from 1.35(CL = 1.25, 1.46) in 2007-10 to 1.36(1.27, 1.44) for those diagnosed 2015-17. Estimates of cumulative incidence show an increasing proportion of Black and White MM patients initiating treatment over time. For example, the proportion(CL) of Black MM patients initiating treatment within 12 months increased from 0.43(0.39, 0.49) in 2007-10 to 0.58(0.53, 0.62) in 2015-17. Cumulative incidence of White MM patients initiating treatment within 12 months increased from 0.54(0.51, 0.56) in 2007-10 to 0.69(0.67, 0.70) in 2015-17. Amidst increased treatment initiation for both Black and White patients, we found White MM patients were significantly more likely to initiate treatment than Black MM patients for all treatment initiation windows and diagnosis time periods. Differences in proportions of Black and White MM patients initiating treatments were consistent (ranging from 0.9(0.02, 0.15) to 0.11(0.05, 0.17) across treatment initiation windows and time periods. These data suggest that Black/White disparities are not changing over time. **Conclusions:** We report substantial, entrenched Black/White disparities in MM treatment initiation. Our results show that newly diagnosed Black MM patients are more likely to initiate treatment later than White patients and further that Black MM patients are less likely than White patients to ever receive MM treatment. Contrary to our hypothesis, Black/White disparities are not increasing over time, remaining substantial and unchanging. Further studies are needed to gain a deeper understanding of the multilevel determinants of these entrenched disparities among older newly diagnosed MM patients.

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Multiple Myeloma Patients Who Are in VGPR or Better Benefits From Continued Treatment With Zoledronic Acid Beyond Two Years

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Introduction: Bone destruction is common multiple myeloma. At diagnosis 79% of multiple myeloma (MM) patients has radiological bone disease and 59% has bone pain. This usually increases further during the course of their disease. Risk of progressive bone disease can be minimized with monthly ZOL treatment and the original bisphosphonate studies had a median treatment period of 21 and 24 months respectively. We have showed earlier that monthly treatment beyond two years offers significant protection from progressive bone disease in newly diagnosed MM patients treated with zoledronic acid (ZOL) for two years and then randomized to either continued ZOL or observation. But is this true for all patients regardless of depth of response, as other groups have shown the bone protection of ZOL to be most pronounced in patients with a suboptimal response? To answer this question we made a post-hoc analysis of the Magnolia trial looking at patients who had achieved at least VGPR at latest time point prior to randomization. **Methods:** All patients in study were classified according to International Myeloma Working Group (IMWG) Uniform Response Criteria achieved at latest time point before randomization after two years of ZOL treatment. All patients who had not achieved at least VGPR was excluded. We similarly analyzed patients achieving at least CR. Analysis was performed as a cox regression with PBD as the failure state. This was done to include patients risk time in study. Criteria for PBD were unchanged from earlier investigation and required ≥25% increase in size of existing osteolytic lesions or new osteolytic lesions (both at least 10 mm increase/diameter), new fractures, or lesions needing irradiation therapy or surgery. **Results:** Of 193 patients in the main study 150 patients had achieved at least VGPR at latest time point before randomization after two years of ZOL treatment. 77 remained in monthly ZOL and 73 moved to observation. 25 cases of PBD were found (observation n =18, ZOL n = 7). The hazard ratio favored continued ZOL treatment with hazard ratio for treatment group of 0.37 and 95% CI (0.15-0.89) p = 0.027. For patients achieving at least CR the hazard was still in favor of ZOL 0.47, but it was not significant due to lack of statistical power; number of patients (n = 69), number of PBD cases 9 (observation n =6, ZOL n = 3) CI (0.12-1.84) p = 0.278. **Conclusions:** Continued treatment with ZOL offers decreased risk of PBD in myeloma patients who had achieved at least VGPR at latest treatment after two years initial ZOL treatment compared to observation.

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A Retrospective Comparison of Single Versus Tandem Transplant in Newly Diagnosed Multiple Myeloma: A Real-World Study

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Introduction: Autologous stem cell transplant (ASCT) has been the backbone of therapy in newly diagnosed Multiple Myeloma (NDMM). The main issue regarding ASCT has been the debate between single or tandem transplant to further improve progression free survival (PFS). Only a few studies have been published and almost all predate recently introduced treatment options. The aim of this retrospective analysis is to compare the progression-free survival (PFS) of Single Transplant (ST) versus Tandem Transplant (TT) in patients with newly diagnosed multiple myeloma in a real-world setting. **Methods:** Data from 30 patients with newly diagnosed multiple myeloma who underwent ASCT after induction treatment with VTD and a follow-up >24 months at a single center from 2018 to 2023 were analyzed. 21 underwent ST and 8 underwent TT. The PFS of the two groups was compared using Kaplan-Meier survival analysis. **Results:** The median PFS of the ST group was 35.5 months, while that of the TT group was 39.5 months. **Conclusions:** ASCT has been a fundamental aspect of the therapy in multiple myeloma, despite the introduction of numerous drugs. Indeed, the introduction of Daratumumab and, more recently, the first trials exploring the use of CAR-T products as alternative to ASCT has reduced the absolute need to transplant patients with NDMM. Even more, numerous studies demonstrated the toxicity of tandem myeloablative treatment regarding the bone marrow and the potential risk of developing mutations and secondary neoplasms.This retrospective single-center analysis suggests that there is no significant difference in PFS between ST and TT in patients with multiple myeloma. Despite the small sample size and the retrospective nature of the data, these findings are consistent with previous studies and provide further evidence that TT does not confer a significant advantage over ST in terms of PFS. ASCT as consolidation in NDMM has still significant relevance due to the experience regarding its use compared to CAR-T or bispecific antibodies. Despite the incredible evolution in MM treatment, ASCT and especially ST can be considered a valuable resource for patients with NDMM.

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Single vs Tandem Transplant in High-Risk Multiple Myeloma Patients: A Real-Life Single-Centre Analysis

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Introduction: Autologous stem cell transplant (ASCT) remains the recommended treatment in eligible Multiple Myeloma (MM) patients. Some studies (EMN02, STAMINA) have proven an advantage in terms of PFS and OS in high-risk (HR) MM that received tandem (T) ASCT, leading it to be the standard of care in many European countries, despite data being based on post-hoc analyses including a very small number of patients. Furthermore, no modern study has been designed with T ASCT and the validity of these results are yet to be confirmed with newer drug combinations. **Methods:** We retrospectively analyzed data from newly diagnosed MM patients who underwent ASCT in a single tertiary care center

in order to evaluate outcomes of single (S) vs tandem (T) ASCT in HR patients according to cytogenetics [t(4;14, t(14;16), del17p, chromosome 1q and 1p abnormalities] and R2-ISS stage 3-4. PFS and OS were analysed by Kaplan-Meier methods and compared by log-rank test. Factors affecting PFS were searched by Cox regression analysis. **Results:** a total of 157 patients were included in the study, 105 who received S (67%) and 52 (33%) T ASCT. The two groups of patients were similar regarding age (60 years in both populations), ISS stage 3 (23% in the S subgroup vs 17% in the T), HR cytogenetics (31.5% vs 27%), R-ISS stage IR-HR (67% vs 65.4%), R2-ISS 3-4 (39% vs 33%), renal failure (13.3% vs 17.3%), as well as the proportion of patients receiving 3 drugs induction treatment (66.3% vs 67.5%), undergoing consolidation (33.3% vs 23%) and receiving maintenance post ASCT (49.5% vs 42.3%). Post-transplantation, CR or better was achieved by 53.3% and 50% of S and T ASCT (p=0.411), respectively. After a median follow-up of 84 months (range 36-160), PFS of patients receiving S or T ASCT were not significantly different neither according to cytogenetic HR (31.3 vs 36.5 months; p=0.292), nor by R2-ISS stage 3-4 (44.7 vs 42.7 months; p=0.691). Overall survival was also similar between HR patients according to cytogenetics or R2-ISS 3-4 receiving either S or T ASCT (78.4 vs 65.5 months, p=0.855; 82.3 vs 85.1 months; p=0.983, respectively). Univariate Cox regression analysis selected HR cytogenetics, R2-ISS 3-4, no consolidation, no maintenance and response < CR as factors negatively affecting PFS while number of ASCT was not statistically significant. HR cytogenetics (HR=2.9; CI 95%: 1.5-5.8; p< 0.001), no maintenance (HR=1.8; CI 95%: 1.2-2.8; p=0.008) and suboptimal response (HR=2.1; CI 95%: 1.4-3.2; p=0.001) remained significant in multivariate analysis. **Conclusions:** our study showed that, in the era before anti-CD38 antibodies, single transplant seems to have had the same effectiveness as tandem transplant in terms of both PFS and OS in HR MM patients defined by cytogenetics or by R2-ISS stage.

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Impact of Obesity on Outcomes of Multiple Myeloma Patients Undergoing Upfront Autologous Stem Cell Transplant

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Introduction: Upfront autologous hematopoietic stem cell transplantation (auto-HCT) is standard of care for eligible patients with multiple myeloma (MM). Obesity is a rising global health concern and small cohort studies have had conflicting results regarding its impact on outcomes of MM patients undergoing auto-HCT. We evaluated the impact of body mass index (BMI) on survival outcomes of patients with MM undergoing upfront auto-HCT. **Methods:** In this single-center retrospective study, we included patients undergoing upfront auto-HCT between 2000-2021. We evaluated differences in outcomes between patients with normal BMI (18.5 – 24.9 kg/m2, BMI-N) and those with high BMI (≥25kg/m2, BMI-H). Ten patients (0.4%) were underweight (BMI< 18.5 kg/m2) and were excluded from the analysis. Primary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** A total of 2785 patients were included in our analysis. Six hundred and nine (22%) patients were in the BMI-N group and 2176 (78%) were in the BMI-H group. Within the BMI-H group, 1094 (50%) patients were overweight (BMI 25-29.9 kg/m2), 668 (31%) were moderately obese (BMI 30-34.9 kg/m2) and 414 (19%) were severely obese (BMI ≥35kg/m2). Median age of patients in the entire cohort was 61 years (range 25-83). The most common induction regimen was bortezomib, lenalidomide and dexamethasone (VRD), used in 758 (27%) patients. Patients in the BMI-H group were more likely to be male (63% vs 45%, p< 0.001), younger (median 60 vs 62 years, p< 0.001), black (19% vs 15%, p=0.012) and to have a higher comorbidity burden (26% vs 16% HCT-CI >3, p< 0.001), yet were less likely to have R-ISS III disease (8% vs 14%, p=0.002), compared to those in the BMI-N group. Patients in the BMI-H group more often achieved a response of ≥VGPR prior to auto-HCT (53% vs 48%, p=0.017) and had a higher rate of pre-transplant MRD negativity (43% vs 37%, p=0.023). After a median follow-up of 53.8 months, median PFS was 41.0 months (95% CI 38.6, 43.9) and 38.6 months (95% CI 34.6, 43.5) for patients in the BMI-H and BMI-N groups, respectively. Median OS was 101.5 months (95% CI 96.1, 106.2) and 113.3 months (95% CI 98.6,128.3) for patients in the BMI-H and BMI-N groups, respectively. In multivariable analysis, elevated BMI was not associated with either PFS (HR 0.95 [95% CI 0.85, 1.07], p=0.40) or OS (HR 1.15 (95% CI 0.97, 1.36], p=0.11). **Conclusions:** In a large cohort of patients undergoing auto-HCT for MM, elevated BMI was not associated with a significant difference in survival outcomes. Our findings suggest that obesity may not be a significant determinant in auto-HCT eligibility for myeloma patients.

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Stem-Cell Mobilization and Transplantation in Newly Diagnosed Multiple Myeloma Patients Treated With Carfilzomib-Lenalidomide-Dexamethasone With or Without Isatuximab: Results From the IsKia Trial

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Introduction: In the phase 3, randomized EMN24/IsKia trial, the addition of isatuximab to carfilzomib-lenalidomide-dexamethasone (Isa-KRd) as induction and consolidation in transplant-eligible NDMM patients (pts) significantly improved the measurable residual disease negativity (10-5) rate at the end of consolidation (Isa-KRd 77% vs KRd 67%, p=0.049). Here we present a preplanned analysis on stem-cell (SC) mobilization and collection and transplantation outcomes. **Methods:** Pts received 4 28-day induction cycles with Isa-KRd vs KRd and subsequently started SC mobilization 4–6 weeks after day 21 of cycle 4 with either cyclophosphamide (Cy; 2–3 g/m^2) plus granulocyte colony-stimulating factor (G-CSF; 10 µg/kg) from day 5 until SC collection was completed or G-CSF alone ±plerixafor (PLX) according to its label. Pts received autologous SC transplantation (ASCT) conditioned with melphalan at 200 mg/m2. **Results:** 302 pts were randomized to Isa-KRd (151) or KRd (151) induction. 140 (93%) vs 141 (93%) pts in the Isa-KRd vs KRd arms started SC mobilization at a median time of 25 days from the end of induction. A similar percentage of pts in the Isa-KRd (97%) vs KRd (99%) arms completed SC mobilization (p=0.4). A higher percentage of pts in the Isa-KRd (75%) vs KRd (62%) arms received Cy as part of mobilization (p=0.02); PLX use was similar in the two arms (39% vs 29%, p=0.1). The median number of CD34+ SCs collected was 5.0×10^6 cells/kg (IQR 3.7×10^6–6.6×10^6) in the Isa-KRd vs 5.5×10^6 (IQR 3.8×10^6–7.8×10^6) in the KRd arm (p=0.14). The median number of apheresis days was 2 (IQR 1–2) in the Isa-KRd vs 1 (IQR 1–2) in the KRd arm (p=0.08). The successful mobilization rate (≥2×10^6 cells/kg) was similar in pts mobilized with Cy+G-CSF vs G-CSF (99% vs 96%, p=0.2), although a higher SC yield was obtained with Cy+G-CSF vs G-CSF (6.37×10^6 vs 3.74×10^6 cells/kg; p< 0.001), without significant differences in the two induction arms. A second mobilization, mostly with G-CSF±PLX (73% of pts) was performed in 19 pts (14%) in the Isa-KRd and 7 pts (5%) in the KRd arm, mainly due to <2.0×10^6 cells/kg collected with the first attempt (15 vs 6 pts); of these, 15 vs 7 pts in the Isa-KRd vs KRd arms successfully completed SC collection. Among pts who underwent mobilization, 134 (95%) in the Isa-KRd vs 137 (97%) in the KRd arm underwent ASCT. The median number of CD34+ transplanted cells was 3.1×10^6 cells/kg (IQR 2.4×10^6–4.0×10^6) in the Isa-KRd vs 3.3×10^6 (IQR 2.7×10^6–4.4×10^6) in the KRd arm (p=0.10). The median time to neutrophil recovery (≥0.5×109/L) was 15 days (IQR 12–27) in the Isa-KRd vs 14 (IQR 12–27) in the KRd arm (p=0.3); the median time to platelet recovery (≥20×109/L) was 18 days (IQR 14–24) in the Isa-KRd vs 16 (IQR 13–24) in the KRd arm (p=0.1). **Conclusions:** SC collection with either Cy+G-CSF or G-CSF was feasible after KRd ±isatuximab induction in the majority of pts and allowed for hematopoietic reconstitution in all transplanted pts. The upfront use of PLX could be considered to optimize SC collection.

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Real-World Comparison of Progression Free Survival and Time to Next Therapy Endpoints in Newly Diagnosed Patients With Multiple Myeloma

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Introduction: The IMWG 2016 progression criteria are used to determine the progression free survival (PFS), a common clinical trial endpoint. Real-world health administrative databases studies lack the granular biomarker data required to assess disease progression, and therefore often use time to next treatment (TTNT) as a proxy for PFS. However, the timing of next-line treatment initiation can vary based on a patient's demographic or disease characteristics or treatment tolerability, and this may lead to discrepancies between the PFS and TTNT. Therefore, we aimed to assess how first-line PFS and TTNT compare in real-world patients, and whether these endpoints differed among high cytogenetic risk, transplant eligible, or transplant ineligible patients with newly diagnosed MM (NDMM). **Methods:** This single-center Canadian retrospective cohort study included patients diagnosed with MM after January 2015 treated with standard of care novel agent regimens in a non-clinical trial setting. PFS was defined as the time between first line treatment initiation and disease progression (as per the IMWG 2016 criteria) or death, and patients were censored if treatment was changed reasons other than progression. TTNT was defined as the time between first line treatment and initiation of next line therapy for any reason or death. High risk cytogenetics was defined as the

presence of del(17p), t(4;14), t(14;16) or amplification 1q. Time to event analysis was conducted using the Kaplan Meier method. **Results:** A total of 483 NDMM patients were included in this study. The median age at diagnosis was 69.1 (interquartile range 62.2-76) years, 83 (17%) patients had high risk cytogenetics at diagnosis, and 242 (49%) patients underwent an upfront autologous transplant. During study follow up, 198 (41%) patients met IMWG progression criteria, 9 (5%) of whom did not receive second line treatment (n=1 was lost to follow up, n=8 were palliated). Overall, 27 (6%) patients transitioned to second line treatment without meeting IMWG progression criteria (n=11 due to toxicity on first line therapy, n=10 to deepen disease response, and n=6 for unknown reasons). In the overall cohort, the median PFS was 40.1 (95% CI 34.8-47.3) months whereas the median TTNT was 39.2 (95% CI 34.8-43.8) months (p =0.573). There was no significant different in the median PFS or TTNT among patients with baseline high risk cytogenetics (mPFS 27.8 [95% CI 16.7-49] months vs mTTNT 23.8 [95% CI 15-38.3] months, p=0.545), transplant eligible patients (mPFS 61.9 [95% CI 49-80] months vs mTTNT 64 [95% CI 54.6-76.3] months, p=0.874), or transplant ineligible patients (mPFS 26 [95% CI 20.9-30.1] months vs mTTNT 23.9 [95% CI 20.2-28.5] months, p=0.456). **Conclusions:** This was the first study to compare the PFS and TTNT of real-world NDMM patients treated with novel agents. We showed that PFS and TTNT were comparable endpoints, which supports the use of TTNT as a surrogate measure of PFS in real-world studies.

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Melphalan vs Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) As Preparative Regimen for Newly Diagnosed Patients With Multiple Myeloma Undergoing Autologous Stem Cell Transplant

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Introduction: ASCT has been shown in multiple prospective randomized trials to result in superior progression-free survival (PFS), and in some studies, better overall survival (OS) for patients with multiple myeloma (MM). Prior comparisons between BEAM and MEL have been retrospective and suggest that BEAM may be more efficacious than MEL in MM. Here we present results of a prospective randomized trial between MEL and BEAM regimens for patients with MM undergoing transplant in first remission. **Methods:** Patients with newly diagnosed MM without severe comorbidities, received at least 2 cycles of induction therapy with a minimum of partial response, were randomly assigned to receive either BEAM or MEL prior to ASCT. The clinical decision to treat patients using ASCT was made prior to study enrollment. Patients were stratified utilizing the following parameters: serum beta-2-microglobulin < 5 or ≥5, and the presence or absence of high-risk genetics as defined by IMWG criteria. BEAM was administered in-patient as follows: Carmustine 300 mg/m2 IV day -7; Etoposide 100 mg/m2 IV days -6,-5,-4,-3; Cytarabine 100 mg/m2 IV BID on days -6, -5, -4 and -3; MEL 140 mg/m2 IV on day - 2. MEL was given at a dose of 200 mg/m2 IV on Day -2. Patients filled out quality of life questionnaires (FACT-MM) during pre-transplant period, day +30 and day +100 post cell infusion. **Results:** 39 patients have been enrolled. Two patients (MEL=1, BEAM=1) received dose adjusted MEL or BEAM for renal dysfunction. Neutrophil engraftment day occurred a median 12.5 days after ASCT in MEL cohort and 11 in BEAM cohort. Platelet engraftment occurred at a median 15 days in MEL cohort and 14 days in BEAM patients. Neutrophil count nadir occurred sooner in the BEAM cohort. Neutropenic fever was observed in 14 (70%) of MEL patients and 17 (89%) of those who received BEAM. The number of infections by day 30 was 6/20 (30%) and was 5/19 (26%) in MEL and BEAM patients, respectively. ASCT infusion was given as outpatient setting for 16/20 (80%) in MEL and 8/19 (42%) in BEAM. 8 BEAM patients (47%) were discharged after preparative regime and received stem cells in outpatient setting. PFS at 3 years post-transplant was 53% in the Melphalan arm and 74% in the BEAM arm. At time of data cut-off, overall survival was 70% in the MEL arm and 94% in the BEAM arm. In the MEL arm, 1 patient developed ALL and 1 patient died from alternate causes. Quality of life measurements through well-validated scoring systems were similar in both arms. **Conclusions:** The results signal that both regimens lead to similar rates of engraftment, unplanned hospitalizations, and non-hematologic adverse events. There appears to be a trend towards higher PFS in patients who receive BEAM. Therefore, we aim to complete enrollment by including 40 patients on each arm of the study for the results to achieve statistical significance. High dose chemotherapy can be safe, effective, and more financially feasible for patients worldwide compared to novel immunotherapies not yet available.

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Prognostic Impact of t(11; 14) in Newly Diagnosed Patients With Multiple Myeloma

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Introduction: Translocation t(11;14) has emerged as a crucial genetic aberration and is one of the most common primary translocations in multiple myeloma (MM). One of the key features linked with t(11;14) is the BCL2 dependency, which is a druggable target with BCL2 inhibitors. In the era of the novel anti-myeloma agents, the exact prognostic role of t(11;14) remains to be determined. **Methods:** We analyzed data from 1011 consecutive

patients with newly diagnosed MM (NDMM), who were diagnosed and treated in our department, from 1997 to 2023. All were tested for t(11;14) at diagnosis using standard fluorescent in-situ hybridization in CD138+ selected cells. Positivity was defined as at least 20% of clonal cells harboring t(11;14). The presence of +1q21, t(4;14), t(14;16), del(17p), del(13q), were also determined by FISH. **Results:** At baseline, 89 out of 1011 patients (8.8%) had the t(11;14), whereas 922 (91.2%) were negative. The median age was 68 years for both subgroups (range 37-88 and 34-93, respectively), whereas 42 (47%) and 502 (54%) were males (p=0.35), respectively. Overall, patients with t(11;14) did not have a statistically significant difference in progression-free survival (PFS) compared with those who did not had t(11;14) [hazard ratio (HR) 1.25, 95% confidence interval (CI) 0.92 – 1.70, p=0.15]. Patients with no cytogenetic abnormalities at diagnosis had superior PFS compared with those who were positive for t(11;14) (HR 1.41, p=0.04) or any other cytogenetic aberration (HR 1.39, p=0.001). Interestingly, those with isolated positivity for t(11;14) did not have a statistically significant difference in PFS compared with those without any abnormalities (HR 1.28, 95%CI: 0.81-2.03, p=0.282). However, patients with t(11;14) and at least another cytogenetic abnormality had inferior PFS (HR 1.38, p=0.001). More specifically, those with t(11;14) and del17p (HR 3.74, 95%CI: 1.53-9.17, p=0.004) and those with t(11;14) and 1q21 amplification/addition (HR 1.67, 95%CI: 1.00-2.78, p=0.05) had particularly dismal outcomes. Similarly, there was no statistically significant difference in overall survival (OS) between patients with and without t(11;14) (HR 1.31, 95%CI: 0.86-2.00, p=0.21). However, patients who had at least an additional cytogenetic abnormality had inferior OS (HR 1.68, p< 0.001). Furthermore, patients with t(11;14) had inferior OS compared with those without any aberrations (HR 1.62, 95%CI: 1.03-2.55, p=0.04). Interestingly, patients with isolated t(11;14) did not demonstrate inferior OS compared with those without any abnormalities (HR 0.61, 95%CI: 0.22-1.67, p=0.33). However, the co-presence of del17p (HR 6.03, 95%CI 2.20-16.52, p< 0.001) or 1q21 amplification/addition (HR 2.51, 95%CI: 1.30-4.86, p=0.006) with t(11;14) had a detrimental impact on OS. **Conclusions:** Isolated t(11;14) in patients with NDMM does not seem to be a marker of adverse prognosis, whereas the presence of other high-risk cytogenetic abnormalities confer dismal outcomes.

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Outcomes of Multiple Myeloma Patients With Prior Solid Tumors Undergoing an Autologous Transplant

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Introduction: Autologous hematopoietic stem cell transplantation (autoHCT) remains standard care for patients with multiple myeloma (MM). Prior solid tumor is the highest scoring variable in the hematopoietic cell transplantation specific comorbidity index (HCT-CI), which is used to estimate mortality risk after transplant. There are limited data on the impact of prior solid tumors on the outcomes of MM patients undergoing autoHCT. **Methods:** Single-center retrospective study in a large tertiary referral center. We included all consecutive MM patients who received upfront autoHCT between 1997 and 2021 and divided them into two groups: with or without prior solid tumor (PSM+ and PSM- groups, respectively). High risk cytogenetic abnormalities were defined as t(4;14), t(14;16), del(17p), and 1q21 gain or amplification by fluorescence in situ hybridization (FISH) analysis. Primary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** 2853 MM patients were included in the study, of whom 274 were in the PSM+ group, the most prevalent being prostate cancer (n=81), breast cancer (n=50), melanoma (n=31), renal cell carcinoma (n=19) and colorectal cancer (n=13). Patients in the PSM+ group were older than those in the PSM- group (67 vs. 60 years; p< 0.001), more often male (66% vs. 58%; p=0.010) and more often transplanted after the year 2010 (78% vs. 69%; p=0.003). There was a trend towards increased incidence of high-risk cytogenetic abnormalities in patients in the PSM+ group (30% vs. 24%; p=0.06). There was no significant difference in pre-transplant (p=0.33), day 100 post-transplant (p=0.35) and best post-transplant (p=0.27) hematological responses between the PSM+ and PSM- groups. Similarly, there was no significant difference in pre-transplant (p=0.34) or best post-transplant (p=0.44) minimal residual disease (MRD) status between the two groups. There was no difference in PFS between the PSM+ and the PSM- groups (36.7 months vs. 39.9 months; p=0.31). In contrast, patients in the PSM+ group had worse OS compared to those in the PSM- group (81.3 months vs. 104 months; p=0.020). Within the PSM+ group, median OS for specific cancer subtypes were: thyroid cancer not reached; colorectal cancer 154.9 months; renal cell carcinoma 85.0 months; melanoma 81.3 months; prostate cancer 80.1 months; breast cancer 73.5 months; and bladder cancer 65.5 months. In multivariate analysis, prior solid tumor retained its negative predictive impact on OS (HR 1.34, 95% CI 1.07-1.68; p=0.011). 102 patients in the PSM+ group died during follow up. The most common cause of death was progression of MM (77/102, 75%); 3 patients died of their prior malignancy (lung cancer, breast cancer and melanoma, 1 each), and 7 died of a second primary malignancy that developed following transplant. **Conclusions:** Patients with MM and a prior solid tumor had inferior overall survival after an autoHCT, confirming its adverse prognostic impact on transplant outcomes.

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Outcomes of Standard-Risk Multiple Myeloma Patients Who Undergo Upfront Autologous Hematopoietic Stem Cell Transplantation

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Introduction: Autologous hematopoietic stem cell transplantation (autoHCT) is considered standard of care for eligible patients with multiple myeloma (MM). Patients without high-risk cytogenetic abnormalities are considered to have standard-risk MM (SRMM). There are limited data focusing specifically on the outcomes of SRMM patients after an upfront autoHCT. **Methods:** We conducted a single-center retrospective analysis that included consecutive MM patients who received an upfront autoHCT between 2013 and 2021, had available cytogenetic information, and had no high-risk abnormalities on fluorescence in situ hybridization (FISH), defined as t(4;14), t(14;16), del(17p), or 1q21 gain or amplification. Primary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** 1000 patients with SRMM were included in the study, with a median age of 61 years (range 25-83), and 61% were male (n=612). The most common induction regimen was bortezomib/lenalidomide/dexamethasone (n=398, 40%), and the majority of patients (87%) received single-agent melphalan as conditioning. Overall, 571 (57%) patients achieved ≥VGPR prior to autoHCT, with 401 (40%) patients achieving minimal residual disease (MRD) negative status prior to transplant. 873 (87%) patients received post-transplant maintenance, mostly with lenalidomide +/- dexamethasone (81%). At day 100 post-autoHCT and at best post-transplant response, 772 (77%) and 885 (89%) patients achieved ≥VGPR, respectively; 367 (37%) and 624 (63%) achieved CR, respectively. After a median follow up of 42 months, the median PFS for the entire cohort was 68.3 months (95% CI 60.1-72.1), and median OS was not reached (95% CI 102.3-not reached). 5-year PFS and OS rates were 55% and 83%, respectively. In multivariable analysis, achieving MRD-negative CR prior to autoHCT [hazard ratio (95% CI): 0.64 (0.44 – 0.95), p=0.027] and use of post-transplant maintenance [0.67 (0.50 – 0.90), p=0.008] were associated with better PFS. Use of post-transplant maintenance [0.48 (0.32 – 0.70), p< 0.001] was also associated with better OS in multivariable analysis. In contrast, R-ISS stage III was associated with worse OS [2.34 (1.01 – 5.43), p=0.047] and HCT-CI >3 exhibited a trend towards worse OS [1.40 (0.98 – 2.00), p=0.06]. **Conclusions:** Patients with SRMM who received upfront autoHCT had a median PFS of >5.5 years and a 5-year OS rate of 83%. Use of post-transplant maintenance was associated with significantly better outcomes. These results may further improve in the future with the use of quadruplet induction and MRD-guided maintenance.

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Survival of Patients With Multiple Myeloma Treated With Bortezomib-Based Triplets and Autologous Hematopoietic Stem Cell Transplant As Frontline in Latin America

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Introduction: Anti-CD38 monoclonal antibodies have emerged as pivotal in newly diagnosed multiple myeloma (NDMM) management. However, in Latin America (LA) there is not widely access to them, and bortezomib-based triplets (BBT) followed by autologous stem cell transplant (ASCT) and post-ASCT maintenance with lenalidomide remains the best option. The aim of this study was to assess the efficacy of BBT and ASCT consolidation in Latin American NDMM patients. **Methods:** Retrospective international multicenter cohort study. Patients with NDMM who received BBT followed by ASCT as frontline, between 2010 and 2023 were analyzed. Data were collected from clinical records in a standardized report form. Efficacy was evaluated in terms of post-induction response according to IMWG criteria, overall survival (OS) and progression free survival (PFS). Difference in outcomes were explored by risk-group stratification using the Kaplan-Meier method and the Log Rank test. **Results:** A total of 534 patients from 7 Latin American countries with NDMM were included. Median age was 57 years (range 29-75) with a male predominance (59%). 54% were treated in private centers. 59% of MM were IgG subtype, 24% IgA and 16% light chain, and 64% and 77% were classified as stage II or III according to ISS and R-ISS, respectively. Bone disease was the most frequent myeloma-defining events (79%), followed by anemia (47%), renal failure (20%), and hypercalcemia (20%). 14% reported extramedular disease. FISH analysis was performed in 50% of patients (only 34% with sorting), del17p was the most frequent abnormality (14%), followed by t(4;14) (6%), and t(14;16) (3%). The most frequently used BBT was cyclophosphamide-bortezomib-dexamethasone (CyBorD) (44%), followed by bortezomib-thalidomide-dexamethasone (VTD) (31%), and bortezomib-lenalidomide-dexamethasone (VRD) (25%). Very good partial remission (VGPR) or better was achieved in 80% for VRD, 78% for VTD, and 64% for CyBorD (p=0.008). Median time from diagnosis to ASCT was 273 days (range 94-1625). Maintenance treatment was administered to 85% of patients and was based on lenalidomide, thalidomide, and bortezomib in 72%, 9% and 7%, respectively. With a median follow-up of 62 months, median PFS was not reached (NR) and the 3-year PFS was 76% (95% CI, 72-80%). Median OS of the whole cohort was NR, and the 3-year OS was 91% (95% CI, 89-94%). No significant difference between the 3 triplets was

found. In the multivariate analysis, hypercalcemia, extramedullary disease, and not receiving maintenance were independent risk factors for OS. **Conclusions:** The use of BBT and ASCT as frontline is very effective approach for NDMM in LA, with long PFS and OS, and with similar results as internationally described. No differences between the 3 BBT were found in regard of survival. The major prognostic factors are hypercalcemia, extramedullary disease, and not receiving maintenance. In conclusion, this approach is effective and a good option for patients in LA.

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Impact of Daratumumab/Bortezomib/Thalidomide/Dexamethasone (DVTD) Induction Therapy on Chemo-Free Stem Cell Mobilization in Newly Diagnosed Multiple Myeloma Patients: A Real Life Experience

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Introduction: Daratumumab-based induction followed by autologous stem cell transplantation (ASCT), is the standard of care for transplant-eligible newly diagnosed multiple myeloma patients (NDMM). Daratumumab (Dara) adversely affects stem cell mobilization, and this is clearly reported in prospective clinical trials. Here, we described a real-life experience on peripheral blood stem cell (PBSC) mobilization in patients treated with Dara-based induction. **Methods:** From 2022 to 2024, NDMM patients treated with Dara, bortezomib, thalidomide and dexa (DVTD) were mobilized using G-CSF 10 µg/kg/day, in 2 centres. PBSC minimum target was 2.5x106 cells/kg for 1 ASCT and 5x106 cells/kg for 2 ASCT. Plerixafor (Plx) 240 µg/kg was used on demand when circulating CD34+ was less than 20/µL at day +5. Categorical variables were reported as count with percentage and continuous variables as median with range. Chi-square tests were used to compare categorical variables and p value < .05 was considered for statistical significance. **Results:** 100 patients were included. Median age was 61 years (range 42-71). Median induction cycles were 4 (3-6); 63% of patients mobilized after fourth cycles, 37% after third cycle; median time from last Dara to G-CSF start was 25 days (9-109). Responses to induction were: CR 16%, VGPR 60%, PR 16%, SD 1%. PBSC mobilization was successful in 90% of cases. Plx was added in 36%. The median CD34+ peak was 39/µL (0-490); the median of CD34+ cells harvested was 6.7x106/kg (2.5-23.9) with 66% of patients harvesting more than 5×106/kg. The median number of apheresis was 1.7 (range 1-3). 10 patients failed first mobilization, and 9/10 were subsequently mobilized with chemo-based regimen. In univariate analysis, age (>60y vs < 60y), response after induction (≥VGPR vs < VGPR) and days from last Dara (>25 vs < 25) did not affect Plx use and number of apheresis. The number of apheresis' day was longer in pts mobilized after 4 vs 3 induction cycles (p=0.049). All patients received ASCT. The median time to absolute neutrophils count >0.5 and platelets count more than 20 was 11 (6-24) and 13 days (7-30) respectively. **Conclusions:** our study showed that chemo-free PBSC mobilization is feasible and effective even after DVTD induction. However, the use of Plx seems to be higher. 10% of patients failed to mobilize, and a second round of mobilization was effective for harvesting stem cells.

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Busulfan Plus Melphalan versus Melphalan Alone as Conditioning Before Autologous Hematopoietic Cell Transplantation for Multiple Myeloma: Long-Term Follow Up of a Randomized Phase III Trial

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Introduction: In a phase III randomized trial for conditioning regimen for autologous hematopoietic stem cell transplantation (auto-HCT) for patients with newly diagnosed multiple myeloma, we showed that busulfan plus melphalan (Bu-Mel) was associated with longer progression-free survival (PFS) compared to melphalan alone (Mel alone). Here we report updated results for this trial based on long-term follow up. **Methods:** Patients were randomized to either Bu-Mel or Mel using dynamic adaptation to balance on patient covariates. Eligible patients, aged 70 years or younger, with at least stable disease, were randomly assigned to either Bu-Mel, with a pharmacokinetically adjusted doses of Bu on days –7, –6, –5, and –4 to achieve a target daily area under the curve (AUC) of 5000 µmol-minute and Mel 70 mg/m2 per day on days –2 and –1 or a Mel dose of 200 mg/m2 on day –2. The primary objective was to compare PFS between the two arms. **Results:** Between Oct 2011, and March 2017, 202 patients received the treatment: 104 in the Bu-Mel group and 98 in the Mel alone group. There was no significant difference between the two arms in age, gender, race, cytogenetic risk status, R-ISS stage, induction regimens, response to induction, or maintenance therapy. Overall, 28 of 101 (28%) patients and 27 of 93 (29%) patients had high-risk cytogenetics, defined as t(4;14), t(14;16), del17p, and 1q gain or amplification, in the Bu-Mel and Mel arms, respectively. There were no treatment-related deaths by day 100 in either group. Grade 1-3 mucositis (96% vs. 49%, p < 0.001), rise in ALT (33% vs 1%, p < 0.001) and neutropenic fever (71% vs. 30%, p < 0.001)

were seen at a higher rate in the Bu-Mel arm. At day 90 after auto-HCT, 29 (28%) and 34 (35%) patients had achieved complete remission (CR), which increased to 61 (59%) and 63 (64%) patients at best post-transplant response evaluation in Bu-Mel and Mel arms, respectively. The median follow-up in the Bu-Mel group was 96.6 months (5.6–146.7) and 88.4 months (10.7–146.2) in the Mel alone group. Median PFS was 62.2 months (95% CI: 48.1–81.9) in the Bu-Mel versus 56.8 months (95% CI: 34.7–82.5) in the Mel alone. Median overall survival has not been reached in either group. Second primary malignancies were seen in 17 (16%) and 15 (15%) patients in the Bu-Mel vs. Mel alone arms, respectively. In a fitted Bayesian regression model for PFS, there was no meaningful Bu-Mel vs. Mel alone effect, with a 55% posterior probability of benefit for Bu-Mel. Only high-risk cytogenetics was predictive, with a 99% posterior probability of shorter PFS. **Conclusions:** Contrary to our original report, after a longer follow up of almost 8 years, there was no significant difference in PFS between the Bu-Mel and Mel alone arms. Mel 200 mg/m2 remains the standard conditioning regimen for auto-HCT for multiple myeloma.

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A Real-World Study to Assess Treatment Patterns and Outcomes of Patients (pts) with 2L+ Relapsed or Refractory Multiple Myeloma in Italy, Germany, and the United Kingdom

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Introduction: Despite available treatments, multiple myeloma (MM) remains incurable, and most pts experience relapses. Pts with relapsed or refractory MM (RRMM) have a poor prognosis, with limited survival. The use of daratumumab (dara) as part of frontline combinations, including with lenalidomide (len), has shifted the treatment landscape for RRMM. This study describes treatment patterns of pts with RRMM who initiated second-line (2L) therapy in Italy, Germany, and the UK, with a focus on dara and len use in first-line (1L) and 2L treatment. **Methods:** This was a retrospective, physician panel-based chart review study. Data on clinical and demographic characteristics of pts and treatment patterns were collected from medical charts for pts with RRMM who initiated 2L therapy between Jan 2018 and Dec 2022. Pts were ≥18 years old at the time of 2L initiation. **Results:** For participating physicians (N=214; Italy, n=79; Germany, n=69; UK, n=66), most (90.2%) were in urban settings and 67.3% were at academic hospitals. The study cohort included 611 pts, 246 from Italy, 192 from Germany, and 173 from the UK; 69.2% were male. Age at 2L initiation was similar across countries, with a mean ± standard deviation of 66.1 ± 10.2 years overall. The UK had a higher percentage of pts with Black/African/Caribbean ethnicity (19.7%) compared with Italy (0.8%) and Germany (3.6%). Fewer pts in Italy (2.4%) reported a family history of MM versus Germany (6.8%) and the UK (10.4%). Most (51.7%) pts had an ECOG score of 1 (Italy [52.4%], Germany [47.9%], UK [54.9%]). At diagnosis, most pts in Germany presented with ISS/R-ISS Stage II MM (54.2%); in Italy and the UK, the majority presented with ISS/R-ISS Stage III MM (60.2% and 48.6%, respectively). All pts received 2L therapy; 83.0% pts had 2L as last line of therapy (Italy [89.8%], Germany [81.8%], UK [74.6%]), while 17.0% had 3L+ (Italy [10.2%], Germany [18.2%], UK [25.4%]). Overall, stem cell transplantation (SCT) occurred in 25.2% and 7.4% of pts during 1L and 2L. For non-SCT pts, 68.5% and 71.6% received combination therapy in 1L and 2L, with len + bortezomib + dexamethasone (dex) (16.3%) and len + dara + dex (18.3%), respectively, being the most common regimens. Any len use was 40.3% and any dara use was 11.3% in 1L, and 45.2% and 32.2%, respectively, in 2L. Len use was relatively steady from 2018–2022 for 1L (39.8%–47.8%) and from 2019–2022 for 2L (40.2%–52.5%). Dara use (2018–2022) ranged from 8.7%–17.8% for 1L, and 21.8%–37.2% for 2L. **Conclusions:** In this EU real-world population, dara use was relatively low for 1L and increased for 2L during the study period. Following regulatory approvals of the MAIA dara + len + dex regimen, it is likely that 1L use of this combination will increase over time, potentially increasing the proportion of pts refractory to len-based treatments. Due to variations in pt profiles observed across countries, results at a country level may not be generalizable to the overall MM population.

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Daratumumab Plus Bortezomib, Lenalidomide, and Dexamethasone in Transplant-Eligible Patients With Multiple Myeloma: A Pooled Analysis of Patients Aged ≥65 Years From Both PERSEUS and GRIFFIN Studies

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Introduction: In the PERSEUS and GRIFFIN studies, adding daratumumab (DARA) to bortezomib/lenalidomide/dexamethasone (D-VRd) induction/consolidation (ind/consol) and R (D-R) maintenance (maint) resulted in deep responses and improved PFS vs VRd/R in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM). Pts ≥65 yrs of age constitute a group whose outcome is of particular interest. In PERSEUS among pts aged ≥65 yrs, PFS hazard ratios (HRs) were 0.97 (computerized algorithm [comp alg]) and 0.87 (Independent Committee Review [IRC]), potentially due to small numbers of events, cytogenetic risk imbalances (high risk: D-VRd 25.5%; VRd 19.5%), and censoring of pts for PFS after ≥2 missing consecutive disease evaluations (events censored: D-VRd, 0; VRd, 3). However, other randomized studies have shown the benefit of DARA in older pts, including GRIFFIN with D-VRd. To better understand the effect of DARA in combination with VRd in older pts with TE NDMM we performed a post hoc, pooled analysis of PERSEUS and GRIFFIN in pts aged ≥65 yrs. **Methods:** In both studies, TE pts with NDMM aged 18-70 yrs were randomized 1:1 to D-VRd or VRd. Pts received 4 ind cycles (PERSEUS 28-day cycles/GRIFFIN 21-day cycles) and 2 post-ASCT consol cycles of VRd, then R maint. Pts randomized to D-VRd also received DARA during ind/consol and maint. In this post hoc analysis, PFS data was used from comp alg in GRIFFIN and IRC in PERSEUS, and HRs and 95% CIs were estimated using a Cox regression model stratified by ISS disease stage and cytogenetic risk, with no censoring of PFS events after ≥2 missing disease evaluations. Pooled analyses were conducted in pts aged ≥65 yrs. **Results:** Pts aged ≥65 yrs represented 25.5% of pts in PERSEUS (D-VRd, 94/355; VRd, 87/354) and 27.1% of pts in GRIFFIN (D-VRd, 28/104; VRd, 28/103). Among pts aged ≥65 yrs, 9.0% in D-VRd and 13.0% in VRd had ISS stage III disease and 22.7% and 19.3% had high-risk cytogenetics. Median PFS was not reached in either treatment group or study. Stratified by ISS and cytogenetic risk and not censoring pts on basis of 2 consecutive missing disease assessments, PFS HRs favored D-VRd in PERSEUS (HR 0.61 [95% CI 0.32-1.14]), GRIFFIN (HR 0.33 [95% CI 0.06-1.76]), and the pooled dataset (HR 0.56 [95% CI 0.31-1.01]). Rates of MRD neg (10–5) were also higher with D-VRd vs VRd in PERSEUS (67.0% vs 49.4%; OR 2.08 [95% CI 1.14-3.79]), GRIFFIN (64.3% vs 17.9%; OR 6.40 [95% CI 1.80-22.75]), and the pooled dataset (66.4% vs 41.7%; OR 2.75 [95% CI 1.61-4.71]). Data on sustained (≥12 mo) MRD and overall response (IMWG), including complete response or better, will be presented. No new safety concerns were identified in pts aged ≥65 yrs. **Conclusions:** D-VRd ind/consol and D-R maint led to improved PFS and MRD neg vs VRd/R in TE NDMM pts aged ≥65 yrs. These data support D-VRd/D-R as a standard of care and highlight the benefit of DARA during ind/consol and maint for all TE pts with NDMM, regardless of age.

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A Large Scale Analysis of Autologous Stem Cell Transplantation for Multiple Myeloma Patients Older than 65 Years

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Introduction: In Multiple Myeloma (MM) patients (pat) older than 65 yo, the value of the consolidation with autologous stem cell transplantation (auto-SCT) is not well defined. Although it is a population underrepresented in CT, SCT is used in many centers. TriNetX is a federated global health research platform that provides researchers with access to electronic medical records from healthcare organizations to conduct research studies. The aim of our study is to evaluate the safety and efficacy of auto-SCT in pat older than 65yo with MM. Thus, we have employed the data from Hospital 12 de Octubre cohort, and we have validated it with the TriNetx network in a large cohort of MM patients. **Methods:** We have analyzed a cohort from our center (H12O) who have received an auto-SCT from Jan 2013 to Mar 2023. We defined two cohorts: Cohort 1, pat with > 65 yo at the time of transplantation (n=61) and Cohort 2 ≤ 65y (n=234). Data from the last 10 yo of the TriNetx platform of 111 centers have been used with the diagnosis of symptomatic MM (CIE-10: C90.0). Cohort 1, included n=5,080; and Cohort 2 included n=10,376. We performed a matcher pair comparison of a subset of closely matched pat based on Propensity Score Matching (PSM). Key factors included in PSM were baseline population characteristics: ethnicity, sex, comorbidities (Hypertensive diseases, Ischemic heart, CKD, DM, Diseases of liver, Chronic lower respiratory diseases), treatment previous. **Results:** In the H12O cohort of pat, the median age was 68 (66-74) in >65yo pat and 57 (28-65) in < 65 y pat. The older population presented greater Charlson Ind (p=0.001), polypharmacy (p= 0.04) and a another neoplasm (p=0.01). There were no differences in the type of conditioning, pre-SCT response or induction treatment.In our center, with a median follow-up of 3.8yo (0.02-10.8) the PFS at 6y was similar in both groups: 47.3% in Cohort 1 and 54.7% in Cohort2 (HR, 1.2 95% CI, 0.7-1.9, p=0.51). The older pat required admission to the ICU more frequently (19.7% vs 9.8%, p=0.03), without an associated increase in NRM (1.6% vs 1.7%, p=0.7). We found no significant diff in the engraftment, transfusion and complications. At TriNetX database, after the PSM, the final population was 4,927pat in each cohort. Cohort 1 with a mean age (+-SD) of 69.8 (3) and Cohort2 of 56.3 (7.4). The variables were balanced. Need of a new treat at 6yo of follow-up was 64.4 % in Cohort1 and 63.6% Cohort2 (HR,

0.9, 95%CI, 0.8-1, p=0.1). Surival at 60 days was similar between both cohorts: 98.2% in Cohort 1 and 98.9% in Cohort 2 (HR, 1.6, 95%CI, 1.1-2.3, p=0.3).The risk of any transplant complication was significantly lower in Cohort 1 vs. Cohort 2 (RR: 0.4, 95% CI, 0.3 to 0.6). **Conclusions:** This large-scale study shows that ASCT in MM patient, older than 65yo have similar NRM and PFS. Additionally, the incidence of severe side effects and mortality related with ASCT was comparable between younger and older pat. Based on this results ASCT should be considered in fit pat older than 65yo.

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Serious and Hematological Adverse Effects of Daratumumab Plus Triple Therapy vs Triple Therapy Alone for Multiple Myeloma: A Systematic Review and Meta-Analysis

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Introduction: The anti CD-38 monoclonal antibody Daratumumab was recently included in multiple protocols for treatment of Newly diagnosed Multiple Myeloma, either alone or in addition to standard care. Some Systematic Reviews with Meta Analysis have already evaluated effectiveness and survival of daratumumab treatment, strengthening the comprehension of the impact of this therapy. Nevertheless, there is still no such study evaluating the adverse effects and toxicities related to the addition of daratumumab to triple therapy as primary outcome, even though data have been and are being released. The goal of this study is to evaluate the Serious adverse effects of daratumumab plus triple therapy in comparison to triple therapy alone for newly diagnosed Multiple Myeloma. **Methods:** This is a Systematic review with Meta-Analysis of randomized controlled data comparing triple therapy plus daratumumab versus triple therapy alone. Our primary outcome was serious adverse events (SAE). Secondary outcomes included Grade 3 and 4 (G3-4) adverse events, infection and secondary malignancies. **Results:** We included 4 randomized controlled trials, totalizing 1139 patients. The occurrence of SAE was not significantly affected by the addition of daratumumab to triple therapy (Risk Ratio [RR] 1.03; 95%; confidence interval [CI] 0.90-1.18) and a lower rate of treatment-emergent adverse event leading to death was found, tough not statistically significant (RR 0.51; 95%; CI 0.14-1.83). Serious treatment-emergent pneumonia was increased and statistically significant in the daratumumab group (RR 1.66; 95%; CI 1.15-2.38), serious pyrexia had no significant difference (RR 0.81; 95%; CI 0.53-1.22). Grade 3 and 4 neutropenia was significantly increased in the quadruplet therapy group (RR 1.69; 95%; CI 1.24-2.32), such as thrombocytopenia (RR 1.51; 95%; CI 1.24-1.85), but lymphopenia had no significative difference (RR 1.50; 95%; CI 0.84-2.69). G3-4 Infections were increased in the daratumumab group (RR 1.25; 95%; CI 1.03-1.52) and G3-4 pneumonia was increased, though not statistically significantly different (RR 1.50; 95%; CI 0.93-2.42), as serious treatment-emergent pneumonia was. Secondary malignancy was not statistically different between groups (RR 1.39; 95%; CI 0.88-2.19). **Conclusions:** Our Meta-Analysis suggests that including daratumumab to triple therapy regimens increases the risk of serious treatment-emergent pneumonia, G3-4 neutropenia, G3-4 thrombocytopenia and G3-4 infections. Furthermore, additional studies are needed to strengthen our comprehension of long term safety.

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Pre-Transplant Factors Predict Long-Term Outcomes in Newly Diagnosed Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation in a Resource-Limited Setting

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Introduction: In low- and middle-income countries, the management of multiple myeloma necessitates a tailored approach to maximize the utilization of scarce resources such as medications, transplant beds, and monitoring examinations. The objective of this research was to evaluate the potential impact of pre-transplant factors on the long-term response of individuals undergoing autologous stem cell transplantation for newly diagnosed multiple myeloma (NDMM) as a first-line therapy at a university-affiliated public cancer center. **Methods:** Retrospective study of charts of patients with NDMM treated with ASCT from 2009 until 2019 at Instituto do Cancer do Estado de São Paulo (Brazil). **Results:** In a cohort of 193 patients who underwent ASCT as their initial treatment for NDMM, the median age at diagnosis was 58 years (IQR 50-63). The majority of patients had the IgG subtype (62.2%) with kappa light chain (72.5%). The median hemoglobin level was 10.7 g/dL (IQR 8.5-12.6), and 92.2% of patients presented with bone disease. Median creatinine levels were 1.0 mg/dL (IQR 0.8-1.3). According to the International Staging System (ISS), 34.2% were at stage 1, 34.2% at stage 2, and 24.9% at stage 3, with 6.7% missing data. Most patients received a triple thalidomide-based regimen (89.1%), while a smaller proportion were treated with bortezomib (4.7%). The median number of induction cycles was 7 (IQR 5-8), and the median time to ASCT after diagnosis was 10.6 months (IQR 8.6-13.9). Complete hematological response was achieved by 27.5% of patients before ASCT and 56.5% after the procedure. The median overall survival (OS) was 8.7 years (IQR 7-11.3). The median progression-free survival (PFS) after ASCT was 2.6 years (IQR 2.3-2.9). Patients with ISS stage 1 had better outcomes, including hematological response, PFS, and OS. Achieving complete response (CR) before ASCT was associated with improved OS (HR 0.57, CI 0.35-0.94, p = 0.021). Long-term survival was similar among patients who achieved CR only after ASCT and those with very good partial

response (VGPR) or less during first-line therapy. A small percentage of patients received thalidomide as maintenance (11%), which did not improve PFS or OS, nor the time from diagnosis to ASCT. By combining ISS at diagnosis and hematological response before ASCT, a subgroup of patients (12%) was identified with favorable long-term outcomes, showing a remarkable 79% OS rate after 10 years. **Conclusions:** The study demonstrates that achieving complete response before ASCT and having an early-stage diagnosis (ISS stage 1) are significant predictors of long-term survival in NDMM patients. Despite the challenges in resource-limited settings, timely ASCT and effective pre-transplant management can lead to excellent long-term outcomes for a subset of patients.

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Cost Analysis for Adult Patients With Multiple Myeloma Undergoing Autologous Hematopoietic Cell Transplantation

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Introduction: Multiple myeloma (MM) is a malignant hematological disease diagnosed by presence of clonal plasma cells in the bone marrow. Hematopoietic cell transplantation (HCT) is indicated for eligible patients and prolongs progression free survival. Despite its fundamental role in increasing efficiency in the allocation of resources by transplant programs, few studies have been published on the costs of HCT. Therefore, economic evaluation studies in the transplant scenario are extremely important to help improve the management of the procedure worldwide. **Methods:** This cost cohort study of adult MM patients who underwent the first autologous HCT. Period of analysis 01/2010 to 12/2021 from D+30. The method used for cost analysis was absorption costing and the effect of inflation was eliminated by using the hospital's standard cost table in force in October 2023 and the currency converison used was the average of the daily monthly values for 2023 (R$4.99). **Results:** The study included 85 patients; median age was 60 years and there was a male predominance, 55% (47) (Table 1). The total median cost at D+30 was $19.704,34 ($17.493,43 - $25.625,18). When analyzing the median cost by stratification of service categories in the D+30, the biggest cost offenders were materials: $12,432.87 ($5,177.17 - $22,560.06) and daily: $12,087.76 ($8,155.69 - $18,165.63). **Conclusions:** The main contributors to MM's costs were materials and per diems. This result is justified by the daily exams and the materials to treat the patient. According to DATASUS in 2023, 1,851 autologous HCT were performed, with an average cost of R$5,132.15 and an average length of stay of 15.2 days. The HCT average cost in SUS compared with the median cost in our institution on D+30, the values were 3.8 higher than the reimbursement made by SUS. In addition to more days of hospitalization, the difference in price could probably be an indication of the use of the institution's

Table 1 (abstract P-367) Demographic and HCT data.

Variables	Total N(%) N=85	≤60 years N=45	>60 years N=40	p-value
Sex				
Female	38 (45%)	20 (44%)	18 (45%)	0.43
Male	47 (55%)	25 (56%)	22 (55%)	
Median age (IQR)*	60 (55–64)	55 (50–58)	65 (63–68)	<0.01
Karnofsky				
≤80%	5 (6%)	1	4	
90%	14 (16%)	5	9	0.73
100%	66 (78%)	39	27	
Median length of stay (IQR)*	19 (17–21)	18 (17–21)	19 (18–21)	0.72
Conditioning				
Mel 200 mg/m²	80 (94%)	43 (96%)	37 (93%)	
Mel 140 mg/m²	4 (4%)	1 (2%)	3 (7%)	**
Bu+Mel	1 (2%)	1 (2%)	0 (0%)	
Cell source				
PBPC	82 (97%)	42 (93%)	40 (100%)	
BM	1 (1%)	1 (2%)	0 (0%)	**
BM + PBPC	2 (2%)	2 (5%)	0 (0%)	
Total costs (IQR)*	$19,704.34 ($17,493.43 – $25,625.18)	$20,694.27 ($18,332.41 – $31,014.69)	$19,164.24 ($17,170.65 – $20,675.27)	0.06

IQR* = interquartile range / ** = not applicable as it contains groups with no individuals

infrastructure, in addition to hotel services. Despite higher prices than SUS, the costs of transplant are lower than several new treatments available for Multiple Myeloma.

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Stem Cell (SC) Yield and Transplant with Daratumumab ± Bortezomib, Lenalidomide and Dexamethasone in Transplant-eligible Newly Diagnosed Multiple Myeloma Patients in the Phase 3 PERSEUS Study

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Introduction: In the primary analysis of the phase 3 PERSEUS study (NCT03710603), subcutaneous daratumumab (DARA) + VRd (D-VRd) induction/consolidation (ind/consol) and D-R maintenance (maint) improved progression-free survival and increased rates of deep and durable responses, such as minimal residual disease negativity, versus VRd ind/consol and R maint in TE pts with NDMM. Here, we report stem cell (SC) yield and ASCT results for pts with TE NDMM receiving D-VRd versus VRd ind prior to HDT/ASCT in PERSEUS. **Methods:** TE NDMM pts (aged 18-70 yrs) were randomized 1:1 to receive up to six 28-day cycles (4 pre-ASCT ind; 2 post-ASCT consol) of VRd ± DARA, given weekly in Cycles 1-2 and every 2 wks in Cycles 3-6. Within 6 wks after completion of ind therapy (Cycle 4) pts underwent SC mobilization per local standard of care. The use of plerixafor (per institutional practice) in addition to standard agents such as cyclophosphamide/GCSF was recommended to ensure adequate mobilization. If impacted by COVID-19 site closures, SCs were collected after Cycle 4 and transplanted immediately after completion of Cycle 6. Melphalan was given as HDT prior to ASCT. **Results:** Of the 698 treated pts (D-VRd, n=351; VRd, n=347), 335 pts in the D-VRd group and 317 pts in the VRd group completed mobilization. Among pts who completed mobilization, plerixafor use was 40.0% with D-VRd and 22.7% with VRd. Median time from last ind dose to first mobilization agent was 22 days. Median number of CD34+ cells collected was lower with D-VRd vs VRd (5.52×106/kg vs 7.44×106/kg, respectively). Nevertheless, the percent of pts who underwent ASCT was similar between D-VRd and VRd groups (315/351 [89.7%] and 302/347 [87.0%], respectively). The median number of CD34+ cells transplanted was 3.25×106/kg and 3.98×106/kg, respectively. Hematopoietic reconstitution rates were high in both D-VRd (314/315 [99.7%] pts) and VRd (300/302 [99.3%] pts) groups. A median (range) of 13 (1-67) and 13 (1-38) days was needed to achieve sustained ANC of ≥0.5×109/L with D-VRd and VRd, respectively; 14 (1-94) and 12 (1-137) days were needed to achieve a platelet count of ≥20×109/L without transfusion. Median (range) time to engraftment post-ASCT was similar between D-VRd and VRd groups (14 [1-94] and 14 [1-137] days, respectively). A total of 58 pts (29 pts/group) underwent ASCT after completion of Cycle 6 with 100% hematopoietic reconstitution and similar median (range) time to engraftment (D-VRd, 14 [1-67] days; VRd, 14 [12-137] days) in both groups. **Conclusions:** Despite D-VRd ind therapy resulting in a lower SC yield compared to VRd alone, SC mobilization and collection remained feasible with D-VRd ind. Overall, successful transplantation was achieved in pts with TE NDMM when combining DARA with VRd ind and when performed after Cycle 6.

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Optimizing the Alcyone Trial: Efficacy of Daratumumab And Bortezomib Maintenance in Non-Transplant Eligible Newly Diagnosed Multiple Myeloma Patients Post Dara-Vmp Induction, 1 Year Analysis

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Introduction: Outcomes for non-transplant eligible newly diagnosed (ND) multiple myeloma (MM) patients have significantly improved with the inclusion of daratumumab (Dara) in the first line of therapy, as demonstrated by the ALCYONE clinical trial. However, its median TTP (39.3 months) was inferior to continuous Dara-Rd (MAIA trial: 62 months). A potential explanation for this disparity is that in ALCYONE patients only received Dara maintenance, whereas patients in the MAIA received Dara + lenalidomide. We aim to investigate whether extended treatment with bortezomib and Dara (Dara-V) may improve survival in these patients. **Methods:** This multicenter, prospective, observational study enrolled patients who planned to receive Dara-V maintenance per usual clinical practice (Dara 1,800 mg SC every month and bortezomib 1.3 mg/m^2 SC every other week) until disease progression or unacceptable toxicity, following 9 cycles of Dara-VMP induction. **Results:** In total 119 patients were recruited. Median age at diagnosis was 78.8 years (66.1 – 91). Among them, 31 (26.1%) had ISS stage III, 24 (20.2%) had extramedullary disease, and 34 (34%) had high-risk cytogenetics. ECOG performance status was assessed in 64 (53.8%) patients and only 3 (4.7%) had a score ≥ 3. Notably, 20 (16.8%) patients had an estimated glomerular filtration rate < 40, which was an exclusion criterion in ALCYONE. After induction therapy, 74 (62.2%) patients had achieved a very good partial response (VGPR) or better. One year after the start of maintenance depth of response continued to improve, with 93 (78.2%) patients achieving VGPR or better. In the ALCYONE, 292 patients were progression-free after induction and 207 after the first year of maintenance (approximately 85 [29.1%] progressions in that time). In our study six (5.0%) patients progressed during the same period and one (0.9%) died due to causes unrelated to progression or toxicity. Consequently, PFS and OS rates were 94.1% and 99.2%, respectively. Regarding safety, 55 (46.2%) patients experienced adverse events (AE), and 14 (11.8%) serious adverse events (SAE). In total 152 AEs and only 19 (12.5%) SAEs. Of these, 13 (9.5%) AEs and 6 (31.6%) SAEs were grade ≥ 3. The most common AE was infections (40.1%), followed by gastrointestinal disorders (9.2%). Five (3.2%) events of peripheral neuropathy were reported. Nine (7.6%) patients experienced hematological toxicity, 5 (55.6%) being grade ≥ 3. One (0.8%) patient discontinued bortezomib; none daratumumab, and 5 (4.2%) required bortezomib dose reduction. **Conclusions:** In real life, the addition of bortezomib to single-agent Daratumumab as maintenance after induction with Dara-VMP in non-transplant eligible NDMM patients seems to improve outcomes, with only 5% of patients relapsing/progressing in the first year. This may be superior compared to data from Alcyone. Long-term follow-up is required to confirm these findings, but this approach could be an alternative for patients intolerant to lenalidomide.

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Autologous Stem Cell Transplantation in Multiple Myeloma Patients with Renal Impairment: A Retrospective Analysis

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Introduction: Renal impairment is a common and serious complication in multiple myeloma (MM), affecting treatment decisions and prognosis. Understanding the relationship between MM and renal impairment is essential to achieve improved outcomes. The purpose of this study is to assess the effectiveness of autologous stem cell transplantation (ASCT) in patients with impaired renal function in conjunction with MM, aiming to provide data on the efficacy. **Methods:** We retrospectively analyzed 21 patients with renal failure (creatinine > 2.0 mg/dL, < 40 mL/min/1.73 m^2) at the diagnosis of MM who underwent ASCT between 2014 and 2024 at our center. Disease characteristics were noted, as well as the HCT-CI score for risk assessment, induction and conditioning regimens, responses based on International Myeloma Working Group criteria, and survival analysis. **Results:** Twenty-one patients were enrolled in this study. Fourteen were male, and seven were female. The median age at diagnosis was 58 years (42-68). The median follow-up time was 56 months (15-111). Sixteen patients (76%) had ISS stage III. The HCT-CI score indicated that 12 patients (57%) had a high-risk score. At diagnosis, five patients were undergoing renal replacement therapy (RRT), while for non-RRT patients, the median eGFR was 24.6 mL/min/1.73 m^2 (8.7-35.7). The median time from diagnosis to ASCT was 10 months (2-24). Thirteen patients (62%) proceeded to ASCT after a single line of therapy. During the transplant, a low-dose melphalan regimen was used in 9 patients (43%) considering their renal impairment status. For non-RRT patients, the median eGFR at transplantation was 57.3 mL/min/1.73 m^2 (15.5-113.6), with four patients on RRT. Induction treatment responses were: PR in 8 patients (38%), VGPR in 9 patients (42%), and CR in 4 patients (19%). ASCT was performed with a median stem cell count of 4.1x10^6 cells/kg (2.2x10^6-6.3x10^6). No patients experienced

graft failure. The median duration of neutrophil and platelet engraftment was 10 days (9-13) and 11 days (6-16), respectively. At day +100 post-ASCT, 11 patients (52%) achieved CR, 7 patients (33%) achieved VGPR, and 2 patients (9%) achieved PR, while 1 patient experienced disease progression. Thirteen patients received lenalidomide as maintenance therapy, and eight were followed without maintenance treatment. The median progression-free survival was 46 months (13-86), and the overall survival was 56 months (12-116). **Conclusions:** ASCT can be a safe and effective treatment option for MM patients with renal impairment, including those on RRT, as long as careful patient selection and monitoring are performed. Approaches like melphalan dose reduction allow for tailored treatment strategies that address the unique challenges faced by these patients, ensuring optimal outcomes and minimizing potential complications. By demonstrating the feasibility of ASCT in this group, our study underscores the importance of individualized care and follow-up to achieve successful transplantation results.

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Bortezomib thalidomide dexamethasone as first-line treatment in Newly Multiple Myeloma Patients in Perú

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Introduction: Treatment in multiple myeloma is based on triplet or quadruplet including lenalidomide, however in low-and middle-income countries novel therapies are not readily available. Bortezomib thalidomide dexamethasone (VTd) is the standard treatment in our institution. We aimed to determine the outcomes with VTd regimen. **Methods:** We review retrospectively medical records of patients with newly diagnosed multiple myeloma treated at the National Cancer Institute in Perú from 2015-2018. Baseline characteristics were evaluated. Overall survival was analyzed using STATA program. **Results:** During the period of study 16 patients were included. The median age was 54 (range 31-69). Most were male (69%). Ig G Myeloma was seen in 56%, followed by Ig A (25%). 62% were ISS II. Complete response was obtained in 50%, followed by 25% of very good partial response. Cytogenetics risk stratification was not available. The median follow-up was 66.5 months. The median overall survival was not achieved. The 5-y OS was 68.75% (95 IC, 40.4-85.6). **Conclusions:** Bortezomib thalidomide dexamethasone is highly effective in patients with newly diagnosed multiple myeloma which is similar to international literature. Overall survival is good compared to other reports; however, the lack of the availability FISH test is very important to stratify our patient in order to give a better treatment.

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Treatment of Multiple Myeloma in the Public Health System in Brazil: Results of 9 Years of Treatment

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Introduction: Brazil lacks national statistics on epidemiological, clinical aspects and treatment results in multiple myeloma (MM). Furthermore, bortezomib was only incorporated into the Brazilian public system (SUS) in September 2020, until then patients were treated with CTd and those ineligible with MPT. At the Hospital Universitário de Brasília (HUB) we follow patient with MM with the aim of developing national data to better understand the disease, patients and treatment results. **Methods:** In this single-center retrospective study, patients with new diagnose MM were consecutively included from November 2014 to May 2024. We evaluated clinical data (age, sex, diagnosis, prognosis, regimens, lines, transplant eligibility, response) and calculated progression-free survival (PFS) and overall survival (OS). **Results:** We included 91 patients. The median age was 63.1 years, 61% were men, 59% IgG, 25% IgA and 14% light chain, 62% had kappa chain restriction, 61% underwent FLC at diagnosis (36% rate above 100), 60% had anemia, 26% hypercalcemia, 30% Cr >2, 79% bone lesions, 37% plasmacytoma and 22% more than 60% marrow infiltration. No patient underwent FISH and 41% did not have ISS calculated due to unavailability of B2-microglobulin, but 20% had elevated LDH. The clinical stage was advanced in the majority (82% DS III and 52% ISS III). Due to their age plus comorbidity, 31% were ineligible for ASCT. The most used 1st line treatments were CTd (46%), VCd (20%), MPT (15%), VMP (7%), MPT (4%) and VTd (3%). Bortezomib was used in the first line in 30%. The median number of cycles was 6. Response to 1L was 4% CR, 32% VGPR, 48% PR, 3% stable disease, and 14% disease progression. 54% of eligible patients underwent ASCT (77% at 1L) and 82% maintenance after ASCT, preferably with biweekly bortezomib, since lenalidomide was not incorporated into SUS. The median number of rescue treatments was 1 (0-8). For all patients, median PFS and OS were respectively 57 months (5-year PFS 43%) and 111.9 months (5-year OS 71%) (111.9 months ASCT-ineligible and 161.1 months ASCT-eligible). For transplant-eligible patients median PFS was significantly longer in patients who received ASCT (median 68.2 months vs. 23.8 months, $p< 0.001$). The same for patients treated with CTd (median 65.9 months vs. 23.8 months, $p=0.0002$) and there was a trend in patients treated with VCd or VTd before ASCT (median PFS not reached in 105 months vs. 14 months, $p=0.0877$). At 50-months, PFS with MPT and VMP were 51% vs 38%. First line with CTd, VMP, VCd/VTd and VMP, resulted in 60-month OS of 68%, 75%, 68% and 66%, respectively. OS was significantly higher in patients that proceeded to ASCT after CTd or VTD/VCd. **Conclusions:**

There has been a substantial improvement in survival amongst MM in SUS that can be in part attributed to the incorporation of the proteasome inhibitor in the induction, rescue, and maintenance. ASCT remains an important factor improving survival.

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Autologous Stem Cell Transplantation (ASCT) for Real-World Multiple Myeloma in the Era of Novel Therapeutics: A Necessary Reevaluation among Chinese

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow. Despite significant advances in progression-free survival (PFS) due to novel therapies and autologous stem cell transplantation (ASCT), the impact of ASCT on overall survival (OS) remains contentious, especially in China where its adoption lags behind that of Western countries. This discrepancy raises concerns regarding adherence to international treatment standards and their influence on patient outcomes. **Methods:** This retrospective cohort study included 1,172 newly diagnosed MM patients treated at Zhongshan Hospital, Fudan University, from January 2010 to April 2021. After excluding patients with concurrent conditions, monotherapy, follow-up of less than six months, unspecified treatments, or age over 75, a total of 727 patients were deemed eligible. These patients were divided into two groups: 137 underwent ASCT and 309 did not wish to undergo immediate transplantation. Eligibility for transplantation was determined based on good performance status, absence of significant comorbidities, and discontinuation of hemodialysis post-induction. Survival outcomes were analyzed using standard statistical methods, adhering to IMWG criteria and the Helsinki Declaration. **Results:** ASCT significantly extended the median PFS from 36.0 months in non-transplanted patients to 72.5 months in transplanted patients (P< 0.001). However, the improvement in OS was not statistically significant (122.6 months; P=0.054), suggesting that ASCT mainly benefits PFS with limited impact on OS. Subgroup analysis showed that younger patients (under 60) and those with a 1q gain derived specific benefits from transplantation. In contrast, patients with p53 mutations, t(14;16), or t(4;14) did not experience improved PFS or OS. Additionally, transplantation enhanced PFS in patients with type EM-B extramedullary disease, but not in those with type EM-E. Patients who were MRD-negative or achieved complete remission (CR) also did not see improved survival post-transplantation. **Conclusions:** This study confirms that ASCT significantly improves PFS, particularly among younger patients and those with favorable prognostic markers who do not achieve complete response to initial therapy. The minimal impact on OS highlights the need for personalized treatment strategies, taking into account individual risk profiles and disease characteristics. These findings support a more tailored approach to ASCT in MM to optimize treatment efficacy and patient-specific outcomes.

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Real World Analysis Over 15 Years of Newly Diagnosed Multiple Myeloma in China

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Introduction: Multiple myeloma (mm) is the second most common hematopoietic malignancy. Although the disease remains incurable at present, significant advancements in precise diagnostic techniques and prognostic stratification systems over the past decade have led to substantial evolution in treatment approaches for MM. These advancements have substantially prolonged patient prognosis and have even made the possibility of "functional cure" achievable for patients. **Methods:** From 2003 to June 2021, a total of 2340 patients with MM were treated at the Lymphoma and Myeloma Department of our hospital. After screening, 1142 patients who were initially diagnosed and received regular treatment at our hospital were included in the study. We conducted a retrospective analysis of their clinical characteristics, disease staging, treatment regimens, and outcomes. In this study, high-risk cytogenetic abnormalities (HRCA) were defined as the presence of t(4;14), t(14;16), del(17p), or 1q21 abnormalities detected by FISH. **Results:** From 2003 to June 2021, a total of 1142 MM patients were initially diagnosed and received regular treatment at our hospital. This period was divided into four groups: 2003-2007, 2008-2012, 2013-2017, and 2018-2021, with patient numbers of 64, 185, 466, and 427 respectively. The median age of the patients was 58 years, with a slightly higher number of male (59.8%) compared to females (40.2%). The main M protein subtype was IgG (48%), followed by IgA (23.5%) and light-chain type (19.7%). The proportion of patients with HRCAs was 31.6%. First-line induction therapies were categorized as Chemo-based, IMIDs-based, PIs-based, PIs+IMIDs-based, and CD38-included. With the introduction of new drugs, the proportions of patients receiving PIs+IMIDs-based and CD38-included regimens increased over time, reaching 62.5% and 5.2% respectively during 2018-2021. The overall proportion of patients undergoing first-line ASCT was 42.5%. With the development of treatment regimens, the prognosis of patients have shown remarkable improvements. The proportion of patients achieving deep remission (≥CR) reached 67.2% during 2018-202. Up to July 2023, the median follow-up time for the cohort was 61.6 months, with median PFS and OS of 35.5 months and 88.3 months, respectively. Cox regression analysis incorporating patient gender, age, ISS stage, LDH level, presence of HRCA, first-line treatment regimen, and whether first-line transplantation was performed revealed that ISS stage III, HRCA, high LDH levels, use of PI+IMIDs, and transplantation were independent prognostic factors. **Conclusions:** Overall, this study illustrates the evolution of multiple myeloma treatment at a single center in China over nearly two decades, highlighting significant improvements in patient outcome and prognosis.

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The Significance and Predictive Performance of Gait Speed and Grip Strength in Dynamic Frailty Assessment of Newly Diagnosed Transplant Non-Eligible Elderly Patients With Multiple Myeloma

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Introduction: Frailty assessment is crucial to the treatment of elderly patients with multiple myeloma. By frailty assessment, frail and non-frail populations can be distinguished to avoid insufficient or excessive treatment. Studies have confirmed that frailty is dynamically changing, and that dynamic frailty assessment is of a greater value in prognosis. However, there is no conclusion on the selection of the frailty assessment tools due to insufficient evidence. Among the assessment tools, IMWG-FI allows for dynamic assessment, but there are still some shortcomings. **Methods:** Fifty-eight newly diagnosed elderly patients with multiple myeloma who were ineligible for transplantation were included and underwent frailty assessment by gait speed, grip strength, IMWG-FI, IFM, and MRP at baseline and treatment courses 3 (C3) and 6 (C6), and the consistency of gait speed, grip strength, MRP and IFM with IMWG-FI was compared. **Results:** 1. The assessment consistency between MRP and IMWG-FI results was the best at baseline, with an AUC value of 0.795, followed by gait speed, with an AUC value of 0.785. In dynamic assessment, gait speed and IMWG-FI showed the best consistency, with an AUC value of 0.844. Further analysis showed that the consistency of gait speed grip strength and IMWG-FI increased at C3, with AUC values of 0.823 and 0.746, respectively. At C6, gait speed was equivalent to IMWG-FI with an AUC value of 1.0, followed by grip strength with an AUC value of 0.857. 2. Among frail patients with an IMWG-FI score of 2-5, under 80 years of age at C6 follow-up, frailty improvement was observed with dynamic improvements in gait speed but insignificant grip strength change in patients ; while in the patients over 80 years old, no change in IMWG-FI frailty was observed at C3 follow-up, but there was a significant improvement in gait speed and a insignificant improvement in grip strength. **Conclusions:** As a simple and feasible indicator for assessing frailty, gait speed was highly consistency with IMWG-FI in assessment results and showed greater advantages in dynamic assessment. In patients who cannot be dynamically assessed by IMWG-FI, the frailty state remains unchanged, while gait speed shows significant changes. The combination of gait speed and IMWG-FI can better improve the effectiveness of dynamic frailty assessment, identify patients who may be missed by IMWG-FI alone. This is worth for exploration especially for MM patients over 80 years old, where gait speed can be a highly potential dynamic frailty assessment indicator with grip strength as an effective supplementary.

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Gait Speed, Grip Strength, and Clinical Outcomes in Newly Diagnosed Transplant Non-Eligible Elderly Patients With Multiple Myeloma

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Introduction: Gait speed and grip strength are objective indicators of body function that are easily obtainable and cost short time in measurement. The International Myeloma Working Group (IMWG) recommends using frailty assessment tools to assess the level of frailty in patients and providing individualized treatment based on frailty, disease characteristics, and patient preferences. The consistency among the assessment results measured by gait speed and grip strength as well as IMWG has been demonstrated in previous studies, however, there are few studies reporting the significance of gait speed and grip strength in predicting the prognosis of patients with multiple myeloma. **Methods:** Fifty eight elderly patients with MM who were ineligible for transplantation were included to analyze the differences in AE, early mortality, and discontinuation rates among different frailty groups assessed using gait speed, grip strength, and IMWG-FI, respectively. A univariate comparison was conducted to test the effects of gait speed, grip strength, IMWG-FI, MRP, IFM, DXA, IL-6, ADL, IADL, CCI, age, ISS staging, and treatment regimen on OS. This was followed by a multivariate Cox regression analysis. **Results:** 1.Comparison of nonhematological AEs of above Grade3: there were statistical differences in groups with different gait speeds, grip strength, and IMWG-FI; Comparison of hematological AEs of above Grade 3: there were differences among different grip strength groups; Comparison of discontinuation rates: there were differences among groups with different gait speeds and IMWG-FI, while there was no difference between grip strength groups; Comparison of 3-month, 6-month, and 12-month early mortality: no differences were observed except for differences in grip strength groups at 3 months. 2. There were statistical differences in OS among different gait speed, grip strength, IMWG-FI, MRP, DXA, IL-6, ADL, and age groups. Multivariate Cox regression analysis was conducted by incorporating age, gait speed, grip strength, ADL, and IL-6, and gait speed was identified as a significant influential factor on OS. **Conclusions:** The study demonstrated that gait speed is predictive of OS in MM patients and is an independent prognostic factor, it also can predict the incidenct of AE events and treatment discontinuation. Therefore, gait speed reflects not only the functional status but also the frailty condition of patients, it is a promising indicator of frailty assessment. Additionally, for elderly MM patients, many of them are suffering from bone diseases that affect gait speed, and grip strength can be an effective supplement to gait speed.

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Impact of Weekly Versus Twice Weekly Bortezomib on Rates of Peripheral Neuropathy in Combination With Lenalidomide, Dexamethasone and Daratumumab

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Introduction: Daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) is standard of care for newly diagnosed multiple myeloma (MM). This is based on results from the phase II GRIFFIN and phase III PERSEUS trials. In these trials, bortezomib, a proteasome inhibitor, was administered twice weekly on days 1, 4, 8 and 11 of each 21-day or 28-day cycle respectively. A common side effect of bortezomib is peripheral neuropathy (PN) which was seen in 59.6-72.5% of patients in the GRIFFIN trial and 51.6-53.6% in the PERSEUS trial. Single-center studies and real-world data have shown similar efficacy and lower rates of PN with weekly verses twice weekly bortezomib in various bortezomib-containing regimens, but none evaluated this exclusively in D-VRd. As clinical guidelines cite the aforementioned trials, some patients still receive twice weekly bortezomib. This study will analyze the tolerability of weekly versus twice weekly bortezomib in D-VRd. **Methods:** This is a single-center, retrospective cohort study performed on eligible patients treated at Yale Cancer Center including network sites from January 1, 2017, to November 1, 2023. MM patients ≥18 years of age who were treated with D-VRd and received at least two doses of bortezomib were included. Patients were excluded if they had a diagnosis of PN prior to starting D-VRd, received anti-neuropathic medications prior to D-VRd treatment, received bortezomib in a regimen prior to D-VRd or if they switched from twice weekly to once weekly regimen for reasons other than PN. The primary objective is to assess rates of PN in patients with MM receiving D-VRd in once weekly versus twice weekly bortezomib. Secondary objectives include number of bortezomib dose reductions and/or dose discontinuations due to PN, rate of PN stratified by grade and use of anti-neuropathic pain agents. **Results:** 21 of 58 patients (36%) receiving weekly bortezomib developed PN, which was significantly lower than the 17 of 24 patients (74%) on twice weekly dosing ($p< 0.001$). The observed incidence of PN in the twice weekly group is similar to that reported in the GRIFFIN and PERSEUS trials. While there was no difference in the severity of PN as graded by the CTCAE version 5.0, significantly fewer patients required dose reductions due to PN ($p< 0.001$) and treatment for PN ($p< 0.001$) in the weekly group compared to the twice weekly group. The median number of days from starting bortezomib to diagnosis of PN was 77 days in the weekly group and 63 days for the twice weekly group. The number of bortezomib doses and D-VRd cycles prior to diagnosis were similar between groups. **Conclusions:** This study continues to demonstrate clinically relevant reduction in PN for patients receiving once weekly versus twice weekly bortezomib, extending the data to the D-VRd regimen. Further analysis is needed in this context to prospectively evaluate weekly versus twice weekly bortezomib. It is important to advocate for intensity modification in future clinical trials.

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A Retrospective Study of Serum Indicators in Functional High-Risk Multiple Myeloma Patients Undertaking Proteasome Inhibitors Treatments

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Introduction: Multiple myeloma (MM) ranks as the second most prevalent hematological malignancy, predominantly affecting the elderly population. The concept of functional high-risk (FHR) has recently emerged, specifically for patients who exhibit disease progression within 12 months of initiating therapy. Studies have shown that individuals classified as FHR have a median overall survival (OS) of only 20.2 months. MM patients who are resistant to PIs have a poor prognosis, particularly when accompanied by renal insufficiency. In this study, we aimed to discuss the effects of RI on FHR status in MM patients, and seek the determining factors among biochemical parameters. We explored the clinical indices related to FHR and sought prognostic roles in transplant-eligible MM patients. **Methods:** 216 patients were included and divided into two groups according to the FHR status. PFS and OS were estimated by using the Kaplan-Meier method and were compared by using a log-rank test. Logistic regression analysis was used to assess the association of baseline characteristics at MM diagnosis with FHR status. $P< .05$ was considered statistically significant. **Results:** This study included a total of 760 newly diagnosed MM patients. A total of 216 patients undergoing PI-dexamethasone based therapy were included in the study, with follow-up data available. An equal distribution of gender was observed, with a male-female ratio of 1.0. Over a median follow-up period of 21 months, 59 (27.3%) patients deceased while 157 (72.7%) remained alive. The median survival time was 91 months. While patients treated with triplet chemotherapy exhibited improved progression-free survival (PFS) and OS compared to those receiving PI-dexamethasone regimens, no significant differences were observed in PFS and OS within the first 12 months. The results of the univariate logistic regression analysis revealed that treatment options did not have a significant impact on FHR status ($p=0.116$). Additionally, there were no significant differences in baseline data between the FHR and functional standard-risk (FSR) groups. Patients with amplification of 1q21 or deletion of 17p13 had significantly shorter PFS and OS. Moreover, our analysis revealed that renal function did not significantly impact PFS or OS in transplant recipients, despite the observed improvements in outcomes for MM patients with RI. Furthermore, transplant-eligible MM patients with elevated AST levels (>40U/L) tended to experience poorer outcomes. In the context of transplant therapy, a marginal elevation in AST levels did not appear to have a significant impact on PFS and OS. Subsequently, our objective was to assess the prognostic significance of abnormal AST levels. **Conclusions:** Our investigation revealed a notable disparity in biochemical parameters between patients with FHR and FSR MM. Patients with varying levels of Scr and AST exhibited divergent clinical outcomes. Consequently, in the era of PIs, transplant therapies remain efficacious for MM patients.

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Outcomes of Multiple Myeloma Patients Relapsing After Upfront Autologous Stem Cell Transplant in a Brazilian Public Center: Real-World Data

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Introduction: Autologous stem cell transplant (ASCT) remains a key component in the initial treatment of multiple myeloma (MM). However, disease relapse post-ASCT is common for most patients. Here, we report the outcomes of patients treated in a tertiary public hospital in Brazil, where advanced therapies such as anti-CD38 antibodies, second-generation immunomodulatory drugs, proteasome inhibitors (except for bortezomib), and CAR-T cell therapy are not available. **Methods:** We performed a retrospective analysis of clinical features and outcomes for 34 MM patients diagnosed between 2018 and 2022 who received a second line of treatment following relapse after upfront ASCT. Patients with amyloidosis, isolated plasmacytoma, and those who received more than one treatment line prior to ASCT were excluded from the study. **Results:** The median age of patients was 56 years (range: 39-69), with 53% being male. IgG and IgA heavy chain isotypes were observed in 22 (67%) and 5 (15%) patients, respectively. According to the International Staging System, 17 (53%) patients were stage III at diagnosis. Hemoglobin levels < 10 g/dL and creatinine levels >2 mg/dL were found in 18 (55%) and 10 (30%) patients, respectively. Initial treatments included bortezomib for 10 (29%) patients and thalidomide for 20 (59%) patients, with a median of 8 cycles before ASCT. After first-line treatment, 22 (65%) patients achieved at least a very good partial response. The median time from MM diagnosis to ASCT was 11 months (range: 7-47 months). Melphalan conditioning doses were 200 mg/m2 in 22 (65%) patients and 140 mg/m2 in 12 (35%) patients. Maintenance therapy post-ASCT was administered to 9 (27%) patients. The median time from ASCT to relapse was 17 months (range: 5-55 months). Second-line treatments included bortezomib for 14 (41%) patients and thalidomide for 6 (18%) patients, with 12 (44%) achieving at least a very good partial response. With a median follow-up of 51 months, the median progression-free survival (PFS) and overall survival (OS) after the first relapse were 8 months and 31 months, respectively. The 12- and 24-month PFS rates were 40% (95% confidence interval [CI] 26%-62%) and 15% (95% CI 5%-44%), respectively. The 12- and 24-month OS rates were 62% (95% CI 48%-82%) and 54% (95% CI 38%-76%), respectively. **Conclusions:** This study highlights the poor PFS in MM patients who relapse after upfront ASCT. Our findings underscore the urgent need for improved treatment options for patients in resource-limited settings.

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Carfilzomib Dosing in Multiple Myeloma: An International Survey of Oncologist Practices

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Introduction: Despite the widespread use of carfilzomib (K) in multiple myeloma (MM), there is no consensus on its optimal dose or dosing schedule. Studied regimens include K 56 mg/m2 twice weekly (K56-2x), K 56 mg/m2 once-weekly (K56-1x), and K 70 mg/m2 once-weekly (K70-1x). We opted to understand global physician access and preferences regarding standard-of-care (SOC) K for patients with MM. **Methods:** We conducted an international online survey (disseminated via social media and targeted emails between 2/2024 and 5/2024) of hematologist/oncologists who treat patients with MM. Questions included demographic information, typical SOC K dosing preferences and dose-reduction considerations, and practices around venous thromboembolism (VTE) prophylaxis. **Results:** Of 231 website visits, 150 responses (65%) were recorded. Practice settings were predominantly academic (65%, n=97), community institution (20%, n=30), or private practice (9%, n=13). A total of 29 countries were represented, most commonly USA (45%, n=68), India (8%, n=12), and Australia (7%, n=11); 24% (n=36) practiced in low- or middle-income countries (LMICs). K70-1x was preferred by 44% of respondents for K doublets, 32% for K triplets, and 11% for K quadruplets; the corresponding proportions for K56-1x were 27%, 44%, and 46%. K56-2x was preferred by < 10% of respondents in all combinations. Of note, 19% of LMIC and 20% of non-LMIC respondents reported no access to K quadruplets. Pluralities of respondents said their preferred K dosing was not driven by cytogenetic findings (38% saying no influence on K dosing), visceral EMD (37%), first-line versus relapsed disease (50%), or ASCT eligibility (50%). In contrast, large majorities felt that K dosing was moderately driven and/or contraindicated for age ≥75 (66%), moderate frailty (72%), mild asymptomatic heart failure (79%), or mild symptomatic heart failure (90%). Regarding renal dysfunction (eGFR < 30 mL/min), 28% said this wouldn't influence K dosing, 34% said it would be a mild influence, 25% moderate impact, while 11% said K would be contraindicated. For regimens containing K and an immunomodulatory drug (IMID), 57% typically used aspirin 81-100mg daily for VTE prophylaxis, 11% aspirin ≥162mg daily, and 22% a direct oral anticoagulant. **Conclusions:** In our survey of 150 MM-treating physicians from 29 countries, < 10% of respondents favored twice-weekly K in their practice. Disease-related factors including cytogenetics or line of therapy rarely impacted K dosing, suggesting that once-weekly K (either K56-1x or K70-1x) likely represents the global SOC in MM

across treatment lines. The impact of renal dysfunction on K dosing requires more study given the range of responses in our survey, as does optimal VTE prophylaxis with K+IMID regimens given the potential inadequacy of aspirin here (Piedra BJH 2022). Commercial access to K-containing quadruplets, which are increasingly being used in trials, remains an international problem.

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Talquetamab Utilization Patterns and Dose Schedules in the United States: A Real-World Analysis

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Introduction: Talquetamab (Tal) is a first-in-class GPRC5D-targeted bispecific antibody recently approved in the United States (US) for multiple myeloma (MM) after ≥4 prior lines of therapy (LOTs). After initial step-up dosing (SUD), Tal can be dosed either weekly (QW) or biweekly (Q2W). There is limited real-world (RW) data on dosing with Tal. **Methods:** Adult patients with ≥1 MM diagnosis code, ≥1 medical claim for Tal (between Aug 9, 2023 [US approval date] and March 4, 2024 [latest data cut]), triple-class exposure, and without clinical trial involvement were identified using the Komodo Healthcare MapTM. The index date was the date of an inpatient (IP) Tal encounter within 28 days prior to the first outpatient (OP) administration (40mg/mL claim), or date of first OP Tal SUD (3mg/1.5mL or 40mg/mL claim). The baseline period to describe patient demographics and clinical characteristics was 6 months before the index date. Patient characteristics and Tal utilization patterns were reported descriptively. **Results:** Among 82 patients treated with Tal (median follow-up, 2.8 months), the median (interquartile range; IQR) age at index was 65 years (57, 71.8). Most patients were male (58.5%), white (65.8%), and had Medicare (56.1%). Median (IQR) time from MM diagnosis to index date was 5.8 (4.1, 7.8) years. Baseline comorbidities before receiving Tal were common, including 46.3% with recent infections and 41.5% with pre-existing hypogammaglobulinemia. Median (IQR) number of prior LOTs was 5 (4, 7). Prior commercial BCMA-targeted therapy was reported in 56 (68.3%) patients: 7.3% of patients received ciltacabtagene autoleucel, 20.7% idecabtagene vicleucel, 39.0% teclistamab (Tec), 1.2% elranatamab, and 20.7% belantamab mafodotin. Overall, 39% were naïve to prior T-cell redirection therapies. Most patients received Tal as monotherapy (n=73, 89.0%) but 3 patients received commercial Tal+Tec and 2 Tal+pomalidomide. Among patients with ≥3 treatment doses after SUD before the data cutoff, 5 out of 11 patients on QW dosing switched to ≥Q2W while 9 out of 33 patients on Q2W dosing switched to ≥Q3W. At data cutoff, 8 (16.0%), 32 (64.0%), and 6 (12.0%) patients were on QW, Q2W, and Q4W dosing, respectively. **Conclusions:** This is the first study investigating real-world Tal dosing since its US approval. Unsurprisingly, patients receiving Tal were heavily pretreated; however, almost a third of patients had not received prior commercial BCMA therapy. Tal was mainly used as a monotherapy while a small proportion of patients were treated with Tal combination therapy. Some patients de-escalated to less frequent dosing, a strategy shown in MonumenTAL-1 to lower toxicities (Chari ASH 2023). Research into RW Tal clinical outcomes with longer follow-up is ongoing.

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Ixazomib in Relapsed/Refractory Multiple Myeloma Patients – Real World Evidence – Experiences of the Croatian Cooperative Group for Hematologic Diseases (Krohem)

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Introduction: Ixazomib is a second-generation proteasome inhibitor which demonstrated its activity in multiple myeloma (MM) patients, both the newly diagnosed and in the relapse/refractory (RR) settings. The aim of this study was to analyse data for RR multiple myeloma patients treated with ixazomib and to compare it with those reported in literature (both RWE and clinical trials). **Methods:** We performed a retrospective analysis of outcomes for RRMM patients treated with ixazomib in 9 Croatian haematology centres in the period between November 2016 and February 2023 (ixazomib was at first available as patient-name program and reimbursed by health care authorities since June 2019). **Results:** A total of 164 patients with RR myeloma were included. Median age at the start of ixazomib treatment was 66 years (range 40 – 91). There were 44% males and 56% females. Median number of previous lines of therapies was 1 (range 2 – 8). The majority of patients (134) were treated with combination of ixazomib, lenalidomide and dexamethasone (IRd) while the rest (30) were treated with other combinations. 50 patients (30%) previously underwent autologous stem cell transplantation (ASCT) in the first line. 155 patients (94%) were bortezomib exposed and 50 (30%) lenalidomide exposed. Only 10 (6%) and 19 (12%) of patients were exposed to carfilzomib and daratumumab, respectively. 65% of patients had performance status 0-1 and 35% ≥ 2, according to Eastern Cooperative Oncology Group (ECOG). Overall response rate (better or equal to partial response; PR) for the whole group was 65.8%. Very good partial response (VGPR) or better was achieved in 42% of patients. Median follow up was 14.6 months and median progression free survival (PFS) was 15.4

months (at 12 months PFS was not reached; 59%). Median overall survival (OS) was 28.2 months (at 12 months OS was not reached; 72%). We did not find statistically significant differences in PFS or OS regarding number of previous lines of treatment, performance status and age. Anaemia, neutropenia, and thrombocytopenia were reported in 53%, 50% and 45% of patients, respectively. Infective complications were reported in 38% of patients. During follow up a total of 85 patients died (52%) and 101 (62%) experienced disease progression. **Conclusions:** This RWE analysis validates efficacy of ixazomib in RR MM patients with acceptable and manageable toxicities. Similar outcomes were also reported in RR MM group of patients by other RWE analyses. There are some discrepancies between RWE data and data reported in clinical trials. These discrepancies are possibly due to different study populations.

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Novel Selinexor Triplet and Quadruplet Regimens (SNd, SPEd, SBd, SDPd): Results from the Phase 1b/2 STOMP Multiple Myeloma Trial

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Introduction: Multiple myeloma (MM) remains incurable, leaving an unmet need for effective new regimens. Selinexor (S), a first-in-class oral XPO1 inhibitor approved in combination with dexamethasone (Sd) in penta-refractory MM and with dexamethasone + bortezomib (SVd) in relapsed/refractory MM (RRMM) after ≥1 therapy, has shown synergy with other anti-cancer treatments and is being investigated in several novel regimens in the STOMP phase 1b/2 trial (NCT02343042). Here we report safety and efficacy from 4 arms: S 60-80 mg QW + ixazomib (N) 4 mg QW + d (SNd); S 40 mg QW + pomalidomide (P) 4 mg QD + elotuzumab (E) 10 mg/kg QW + d (SPEd); S 60 mg QW + belantamab (B) 2.5 mg/kg Q3W + d (SBd); and S 40 mg QW + daratumumab (D) 16 mg/kg QW + P 4 mg QD + d (SDPd). **Methods:** The STOMP trial is evaluating varied dosing of selinexor in 11 arms in dose-escalation and expansion phases for the treatment of MM. We analyzed investigator-assessed efficacy and safety data from the SNd, SPEd, SBd, and SDPd arms. **Results:** As of Jan 2, 2024, 21 patients (pts) were enrolled (SNd: 6, SPEd: 5, SBd: 7, and SDPd: 3) with median 2 prior treatment lines (2, 2, 6, 1). A total of 83% of the SNd cohort and 100% of the other cohorts had prior treatment with a proteasome inhibitor (PI), 100% of all arms had prior treatment with an immunomodulatory drug (IMiD), and 33% of SNd, 80% of SPEd, 85.7% of SBd, and none of SDPd had triple-class exposure to an anti-CD38 monoclonal antibody, a PI and an IMiD. Overall, 95.2% of pts took prophylactic antiemetic; 61.9% took ≥2 antiemetics.Median duration of exposure was 26.5 weeks in SNd (one pt still on treatment at 30.2 months), 7.0 weeks in SPEd, 14.0 weeks in SBd, and 24.0 weeks in SDPd (one pt still on treatment at 27.0 months). Overall response rates were 16.7%, 20.0%, 71.4%, and 66.7% in the SNd, SPEd, SBd, and SDPd arms, respectively. The most common treatment-emergent adverse events (TEAEs) across all arms included fatigue (61.9%), nausea (61.9%), diarrhea (47.6%), and vomiting (47.6%). The most common maximum grade 3-4 TEAEs across all arms included neutropenia (33.3%) and fatigue (23.8%). One grade 5 TEAE of pulmonary nocardiosis was observed in the SPEd arm that was attributed to all drugs in the regimen. Median relative selinexor dose intensity was 93.6% for SNd, 100.0% for SPEd, 83.3% for SBd, and 91.7% for SDPd. One (16.7%) pt in the SNd cohort developed grade 2 rash and 1 pt in the SBd (14.3%) cohort developed grade 3 keratopathy. **Conclusions:** Selinexor was evaluated in a limited number of pts with various partner drugs. The majority of pts tolerated the selinexor regimens at the intended dosing. No increase in partner drug toxicities were observed, which aligns with the combinability profile of S + d with carfilzomib (SKd), P (SPd), and D (SDd) in the STOMP study. While some pts derived clinical benefit, further safety, efficacy, and combinability profiles remain to be established with larger clinical trials.

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A Deeper Look Into Infections Among Myeloma Patients Treated With Daratumumab or Belantamab Mafodotin

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Introduction: Targeting CD38 or BCMA are effective strategies in our current anti-myeloma treatment. As these surface molecules are shared between benign and clonal plasma cells B-lymphocytopenia and hypogammaglobulinemia are inevitable. Despite effective anti-microbial prophylaxis, infections develop resulting in treatment interruptions. To better understand the incidence and severity of infections developing during Daratumumab or Belantamab mafodotin-based treatments among relapsing myeloma patients this retrospective analysis was performed. **Methods:** Nine patients received Belantamab mafodotin in combination with Pomalidomide and Dexamethasone within a clinical trial. A hundred and t patients received Daratumumab alone (n:10) in a combination DVd (n:32), DVCd(n:27), DRd(n:16), DVRd(n:13), DPd(n:17), DKd(n:11), DVTd(n:1). All patients received vaccinations, Valacyclovir, Trimethoprim, and iv Immunoglobulin prophylaxis (to maintain IgG levels >4 gr/dl). CMV DNA monitorizations were performed routinely to determine the cause of CRP level increments. We observed frequent CMV (17.3%) but rare HBV and no Tbc

reactivations. All CMV reactivations were observed among Daratumumab-administered patients. **Results:** Belantamab and Daratumumab patients were similar in regards to age, previous lines of therapy, but differed in the partnering drugs in combination. When Daratumumab-receiving patients were analyzed separately advanced prior lines of therapy, ISS, depth of response or intravenous Immunoglobulin use were associated with better survival. Here in this analysis, we observed a similar rate and severity of infections, but no infection-related mortality. Despite the longer duration of treatment among Belantamab-treated patients, total intravenous Immunoglobulin replacement episodes were similar to Daratumumab-given patients. **Conclusions:** Our results among Belantamab-given patients are based on a small population to arrive at strong conclusions. Nevertheless, infections including CMV reactivation are frequent adverse events associated with antiCD38 but rare among anti-BCMA immunotherapies utilized in analysis. Intravenous Immunoglobulin use per treatment year was less among patients treated with Belantamab.

Table 1 (abstract P-384)

	Belamaf Pom Dex	Dara combos
Number	9	127
Median Age, years (range)	62 (52-70)	56 (32-78)
Median Prior lines of therapy	2 (2-7)	2 (0-7)
ISS I/II/III	2/-/7	43/39/42
PI refractory	-	44/127
IMID refractory	9	70/127
PI and IMID refractory	-	28/127
Treatment duration, months (range)	24 (3-35)	13 (0-68)
Best response CR/VGPR/PR/PD	6/-/3/-	50/18/15/44
Grade 3-4 lymphopenia	5 (55%)	97 (77%)
Hypogamaglobulinemia	4 (44%)	91 (72%)
Grade 3-4 infections	2 (22%)	53/127
Grade 5 infections	0	5/127
CMV reactivation episodes	0	22/127
IV immunoglobulin use	2 (1-9)	1 (0-9)

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Management and Outcomes in Second and/or Third Relapse in Patients With Multiple Myeloma in the Real-Life Setting: EMMY Study Results

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Introduction: Multiple myeloma (MM) remains incurable despite important therapeutic advances such as antiCD38 monoclonal antibodies (mAbs). Guidelines for first line are now well established. In the relapse setting, treatment strategies are more varied with several combinations approved. EMMY is a large-scale epidemiological study to assess the epidemiology and real-life management of MM. Aims: To describe the management of MM in second and/or third relapse (L2/L3) and to assess the real-life effectiveness of the treatments received. **Methods:** EMMY is a descriptive, multicenter, national, non-interventional study conducted in 73 IFM (Intergroupe Francophone du Myélome, sponsor) centers in France. Any patient initiating treatment for MM over a 3-month observation period, from October to December, since 2017, is included. **Results:** At the end of 2021, 4383 patients were included of which 1784 received a treatment for L2 (n=1036, 58%) or L3 (n=656, 37%), or both (n=92, 5%). Among them, 822 (46%) received an antiCD38 mAb and 962 (54%) did not. In the whole population, median age was 72.1 years, 12% (n=213) had high-risk cytogenetics and 25% (n=446) had International Staging System (ISS) stage III. Lenalidomide-refractory patients represented 33% (n=317) and 34% (n=542) of those not treated with an antiCD38 mAb and those treated with this mAb, respectively. AntiCD38 mAb was used in 14% (n=49) in 2017, 21% (n=81) in 2018, 63% (n=242) in 2019, 65% (n=211) in 2020 and in 74% of patients (n=239) in 2021. Median progression-free survival (PFS) was 26.3 months (95% CI, 22.7-29.7) in patients treated with an anti-CD38 mAb versus 14.5 months (95% CI, 13.5-16.5) in those not treated with an anti-CD38 mAb. Median overall survival (OS) was not reached (NR) in patients treated with an anti-CD38 mAb versus 46.1 months (95% CI, 39.2-54.8) in those not treated with an anti-CD38 mAb. Among patients treated with an antiCD38 mAb, 554 (31%) received an immunomodulatory drug (IMiD) which was lenalidomide in 63% (n=350) or pomalidomide in 37% (n=204). In the combination of a proteasome inhibitor (PI) and an antiCD38 mAb, bortezomib was used in 82% (n=155) and carfilzomib in 17% (n=33). Median PFS was 33.3 months (95% CI, 28.7-39) in patients treated with an IMiD and anti-CD38 mAb versus 14.9 months (95% CI, 9.9-18.2) in those treated with a PI and an anti-CD38 mAb. Median OS was NR in patients treated

with an IMiD and anti-CD38 mAb combination versus 44 months (95% CI, 37.3-NR) in those treated with a PI only. **Conclusions:** Use of antiCD38 mAbs increased over the period 2017-2021 in the relapse setting with a PFS and OS improvement. Over the study period, an antiCD38 mAb was mostly used with an IMiD with benefits in terms of survival compared to the combination of a PI and antiCD38 mAb.

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Effect of Prior Selinexor Exposure on Clinical Outcomes of Chimeric Antigen Receptor T-cell (CAR-T) Therapy for Relapsed/Refractory Multiple Myeloma (RRMM): A Real-World Descriptive Analysis

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Introduction: Chimeric Antigen Receptor T-cell (CAR-T) therapy is an active new T-cell based treatment in RRMM that is resource intensive and can be logistically difficult. Alkylating agents and proteasome inhibitors, amongst other patient and disease-related factors, have been shown to decrease T-cell fitness and may affect the efficacy of T-cell-redirecting therapies. In this real-world study, we investigate whether prior treatment with a selinexor-containing regimen impacts clinical outcomes in patients with RRMM after CAR-T therapy. **Methods:** This retrospective cohort study analyzed medical records of 45 patients who received a selinexor-containing regimen prior to B-cell maturation antigen-directed CAR-T therapy at two academic cancer centers in the US. Baseline data collection encompassed patient demographics, disease characteristics, and prior treatments. From the CAR-T infusion date until last follow-up (12/01/2023), data were collected on hematological parameters, adverse events, response rates, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). PFS and OS curves following CAR-T therapy were generated using the Kaplan-Meier method. **Results:** The median age at CAR-T infusion was 64 years, with 80% of patients classified as International Staging System Stage I or II. The CAR-T products given included idecabtagene vicleucel (60%), ciltacabtagene autoleucel (35.6%), and BMS-986354 (4.4%). Approximately 68.9% of patients received a bridging regimen following apheresis. Selinexor and CAR-T were frequently administered at the median 7th and 9th lines of treatment, respectively. The most common selinexor-based regimens were selinexor+bortezomib+dexamethasone (28.9%) and selinexor+carfilzomib+dexamethasone (20%), with 75.6% of patients starting selinexor at a dose ≤ 80 mg and 24.4% at dose ≥ 100mg. The median duration of selinexor therapy was 2.7 months. Only 24.4% of patients received selinexor as part of bridging therapy. Median DOR to CAR-T therapy was 8.1 months (IQR: 2.9 to 39), with 88.9% of patients achieving at least a partial response. The median DOR for ciltacabtagene autoleucel and idecabtagene vicleucel were 9.9 months (IQR: 10.1 to 13.8) and 7.2 months (IQR: 2.6 to 18.9), respectively. At a median follow-up of 68 months the median PFS and OS post CAR-T administration were 8.0 and 35.9 months, respectively. While 75.6% of patients experienced cytokine release syndrome (all grade I or II), 17.8% experienced immune effector cell-associated neurotoxicity syndrome (ICANS), with grade 3 ICANS in only 2 patients. **Conclusions:** In this retrospective analysis, CAR-T clinical outcomes in heavily pretreated RRMM were unaffected by prior selinexor treatment. Further studies are warranted to examine the effect of specific selinexor combinations on clinical outcomes, including promoting an anti-tumor immune microenvironment, particularly pre-, post- and in-between CAR-T and other T-cell engaging regimens.

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Pulmonary Complications in Plasma Cell Dyscrasia: A Case Series Highlighting Clinical Challenges and Management Strategies

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Introduction: Plasma cell dyscrasia (PCD), including multiple myeloma (MM) and AL amyloidosis, significantly impacts pulmonary health. This case-series illustrates the spectrum of pulmonary effects, from plasma cell infiltration to amyloid protein deposition affecting lung function. Despite numerous case reports, systematic reviews and clear epidemiological data on these pulmonary manifestations are limited, highlighting the complexity and variability of respiratory system involvement. **Methods:** We present a case-series of five patients treated in our JACIE-accredited Hematology Department. Data were collected retrospectively from systematic chart reviews. **Results:** Patient 1: A 75-year-old male presented with a 3-month history of dry cough, dyspnea, and chest pain. 18F-FDG PET/CT revealed a large infiltrating hypermetabolic lung tumor. Biopsy diagnosed solitary primary pulmonary plasmacytoma. The patient achieved complete response with a daratumumab-based regimen. Patient 2: A 57-year-old with end-stage relapse/refractory MM, presented with shortness of breath. Chest x-rays showed multiple pulmonary nodules. CT-guided lung biopsy confirmed myeloma origin. Pulmonary dissemination of MM is rare, occurring in less than 5% of cases, often misleading clinicians. Patient 3: A 61-year-old woman with a history of autoimmune disease and light chain MGUS, presented with cardiopulmonary symptoms. Chest x-ray showed lung and pleural calcifications. Pulmonary function testing revealed evidence of impaired CO diffusion. 18F-FDG PET/CT confirmed multiple subpleural and parenchymal hypermetabolic nodules. Biopsy confirmed pulmonary nodular amyloidosis. The patient remains stable without specific treatment. Pulmonary amyloidosis, a rare form of localized amyloidosis, is often asymptomatic and incidentally diagnosed. Patients 4 and 5, both diagnosed with

IgG lambda multiple myeloma: Patient 4, a 66-year-old woman with high-risk cytogenetics at diagnosis, developed cytology-proven myelomatous pleural infiltration and bone progression under second-line daratumumab-based treatment. Switched to teclistamab, she experienced grade III CRS with hypoxemia and acute respiratory distress syndrome, requiring ICU care. Patient 5, a 67-year-old man, developed pleural myeloma invasion during carfilzomib treatment. Despite third-line isatuximab therapy, his disease progressed. He received teclistamab, developing grade II CRS with hypoxemia and CMV disease. Due to active pleural effusion, talc pleurodesis and a thoracic drain were performed. Both of the patients died with uncontrolled pleural effusion. The incidence of myelomatous pleural effusion is estimated to be around 5%. These effusions can lead to a higher risk of severe CRS, and remain difficult to treat. **Conclusions:** This case series highlights the pulmonary involvement in PCD. Comparative analysis emphasizes the need for early recognition and tailored interventions to manage pulmonary complications, ultimately improving clinical outcomes.

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Clinical Efficacy of Isatuximab Plus Carfilzomib-Dexamethasone in Relapsed/Refractory Multiple Myeloma Patients: An Italian Real-Life Multi-Center Retrospective Experience

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Introduction: Isatuximab, a novel anti-CD38 monoclonal antibody, has demonstrated efficacy in combination with carfilzomib and dexamethasone (isa-KD) in patients with relapsed or refractory multiple myeloma (RRMM) in the phase III IKEMA trial. Despite its promising results in clinical trials, its real-world effectiveness remains largely unexplored. **Methods:** One hundred and three RRMM patients from fifteen Hematology Units in Italy who initiated isa-KD outside clinical trials (previous treatment lines 1-3) were enrolled from March 2022 to March 2024. High genetic risk MM and lenalidomide refractoriness were evaluated based on IMWG criteria. **Results:** The baseline characteristics were: median age 64 years (range 45-84), 51% male, ECOG 0-1 in 86%, and high genetic risk MM in 38% with 16% having extramedullary disease. The median weight was 72 kg (range 40-113). Previous therapy lines were 1 in 67% and 2-3 in 33%. Previous treatments included ASCT (76%), bortezomib (93%), anti-CD38 (15%), and thalidomide (78%). Median time since ASCT was 32 months (range 3-178), with 61% having previous lenalidomide maintenance (median duration 23 months, range 2-62); 19% and 71% were lenalidomide exposed and refractory, respectively.The overall response rate (ORR) was 85%, with sCR+CR in 18%, VGPR in 39%, and PR in 27%. The median time to best response was 3 months (range 1-20), with a median of 6 isa-KD cycles administered (range 1-24). Therapy is ongoing in 55%, and consolidation with ASCT was performed in 12% of cases. Reasons for discontinuation included progression (29%), toxicity (4%), death (4%), and ASCT (5%). The median progression-free survival (PFS) was not reached [95% CI: NE], with a one-year PFS rate of 72%. Median PFS was shorter in high genetic risk compared to standard risk [13 months (95% CI: 7.2-18.7) vs. not reached (95% CI: NE); HR: 3.1 (95% CI: 1.3-7.1); P< 0.005], in those with EMD [14 months (95% CI: 8.5-19.4) vs. not reached (95% CI: NE); HR: 2.5 (95% CI: 1.1-5.8); P=0.02], in third-fourth-line vs. second-line therapy [13 months (95% CI: 6.2-21.9) vs. not reached (95% CI: NE); HR: 2.1 (95% CI: 1.1-4.5); P=0.04], and in those previously treated with daratumumab [8 months (95% CI: 5.4-10.7) vs. not reached (95% CI: NE); HR: 3.2 (95% CI: 1.3-7.7); P< 0.005]. **Conclusions:** Our real-world experience indicates that isa-KD is a viable treatment option even for high-risk patients, including those with high genetic risk, extramedullary disease, lenalidomide refractoriness, and prior anti-CD38 exposure. These high-risk patients remain a clinical challenge, suggesting that early incorporation of T-cell reconditioning therapies may offer improved prognosis.

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Phase 3, Two-stage, Randomized Trials of Mezigdomide-Based Regimens Versus Standard Regimens in Relapsed/Refractory Multiple Myeloma (RRMM): SUCCESSOR-1 (MeziVd vs PVd) and SUCCESSOR-2 (MeziKd vs Kd)

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Introduction: Trial in progress. Mezigdomide (MEZI) is a novel oral (PO) CELMoD™ agent with enhanced potency compared to IMiD® agents. In preclinical studies, MEZI synergizes effectively with dexamethasone (DEX) and bortezomib (BORT) (MeziVd) or carfilzomib (CFZ) (MeziKd). MeziVd and MeziKd have shown promising results in patients (pts) with RRMM in the phase 1/2 CC-92480-MM-002 trial. The phase 3 trials SUCCESSOR-1 (NCT05519085) and SUCCESSOR-2 (NCT05552976) will compare the efficacy and safety of MeziVd vs pomalidomide (POM), BORT, and DEX (PVd), and MeziKd vs CFZ and DEX (Kd) in RRMM, respectively. **Methods:** Both multicenter, open-label phase 3 trials comprise 2 stages, using an adaptive inferentially seamless design to optimize MEZI dose (Stage 1) and complete key study endpoints (Stage 2). Stage 1 pts from the selected MEZI dose cohort and comparator arm will also be included in Stage 2 efficacy and safety analyses. In Stage 1 of SUCCESSOR-1, ≥140 pts will be randomized 1:1:1:1 to receive 1.0, 0.6, or 0.3mg MEZI+Vd, or PVd to determine the optimal MEZI dose. Stage 2 will randomize up to ≈620 additional pts 1:1 to MeziVd (at the selected dose) or PVd. SUCCESSOR-2 will enroll ≥128 pts in Stage 1 and randomize 3:3:3:2 to receive 1.0, 0.6, or 0.3 mg MEZI+Kd, or Kd to select the optimal MEZI dose. Stage 2 will randomize ≈397 additional pts 3:2 to MeziKd (at the selected dose) or Kd. Pts will be stratified by age (≤70 vs >70 years), prior lines of treatment (tx) (1 vs >1 [SUCCESSOR-1] or ≤2 vs >2 [SUCCESSOR-2]), and ISS stage at screening (I vs II vs III). Key eligibility criteria for both trials include age ≥18 years; for SUCCESSOR-1 include 1–3 prior lines of tx including lenalidomide (LEN), and no prior tx with POM; and for SUCCESSOR-2 include ≥1 prior line including LEN and an anti-CD38 monoclonal antibody, and no prior tx with CFZ. In SUCCESSOR-1, MeziVd involves 21-day cycles with PO MEZI (Days [D]1–14), subcutaneous BORT (1.3mg/m2) biweekly (biw) (Cycles [C]1–8) then weekly (qwk) C≥9, and PO DEX (20mg) given four times a week (C1–8) then biw C≥9. PVd follows the same Vd schedule with 4mg PO POM (D1–14). In SUCCESSOR-2, MeziKd involves 28-day cycles with PO MEZI (D1–21), intravenous (IV) CFZ (20mg/m2 on C1D1 and 56mg/m2 on D8, 15 of C1, then 56mg/m2 on D1, 8, 15 of C2–12 and D1, 15 of C≥13), and PO/IV DEX (40mg qwk). Kd consists of IV CFZ at 56mg/m2 biw or 70mg/m2 qwk, based on investigator's choice, plus PO/IV DEX. Tx continues until PD or unacceptable toxicity. The primary efficacy endpoint for both trials is progression-free survival. Secondary endpoints include determination of the recommended MEZI dose (Stage 1 only), overall survival, overall response rate, time to and duration of response, time to progression, safety, minimal residual disease assessment, and quality of life. Enrollment began in September 2022 for SUCCESSOR-1 and February 2023 for SUCCESSOR-2 and is ongoing. Stage 1 is complete and dose selection is in progress for both studies. **Results:** n/a. **Conclusions:** n/a.

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Carfilzomib Prescribing Patterns and Outcomes for Relapsed or Refractory Multiple Myeloma (RRMM): A Real-World Analysis

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Introduction: There is no consensus on the most effective dosing schedule of carfilzomib (K) in relapsed/refractory multiple myeloma (RRMM). We retrospectively analyzed factors associated with K prescribing patterns and the association with real-world outcomes among RRMM patients (pts) in a large United States population. **Methods:** We used the nationwide Flatiron Health electronic health record-derived deidentified database and analyzed MM pts diagnosed from 7/2012 to 6/2023 who received a K-containing regimen as a 2+ line of therapy (2L+). We compared three common prescribing patterns: 56 mg/m^2 once weekly (K56-1x; reference), 56 mg/m^2 twice weekly (K56-2x) and 70 mg/m^2 once weekly (K70-1x). Multinomial logistic regression was used to assess factors associated with prescribing patterns. RW progression-free survival (rwPFS) and overall survival (rwOS) from K initiation were estimated using the Kaplan-Meier method and Cox proportional hazards model including transplant as a time-varying covariate and adjustment for other factors. **Results:** Of 2420 pts who received K at any time, 486 (20%) received one of the three prescribing patterns at 2L (n=202, 41%) or beyond (n=284, 58%). K56-2x comprised 18% (n=86), K56-1x 28% (n=136) and K70-1x 54% (n=264). K prescribing patterns changed over time. K56-2x was initially the most common schedule but was eventually surpassed by K70-1x. Partner drugs varied widely. Among pts receiving K56-1X and K70-1X, triplet was preferred over doublet and quadruplet therapy (50% vs 15% vs 19%; 65% vs 20% vs 7%). Immunomodulatory drug-containing triplets were preferred for K56-1X while monoclonal antibody-containing triplets were preferred for K70-1X. Among pts receiving K56-2X, triplets and doublets were equally preferred over quadruplets (43% vs 47% vs 5%) with preference for monoclonal antibody-containing triplets. Median rwPFS was 13.0 months (95% confidence interval (CI) 11.2-20.7 months) for K56-1x, 13.2 months (95% CI 9.0-28.1) for K56-2x and 10.9 months (95% CI 9.9-15.3) for K70-1x. These differences were not statistically significant (log-rank p=0.46). Median rwOS was 44.6 months (95% CI 30.2-NR), 49.1 months (95% CI 38.1-NR) and 39.2 months (95% CI 29.6-60.0) respectively, also found to have no statistically significant difference (log-rank p=0.62). Neither age nor the presence of IMWG-defined high-risk cytogenetic abnormalities was associated with higher odds of receiving K56-2x or K70-1x. The prevalence of heart failure (< 5% in all cohorts) was comparable between treatment groups. **Conclusions:** In this large real-world study of over 400 pts with RRMM, we found that K is dosed once-weekly more often than twice-weekly. Higher doses or more frequent dosing of K were not significantly associated with better outcomes compared to K56-1x. There were no significant differences in toxicities between the three regimens. Our findings support K56-1x (which is increasingly being used in trials) as a reasonable standard of care for clinical trials and real-world practice.

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Isatuximab-Carfilzomib-Dexametasone (Ikd) in Patients with Multiple Myeloma with Relapsed/Refractory Disease: Real-Life Results in Seven Spanish Centers

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Introduction: Patients with relapsed or refractory (R/R) multiple myeloma (MM) have reduced duration and depth of response in the following lines. The goal of therapy is to achieve deep responses until progression or toxicity. Current recommendations are to use triplets whenever possible or previously unused drug families. Isatuximab-containing regimens offer a promising therapeutic option, including those patients who are refractory to lenalidomide, that previously had fewer alternatives of treatment. The anti-CD38 antibody (Isatuximab) in combination with Carfilzomib-dexametasone (Kd) is approved for patients with MMRR after ≥1 prior therapy, according to the primary interim analysis (IA) of the phase 3 IKEMA study. In this trial, IKD vs KD was compared, obtaining statistically significant benefits in terms of progression free survival (PFS) in the Isa-Kd group. **Methods:** Retrospective descriptive real-life study of patients with MM R/R from seven Spanish centers treated with IKD between 2022 and 2024, end of follow-up March 2024. **Results:** 53 patients were included, with a median age of 64 years (41-84), of those, 51.9% were male. 67.9% (n=36) were in first relapse. The overall response rate (ORR) was 88.7%, of which 54.7% were complete responses (CR) in our sample. Subgroup analysis in patients treated at first relapse and patients at second and subsequent relapses showed differences. The ORR in first relapse patients was 97.2% of which CR 63.4%. In patients treated at second and subsequent relapse ORR was 70.6% with a CR rate of 35.3%. We performed subgroup analyses according to glomerular filtration rate without finding significant differences in response rate. In patients with GFR < 30 ml/min the ORR was 100% vs. 87% in the group of patients with GFR >30 ml/min. The CR rate was 57.1% vs. 54.3% respectively. Seven patients with GFR < 30 ml/min were treated. **Conclusions:** Our real-life results by subgroups show better CR rates in patients treated at first relapse compared to the latest published data from the IKEMA study (63.4% vs 48.1%). It confirms the finding that CR rates are higher in patients treated at first relapse vs. second and subsequent relapses. The IKEMA study included patients with estimated glomerular filtration rates (eGFR) up to 15 ml/min/1.73m2. According to published data with a median follow-up of 44 months, there are no significant differences in CR rates between patients with eGFR higher and lower than 60 ml/min/1.73m2. In our sample we also found no differences between patients with eGFR greater and less than 30 ml/min/1.73m2. With a median follow-up of 8.4 months, we have so far not reached median PFS in any of the subgroups.

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A Phase 1 Trial of 225Actinium-DOTA-Daratumumab in Patients with Daratumumab-Refractory Multiple Myeloma: Results from First Cohorts

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Introduction: Studies from our institution demonstrated that CD38 remains expressed and targetable in Dara-refractory MM (Viola et al. 2021). Given the widespread adoption of Dara use in newly diagnosed MM, one can anticipate earlier Dara-refractoriness. We developed a CD38-targeting alpha therapy (TAT) by conjugating actinium-225 (225Ac) to Dara using a DOTA chelator, (225Ac-Dara). Compared to other radionuclides, 225Ac has a short emissions travel path (< 100µm) which may limit off tumor toxicity (Minnix et al. 2021). Herein, we report the initial findings from the first-in-human, dose-finding study of 225Ac-Dara co-infused with the imaging agent Indium-111-DOTA-Dara (111In-Dara). **Methods:** Eligible subjects have received all appropriate therapies according to the investigator and are Dara-refractory (12-week Dara washout). Other key eligibility criteria include adequate hematologic and organ function, performance status ECOG ≤2, no prior radioimmunotherapy, and no prior radiation ≥25% to marrow, liver, or kidneys. Patients receive an IV dose of unlabeled Dara at 45mg 2-4h prior to the TAT. They then receive an IV infusion of 111In-Dara for imaging, immediately followed by 225Ac-Dara conjugated to 5mg total of Dara. Three radioactivity dose levels (DLs) are being tested, 20, 40 and 60 kBq/kg. TAT is a single administration with serial planar (2h, 24h and 144h-168h) and SPECT/CT imaging. Primary endpoints are MTD/RP2D. Secondary endpoints include ORR, PFS, and OS. Exploratory correlatives include characterizing tumor uptake and radiation dose to the blood and vertebral marrow, and assessment of immune microenvironment. **Results:** Four patients have been treated at DL1 and 1 at DL2. Patient 03 was not evaluable for DLT and was replaced. The other three at DL1 did not experience DLTs. Patient 05 treated at DL2 experienced grade 4 neutropenia and thrombocytopenia, possibly related to 225Ac-Dara and therefore DLT. Patient 05 had extensive baseline bone, spleen, and extramedullary disease (EMD) with evidence of progressive disease (PD) during the DLT period, ultimately succumbing to PD at 35d post 225Ac-Dara. There have not been any objective responses. Three patients at DL1 had stable disease (PFS range: 86 – 140d) after the single 225Ac-Dara dose, the other two had PD. Median PFS was 86d (range: 22-140d). 111In-Dara planar and SPECT imaging show target specificity, both in marrow and EMD with SUV preliminarily correlating with MM biomarkers and PFS. CyTOF studies are ongoing and will be presented along with PFS2 data when mature. **Conclusions:** 225Ac-Dara in Dara-refractory MM is a novel strategy to circumvent immune exhaustion and repurpose CD38-targeting. Our phase 1 study is ongoing with primarily hematologic toxicity observed. Several patients had stable disease after a single dose. One anticipates the ORR to improve at higher DLs. This approach can be explored in combination with bispecific antibodies, potentially to sensitize EMD to immunotherapies.

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A real-world UK experience of Daratumumab, Velcade, Dexamethasone and Carfilzomib, Lenalidomide, Dexamethasone as second line therapies in the UK: a South East London retrospective

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Introduction: Daratumumab, Velcade, Dexamethasone (DVD) and Carfilzomib, Lenalidomide ,Dexamethasone (KRD) are funded in the United Kingdom as second line therapies for Multiple Myeloma (MM), though KRD is only permitted in patients who are not lenalidomide-refractory. We set out to investigate the real world effectiveness of DVD and KRD at 1st relapse in MM. **Methods:** Patients who received DVD or KRD as a second line therapy from January 2021 to September 2023 were included in this study. Data was collected manually from King's College Hospital, Guy's Hospital, and Princess Royal University Hospital electronic patient record. Statistical analysis was performed using Prism 10.1.1. Fisher's exact test was used for comparison of proportions and Log-rank (Mantel-Cox) test was used for survival. **Results:** 95 patients were included in this study, with 71 patients receiving DVD and 24 patients receiving KRD. There were more patients with high International Staging System (ISS) within the KRD cohort (DVD: 31 stage 1, 17 stage 2, 16 stage 3, 7 not recorded (NR) vs KRD: 6 stage 1, 4 stage 2, 12 stage 3, 2 NR), P=0.048. There was equal distribution of high risk (HR) and standard risk (SR) cytogenetics (DVD: 25 HR, 27 SR, 18 NR vs KRD: 13 HR, 8 SR, 3 NR), P=0.3129. There were no statistically significant differences in cardiac morbidity (DVD: 28.2% vs KRD: 33.3%) and peripheral neuropathy rates (DVD: 4.2% vs KRD 8.3%). Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, Cyclophosphamide, Etoposide +/- Velcade escalation was used in primary refractory patients. More patients received escalation therapy in KRD (9) compared to DVD (1), P< 0.0001. Conversely, more patients received prior lenalidomide in DVD (18) compared to KRD (1), P = 0.0358. Median follow up was 14 months in KRD and 20 months in DVD. There were no difference in progression free survival (PFS), P=0.2390, and overall survival (OS), P=0.3263. Median PFS was 23 months in DVD and undefined in KRD. Median OS was undefined in both DVD and KRD. A subset analysis of patients receiving escalation therapy showed median

PFS of 1 month in DVD and 8 months in KRD. **Conclusions:** There were more patients treated with DVD compared to KRD, likely due to Lenalidomide refractoriness. Hence, the patient populations receiving KRD and DVD are likely distinct in our centers. Though more patients with high-risk disease were treated with KRD compared to DVD, in our preliminary data PFS and OS were comparable among the two protocols despite risk discrepancy. At present, KRD and DVD remain effective options for first relapse in myeloma. Differences in survival may emerge with longer follow up of our data, especially in the KRD arm. Primary refractoriness leading to escalation therapy use is an area of unmet clinical need as it is associated with much shorter PFS. The introduction of more effective therapies such as antibody-drug conjugates, bispecific T cell engagers, or Chimeric Antigen Receptor T cell, into earlier lines of therapy may improve survival.

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Selinexor Combined With Bortezomib, Thalidomide, and Dexamethasone in Relapsed/Refractory Multiple Myeloma Patients Who Have Undergone Severe Treatment: A Single-Arm, Multicenter, Prospective Study

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Introduction: Selinexor(X), a selective inhibitor of nuclear export protein 1 (XPO1), the XVd regimen has significantly enhanced progression-free survival (PFS) compared to the Vd regimen in bortezomib-sensitive relapsed/refractory(RR) patients(pts) (13.93m vs. 9.46m). This study aims to evaluate the efficacy and safety of a regimen combining X with bortezomib(V), thalidomide(T), and dexamethasone(dex) for RRMM pts. The protocol was approved by the Clinical Ethics Committee of the First Hospital of Zhejiang University School of Medicine (ChiCTR2200055486). **Methods:** Pts aged 18-75, previously treated with at least one new drug-based regimen, and RRMM pts who responded PR or better efficacy to prior therapy with measurable lesions were eligible for enrollment. The treatment regimen consisted of X 60 mg qw, V 1.3 mg/m2 qw, T 100 mg qn, and dex 20 mg, with 1 cycle administered every 28 days. Pts with 12 cycles of XT treatment were entered into maintenance therapy. The primary endpoint was the overall response rate ORR (PR+ VGPR+CR) in pts who completed at least 1 cycle of treatment; secondary endpoints were 12-month OS, 12-month PFS, and safety **Results:** 22 pts were enrolled from May 2022 to March 2024, and 19 pts (42.1% male, median age 67) who completed a full cycle of treatment were into the analysis. According to the Mayo myeloma stratification and risk-adjusted treatment criteria, 5 pts had one risk factor and 12 pts had more than two. All pts had received prior V-based regimens, with 15 pts having more than 3 lines, 3 pts receiving autologous stem cell transplantation (ASCT), and 3 pts treated with CAR-T. There were 17 V-resistant pts. At data cut off April 30, 2024, 10 pts completed 1 cycle of treatment, 9 pts performed 2 or more cycles, while 2 pts were still in treatment. 7 pts (36.8%) were PR and better efficacy, and 14 pts (73.7%)were stable disease (SD).5 pts completed 3 or more cycles , 4 pts had PR or better efficacy. Extramedullary (EMD) plasmacytomas were present in 11 pts, with PR or better in 4 and SD in 5 pts. All 3 post-CART-treated pts had multiple EMD involvements with efficacy PR in 1 and SD in 2 pts. At a median follow-up of 5.33 months, 14 were progressive disease(PD) and 13 pts died. The median PFS was 2.07m (95% CI:1.17m~2.97m), and the 6-month PFS was 23.9%; the median OS was 7.90m (95% CI:3.58m~12.22m), and the 6-month and 12-month OS were 60.2% and 30.6%, respectively. The adverse events observed were consistent with previously reported. Grade 3 and above AEs included granulocytopenia(26.3%), thrombocytopenia (52.6%), anemia (15.8%), neutropenic fever (21.1%), fatigue(10.5%), gastrointestinal (5.3%), hyponatremia (5.3%), neocoronavirus infection (10.5%), and pneumonia (21.1%). **Conclusions:** The XVTd regimen is an effective and safe treatment option for patients with RRMM pts with V-based regimen and multi-drug resistance and might reduce the incidence of X-induced vomiting.

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Updated Results From DREAMM-3, a Phase 3 Study of Belantamab Mafodotin (Belamaf) Versus Pomalidomide Plus Dexamethasone in Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: DREAMM-3 (NCT04162210) is a Phase 3, open label, randomized study comparing single-agent belamaf, an antibody-drug conjugate targeting B-cell maturation antigen, to the doublet pomalidomide plus dexamethasone (Pd). This planned update of the interim analysis from the DREAMM-3 trial evaluated the safety and efficacy of belamaf compared with Pd in adult pts with RRMM at third line of therapy or later. **Methods:** Pts were randomized (2:1) to belamaf 2.5 mg/kg administered intravenously once every 3 weeks (Q3W; 21-day cycle) or pomalidomide 4 mg orally once daily (Days 1–21) and dexamethasone 40 mg (20 mg if >75 years) orally once weekly (28-day cycle). The primary endpoint was progression-free survival (PFS), with a key secondary endpoint being overall survival (OS). Other secondary endpoints included overall response rate (ORR), minimal residual disease (MRD) negativity, duration of response (DOR), safety and tolerability. PFS with subsequent line of therapy (PFS2) was an exploratory endpoint. **Results:** As of March 01, 2024, 28/218 (13%) and 6/107 pts (6%) remained on treatment with belamaf and Pd, respectively with 58 (27%) and 29 (27%) additional pts remaining in follow-up. Median follow-up (range) was 22.4 (0.6–43.0) months and 21.9 (0.0–44.2) months for belamaf and Pd, respectively. With the additional follow-up the PFS hazard ratio (HR [95% CI]) had changed from 1.03 (0.72, 1.47) at the primary analysis to 0.86 (0.63, 1.18). OS data now were 57% mature (compared to 38%) and the OS HR (95% CI) changed from 1.14 (0.77, 1.68) to 0.93 (0.69, 1.26). ORR did not change (belamaf, 41%; Pd, 36%). Rates of MRD negativity in pts with VGPR or better remained higher for belamaf (8%) than for Pd (0%). Median DOR (95% CI) was 24.9 (20.7, 32.5) months for belamaf and 10.4 (7.6, 20.0) for Pd. Median PFS2 (95% CI) was 17.3 (13.8, 21.7) months for belamaf and 13.0 (10.6, 15.8) for Pd. AEs (any grade) were reported in 98% of pts treated with belamaf and 95% treated with Pd. Grade 3–4 AEs occurred in 78% and 74% of pts, respectively and fatal AEs in 8% and 13%. SAEs occurred in 46% of pts treated with belamaf and 43% of pts treated with Pd. The most frequent were thrombocytopenia (4%), pyrexia (4%), anemia (3%) and pneumonia (3%) for belamaf and pneumonia (9%), COVID-19 pneumonia (5%) and febrile neutropenia (5%) for Pd. Ocular AEs (CTCAE) were reported in 68% of pts treated with belamaf, with 49% of pts having only a single occurrence; pts severest events were mostly Grade 1–2. Events had recovered or were recovering in 59% of pts who had an event. **Conclusions:** Longer term follow-up of DREAMM-3 demonstrated that responders in the belamaf group from the primary analysis, continued to respond for a prolonged period, contributing to the HR of PFS and OS improving; MRD negativity was also greater for belamaf vs Pd. This improvement in PFS and OS over time can be attributed to the greater depth and durability of response for belamaf treated pts relative to Pd. No new safety signals were identified.

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Characterization and Management of Ocular Events in Patients (Pts) Treated With Belantamab Mafodotin (Belamaf) Plus Bortezomib and Dexamethasone (BVd) in the DREAMM-7 Study

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Introduction: In DREAMM-7 (NCT04246047), treatment (tx) with BVd led to a statistically significant and clinically meaningful progression-free survival (PFS) benefit (HR, 0.41; 95% CI, 0.31-0.53; P< 0.00001) and early trend toward improved overall survival (HR, 0.57; 95% CI, 0.40-0.80) vs daratumumab + Vd (DVd) in pts with relapsed/refractory multiple myeloma (RRMM) after ≥1 prior line of therapy (LOT). Ocular events, a known risk of belamaf, may impact daily living. We sought to characterize ocular events in pts treated with BVd and assess the effectiveness of ocular event management. **Methods:** Dose interruptions/delays or reductions from the starting dose of belamaf 2.5 mg/kg IV Q3W to 1.9 mg/kg IV Q3W were allowed to manage adverse events (AEs). Ocular examination findings were evaluated using the keratopathy and visual acuity (KVA) scale which drove dose modification. Ocular AEs were also assessed. Post hoc PFS analysis in pts with dose delays

was performed in pts who received ≥6 mo of tx to understand impact of dose delay on efficacy but exclude rapid progression events or early discontinuations. **Results:** In the BVd arm, 78% of pts had a dose interruption/delay and 44% had a dose reduction due to ocular events (ocular AEs or KVA events). Worsening of best corrected visual acuity (BCVA) to bilateral 20/50 or worse was reported in 34% (82/242) of pts with normal baseline (20/25 or better in ≥1 eye). The first event of bilateral 20/50 improved in 98% (80/82) of pts or resolved to baseline in 94% (77/82) by data cutoff (post hoc). In pts with normal BCVA at baseline, prevalence of BCVA worsening (to bilateral 20/50 or worse) declined by time point concurrent with an increase in median time between doses (post hoc), suggesting a potential controlling of ocular events from dose delay. Among pts in the BVd arm on tx ≥6 mo, those with a dose delay of ≥12 wk (n=126) had a median PFS of 36.6 mo (95% CI, 33.2-NR) and estimated 18-mo PFS rate of 84%. At least 1 KVA event (grade ≥2) was reported in 209/242 pts (86%); of those, 190 (91%) continued belamaf on/after the onset of their first event, receiving a median of 8 (range, 1-52) additional doses and deriving benefit; 177 (93%) achieved ≥ partial response (PR; post hoc). Despite the incidence of ocular events in the BVd arm, tx discontinuation due to any ocular event was low (22 pts [9%]). Pts who discontinued due to ocular events received a median of 5 (range, 2-37) doses of belamaf prior to discontinuation and 20/22 achieved ≥PR (post hoc). Additional data on characterization and management of ocular events and efficacy will be presented. **Conclusions:** Results from DREAMM-7 showed statistically significant and clinically meaningful PFS benefit favoring BVd vs DVd in pts with RRMM after ≥1 prior LOT, including the majority of BVd pts who experienced a dose modification due to ocular events. Dose modifications were effective in managing ocular events and allowed most pts to remain on tx and derive benefit.

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Brazilian Single-Center Initial Experience and Safety of Teclistamab for Patients with Heavily Pretreated Relapsed/Refractory Multiple Myeloma

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Introduction: Teclistamab is a B-cell maturation antigen (BCMA)-targeting bispecific T-cell engager approved for commercialization in Brazil in July 2023 for patients with relapsed/refractory multiple myeloma (RRMM) who have received at least a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody. In this retrospective study, we describe a real-world initial experience with teclistamab at a Brazilian single center, highlighting toxicities, including those in patients who would have been considered ineligible for the MajesTEC-1 trial. **Methods:** We included 12 patients with RRMM who received teclistamab as of August 1, 2023. Baseline characteristics were analyzed descriptively. Teclistamab was administered in a step-up dosing regimen with premedications. Patients received antimicrobial prophylaxis, supportive care, intravenous immunoglobulin (IGIV) replacement, and toxicity management according to institutional protocols. Responses to therapy, including overall response rate (ORR), very good partial response (VGPR), and complete response or better (≥CR), were evaluated using the International Myeloma Working Group (IMWG) criteria. **Results:** Of the 12 patients included, 9 had extramedullary disease; the median number of prior lines of therapy (LOT) was 4 (range 2–7). All patients had been exposed to three drug classes. Cytokine release syndrome (CRS) was observed in 8 patients (66.6%), with 6 experiencing grade 1-2 events. However, 2 patients with very aggressive progressive disease developed grade 4 CRS. Following these cases, tocilizumab was administered for grade 1 CRS in our center, particularly if the patient had persistent fever; 5 patients received tocilizumab for grade 1 CRS. Regarding other toxicities, 3 patients experienced hepatic toxicity during the ramp-up phase associated with CRS; 2 cases resolved after a few days, allowing for the resumption of teclistamab, and 1 patient experienced spinal compression with paraparesis due to plasmacytoma flare, which resolved completely with steroids and radiotherapy, allowing for the resumption of teclistamab. After a median follow-up of 3 months, the ORR was 75% for the entire cohort, which was observed after the first cycle of treatment. **Conclusions:** This is a real-world initial experience of teclistamab in RRMM at a Brazilian single center and indicates that, after addressing 2 cases of grade 4 CRS in patients with very aggressive progressive disease, teclistamab was well-tolerated with the use of tocilizumab in grade 1 CRS. Despite the high incidence of extramedullary disease, and tocilizumab use in grade 1 CRS, early efficacy assessment of teclistamab in a real-world setting is encouraging.

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Real-world Effectiveness of Ixazomib, Lenalidomide, and Dexamethasone (IRd) in Asian Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Randomized clinical trials have shown IRd to be efficacious and safe in Asian patients with RRMM; however, real-world data are limited. **Methods:** This multicenter, observational, cohort study was conducted in 16 sites across South Korea (KOR), Malaysia (MY), and Thailand (TH). Patients treated with IRd during 2016–2023 were enrolled; data were collected by retrospective chart review and 6-months prospective follow-up. Patients with RRMM aged ≥20 years who received 1–3 prior lines of therapy, with ECOG performance status 0–2 were included. Co-primary endpoints were median time to next treatment (TTNT) and overall response rate (ORR). **Results:** Overall, 104 patients were enrolled (69 KOR, 27 MY, 8 TH). Median age at treatment initiation was 64.0 years (range 42.0–83.0). At diagnosis, 54.8% were International Staging System Stage II/III; 13.5% had high risk cytogenetic abnormalities (data available for 60.6%). Majority had 1 prior therapy (70.2%), 20.2% had 2; 47.1% had prior autologous stem-cell transplantation. Median number of IRd cycles was 13 (range 1–50). Median ixazomib treatment duration was 14.8 months (95% CI 11.3, 23.0). Median TTNT was 32.1 months (95% CI 22.5–not reached [NR]) but varied across countries (Table 1). ORR was 72.1% (KOR 79.7%, MY 48.2%, TH 87.5%). Median progression-free survival (PFS) was 27.7 months (95% CI 19.5–NR). Median overall survival (OS) was NR. In elderly patients (≥65 years; 49% of patients), median TTNT was 35.7 months (95% CI 28.8, NR); ORR was 80.4% (95% CI 66.9, 90.2). Adverse events (AEs) occurred in 90.4% and serious AEs in 29.8% of all patients; 18.3% discontinued due to AEs. Common Grade ≥3 adverse drug reactions were pneumonia (9.6%), neutropenia (7.7%), and gastroenteritis (2.9%). **Conclusions:** ORR, TTNT, and PFS of IRd in this Asian real-world study are comparable to TOURMALINE-MM1 and other real-world studies. IRd has a manageable safety profile.

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Myeloid Neoplasm Post Cytotoxic Treatment (pCT-Mn) in Patients With Myeloma: a UK Single Centre Experience

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Introduction: Myeloma patients are at higher risk of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML). Cytotoxic treatment, including alkylating agents such as high-dose melphalan, further increases their risk of pCT-MN. We retrospectively reviewed the cases of pCT-MN in myeloma patients in our single centre. This study aimed to describe the patients' characteristics, their cytogenetics and molecular risk, treatment regimen, and outcome. **Methods:** We retrospectively reviewed all new pCT-MDS and AML cases with background myeloma, whose pCT-MDS or AML were diagnosed and treated at the specialist integrated haematological malignancy diagnostic service at University College London Hospital over three years: 01 January 2021 to 31 December 2023. Our standard diagnostic MDS/AML FISH panel consists of breakapart or fusion probes targeting KMT2A, CBFB::MYH11, RUNX1T1::RUNX1, PML::RARA, MECOM, and probes targeting 5q, 7q and 17p. Molecular karyotyping was

Table 1 (abstract P-398) Effectiveness outcomes.

	South Korea (n=69)	Malaysia (n=27)	Thailand (n=8)	Total (N=104)
Primary outcomes				
TTNT, months, median (95% CI)	31.6 (18.2, NR)	27.4 (8.7, 41.8)	NR (6.2, NR)	32.1 (22.5, NR)
ORR, n (%) [95% CI]	55 (79.7) [68.3, 88.4]	13 (48.2) [28.7, 68.1]	7 (87.5) [47.4, 99.7]	75 (72.1) [62.5, 80.5]
Stringent complete response	1 (1.5) [0.04, 7.8]	0 [0, 12.8]	0 [0, 36.9]	1 (1) [0.02, 5.2]
Complete response	18 (26.1) [16.3, 38.1]	5 (18.5) [6.3, 38.1]	4 (50.0) [15.7, 84.3]	27 (26.0) [17.9, 35.5]
Very good partial response	14 (20.3) [11.6, 31.7]	2 (7.4) [0.9, 24.3]	3 (37.5) [8.5, 75.5]	19 (18.3) [11.4, 27.1]
Partial response	22 (31.9) [21.2, 44.2]	6 (22.2) [8.6, 42.3]	0 [0, 36.9]	28 (26.9) [18.7, 36.5]
Secondary outcomes, months, median (95% CI)				
Duration of treatment	14.3 (10.4, 25.4)	13.2 (4.5, 27.1)	47.3 (5.6, 50.5)	14.8 (11.3, 23.0)
OS	NR (NR, NR)	NR (33.0, NR)	NR (20.8, NR)	NR (58.0, NR)
PFS	27.7 (22.5, NR)	16.9 (7.0, NR)	NR (1.7, NR)	27.7 (19.5, NR)

CI, confidence interval

used to assess copy number variations across the whole genome. Targeted myeloid NGS panel analysis (Archer VariantPlex) was used to detect pathogenic variants. **Results:** The date of data cut-off was 20 April 2024. Six patients were included with a median follow-up of 9 months [range: 4-13 months]. All six patients had previous alkylator therapy and presented with progressive cytopenia. Five were male, and one was female. The median age of symptomatic myeloma diagnosis was 66 years [range: 58-77 years]. Four were standard risk on CD138-cell FISH. Two had no FISH result. All five transplant-eligible patients had autograft stem cell transplant (ASCT). The median time from diagnosis of myeloma to diagnosis of pCT-MN was 83 months [range: 18-233 months]. The median lines of myeloma treatment received was two [range:1-6]. Two patients were diagnosed with AML, two with MDS-excess of blast (EB) and two with MDS-multilineage dysplasia (MLD). One AML was 2022 ELN intermediate risk; one AML was ELN adverse risk; three MDS were IPSS-R very high-risk, and one MDS was IPSS-R high-risk. The cytogenetics abnormalities detected were del 5q (3/6), del 7q (2/6), monosomy 7 (2/6), MECOM rearrangement (1/6), 6p chromothypsis (1/6), iAMP21(1/6) and gain RUNX1 (2/6). The pathogenic variants detected by NGS were TP53 (2/6), RUNX1 (2/6), AXSL1 (2/6), DNMT3A (1/6), PTPN11 (1/6), KRAS (1/6) and ETV6 (1/6). The treatment received for pCT-MN was azacytidine alone (5/6) or venetoclax with azacytidine (1/6). At the last follow-up, two patients were still alive. The median overall survival from pCT-MN diagnosis was less than one year. **Conclusions:** In our small cohort, myeloma patients with pCT-MN had high-risk cytogenetics or molecular features in whole bone marrow at pCT-MN diagnosis and short overall survival from pCT-MN diagnosis. With increasingly effective non-ASCT therapies for myeloma, we should consider the risk of pCT-MN when recommending ASCT to newly diagnosed patients, particularly in the context of standard-risk disease and a deep response to induction.

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A Discrete Choice Experiment analysis to understand Treatment Preferences of Patients with Relapsed or Refractory Multiple Myeloma (RRMM) in the United States

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Introduction: The treatment landscape for patients with relapsed refractory multiple myeloma (RRMM) has witnessed remarkable advancements with the introduction of novel therapies as later line options in recent years. Gaining a deeper understanding of how various factors influence patients' treatment preferences is crucial. This study is designed to assess patient preferences between treatment characteristics that are consistent with the therapeutic options available to these patients. **Methods:** Adults patients living in the USA who have received at least one prior line of treatment for MM completed an online discrete choice experiment (DCE) survey comprising of 8 choice tasks (Nov-March 2024). In each task, participants were asked to choose between two hypothetical treatment profiles. Attributes and levels for the DCE were derived from targeted literature reviews and clinical data on late-line treatments, including progression-free survival (PFS) and overall survival (OS) combined into a single attribute, overall response rate (ORR), cytokine release syndrome (CRS), infections (severe and mild), skin and/or nail disorders, taste disorder, and the duration of hospitalization at the start of treatment. Preference data were analyzed using a conditional logit model, and relative attribute importance (RAI) scores and trade-offs were calculated. **Results:** In total, 149 patients completed the DCE. Mean (SD) age was 63 (9) years, and 48% were male. 20% were Black/African American and 69% were White. At the time of the survey, 66% of patients had received 1-2 prior lines of therapy, 15% three prior lines, 19% four or more prior lines. Median disease duration was 5 years, and 93% were currently receiving treatment for MM. Patients significantly preferred treatments with longer PFS/OS combination and higher ORR (RAI: 36.4% and 22.1% respectively). With respect to adverse events assessed in this study, patients showed concern for CRS (RAI: 15.2%) and infections (RAI: 11.9%). Nail/skin disorders, duration of hospitalization, and taste disorder were less important to patients (RAI: 7.9%, 6.5%, and 0%, respectively). However, taste, nail and skin disorders may not be a familiar treatment consideration for many of the study respondents. While ORR was the second most important attribute to patients, they would tolerate a 29% reduction in ORR to reduce the risk of CRS from 72% to no risk, 26% to reduce the risk of infections from 76% to 50%, 17% to reduce the risk of nail/skin disorders from 43%/68% to no risk and 1.5% to reduce the risk of taste disorder to no risk. **Conclusions:** The therapeutic preferences of patients with relapsed myeloma favored optimization of efficacy, representing 60% of the total RAI. Patients would rather avoid adverse events, namely CRS and infections, but this is less important than maximizing their chances of maximizing their chance of achieving remission and living longer.

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Real-World Experience With Talquetamab Clinical Management in Relapsed Refractory Multiple Myeloma (RRMM): A Qualitative Study of US Healthcare Providers

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Introduction: Talquetamab (tal) is the first-in-class GPRC5D x CD3 bispecific antibody for relapsed/refractory multiple myeloma (RRMM), approved in 2023 for QW and Q2W administration. Patients on tal also experience GPRC5D-related on-target off-tumor adverse events (AEs) that may be new to physicians and patients. Given there is limited real-world data on tal, a qualitative study was conducted with US healthcare providers (HCPs) to understand real-world clinical practices associated with dosing and AE management in patients with RRMM. **Methods:** Between February and March 2024, 1-hour in-depth interviews (IDIs) (n=10) were conducted with HCPs from academic centers administering tal in both clinical trial and real-world settings. An expert panel (n=6) was conducted after the IDIs to further explore current practices. **Results:** Participants had a mean of 10 years' experience, collectively treating an average of 100 patients with RRMM per month. The IDIs reported a variety of settings for step-up-dosing (SUD), including inpatient (n=5), outpatient (n=3) and hybrid models (n=2). There was a trend toward shorter inpatient stays to reduce healthcare resource utilization, with half of panel participants (n=3) reporting a 7-day average length of stay during SUD. Most of the IDI participants used a Q2W schedule in the SUD (n=7) and treatment phases (n=8). Eight participants indicated they utilized a Q4W schedule in some patients (switching at 2–6 months); factors driving the decision to switch included response, convenience, and GPRC5D-related AEs. Five of the six panel participants' institutions are developing tal AE management protocols. Mouthwashes/sprays (dexamethasone, dexamethasone+nystatin, Biotène and saliva alternatives), dry mouth lozenges, citrus fruits and sour candy were commonly used to mitigate oral AEs. Prophylactic use of dexamethasone+nystatin liquid 3 times a day at the time of SUD before symptom onset appears promising. The use of an ice wrap around the cheeks 3 times a day every day may be helpful for some patients. In addition, panel participants reported increasing the dose interval from Q2W to Q4W helped alleviate dysgeusia, but dose reduction did not. Other strategies used by the IDI participants included modifying diet or referrals to dieticians (n=6). Topical steroids were used by most (n=7) to mitigate skin AEs such as rashes, as were moisturizers to prevent dryness. Half (n=5) reported using cosmetic products to mitigate nail AEs. **Conclusions:** This study outlines current clinical practices for tal. Findings indicate there is variation in the SUD care setting (half as inpatient and half as outpatient/hybrid models). The selection of a Q2W schedule is most common; however, switching to Q4W is a real-world AE management strategy for some patients. The approach to managing GPRC5D-related AEs is evolving. Further RWE is needed to inform the post-response maintenance schedule of tal to maximize durability while mitigating AE impact.

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Indirect Comparison of Linvoseltamab Versus Teclistamab for Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM): An Updated Analysis Based on 14-Month Follow-Up Data

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Introduction: Anti-B-cell maturation antigen (BCMA) bispecific antibodies have shown high efficacy and significantly advanced the treatment of advanced multiple myeloma. In the absence of head-to-head trials, matching-adjusted indirect comparison (MAIC) is an effective tool to assess relative treatment efficacy. Here, we present updated MAIC results for linvoseltamab vs teclistamab at a more informative, longer follow-up (FU) compared to prior analyses. **Methods:** Patient (pt)-level data from LINKER-MM1 (117 pts receiving 200 mg linvoseltamab in Phase 1/2, data cut-off [DCO] 1/2024, median FU [mFU] 14.3 months [mos]) and published data from the MajesTEC-1 safety population (165 teclistamab pts, DCO 2/2022, mFU 14.1 mos) were analyzed. Ten pts with prior BCMA antibody–drug conjugates exposure in LINKER-MM1 were excluded as MajesTEC-1 excluded such pts. Key prognostic factors were prespecified based on published literature; LINKER-MM1 pts were weighted to match prognostic factors in MajesTEC-1 classified as most important by an international expert panel (i.e., cytogenetic risk, age, refractory status, ISS stage, ECOG, extramedullary disease/plasmacytoma status). Two additional MAICs were conducted: one matched on all available prespecified prognostic factors, the other included all LINKER-MM1 200 mg pts. Objective response rate (ORR), very good partial response or better (≥VGPR), complete response or better (≥CR), and minimal residual disease (MRD) negativity (-; 10–5 threshold) rates, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT) with linvoseltamab and teclistamab were compared. Odds ratios for response and hazard ratios for time-to-event endpoints with 95% confidence intervals (CIs) are reported adjusted after matching. **Results:** Pt characteristics were balanced across trials after matching and linvoseltamab effective sample size was 83. Before matching, linvoseltamab had significantly higher ≥CR rates and longer PFS, OS, and TTNT vs teclistamab; ORR, ≥VGPR and MRD(-) rates, and DOR were numerically higher/longer with linvoseltamab. Adjusted after matching, linvoseltamab showed significantly longer PFS (0.53; 95% CI: 0.34–0.81), OS (0.61; 0.38–0.98), and TTNT (0.60; 0.38–0.95) vs teclistamab; linvoseltamab also showed numerically higher ORR (1.50; 0.97–2.33), and ≥VGPR (1.18; 0.80–1.76), ≥CR (1.40; 0.96–2.04), and MRD(-) (1.19; 0.70–2.03) rates, and trended toward longer DOR (0.61; 0.34–1.10). Results in the additional MAICs were similar except linvoseltamab showed significantly higher ≥CR rates (1.54; 1.01–2.35) and numerically longer TTNT (0.73; 0.44–1.21) vs teclistamab after matching in the MAIC using all prognostic factors.

Conclusions: This updated analysis with approximately 14 mo FU demonstrated statistically improved PFS, OS, and TTNT for linvoseltamab vs teclistamab and numerically favorable results for all other outcomes, highlighting linvoseltamab's potential as a highly effective treatment option for TCE RRMM.

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Indirect Comparison of Linvoseltamab Versus Selinexor Plus Dexamethasone for Penta-Exposed Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: No head-to-head trials have compared effectiveness of linvoseltamab, a human BCMA×CD3 bispecific antibody, with selinexor (an oral selective inhibitor of nuclear export compound) plus dexamethasone (sel-dex) in treating RRMM. This study compared the efficacy of these treatments using a matching-adjusted indirect comparison (MAIC). **Methods:** A feasibility assessment found an unanchored MAIC between the treatments was feasible. Patient (pt)-level data from LINKER-MM1 (linvoseltamab, 117 pts receiving 200 mg in Phase 1/2; data cut-off [DCO] 1/2024; median follow-up [mFU] 14.3 months [mos]) and published data from STORM part 2 modified intent-to-treat population (sel-dex, 122 pts; DCO 9/2019 for objective response rate [ORR], very good partial response or better [≥VGPR], complete response or better [≥CR], and overall survival [OS], mFU 15.5 mos for US pts and 14.6 mos for non-US pts; DCO 8/2018 for progression-free survival [PFS] and duration of response [DOR], mFU not reported) were analyzed. Thirty-six pts from LINKER-MM1 with prior BCMA-targeted therapy or not penta-exposed were excluded to match STORM part 2 criteria. Key prognostic factors were prespecified based on a prior literature review, and LINKER-MM1 pts were weighted to match STORM part 2 pts using the factors classified as most important by an international expert panel (cytogenetic risk, age, refractory status, Revised International Staging System stage, ECOG). ORR, ≥VGPR and ≥CR rates, DOR, PFS, and OS with linvoseltamab and sel-dex were compared. Two additional MAICs were conducted: one matched on all available prespecified prognostic factors, the other included all LINKER-MM1 penta-exposed pts receiving 200 mg regardless of prior BCMA-targeted therapy use. Odds ratios (ORs) for response and hazard ratios (HRs) for time-to-event outcomes with 95% confidence intervals (CIs) are reported adjusted after matching. Differences in restricted mean survival time (RMST) were calculated when the proportional hazards (PH) assumption was violated. **Results:** Matched pt characteristics were balanced across trials after matching and effective sample size of linvoseltamab was 50. All observed outcomes were statistically superior for linvoseltamab compared to sel-dex, both as observed and after matching. Adjusted after matching, linvoseltamab showed significantly higher ORR (6.72 [95% CI: 3.76–11.98]), ≥VGPR rate (23.76 [10.70–52.76]) and ≥CR rate (43.95 [10.51–183.82]) and significantly longer DOR (0.10 [0.04–0.23]) and OS (0.31 [0.18–0.55]) compared to sel-dex. For PFS, linvoseltamab showed significantly longer RMST before progression or death (8.36 mos) compared to sel-dex (4.80 mos, difference=3.56 mos [1.99–5.13]). Other MAIC results, whether matching on all available variables or including all penta-exposed pts in LINKER-MM1, were similar. **Conclusions:** These results indicate that linvoseltamab outperforms sel-dex in all measured outcomes for penta-exposed RRMM, highlighting its potential as a highly effective treatment option.

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The Orphan Nuclear Receptor NR5A2 Regulates Phospholipid Remodeling via MBOAT1 and MBOAT2 To Promote Proliferation and Drug Resistance in Multiple Myeloma Cells

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Introduction: Multiple myeloma (MM) is the second most common hematologic malignancy. Currently, drug resistance in myeloma cells is a clinically imperative issue requiring exploration and resolution. Important intrinsic factors contributing to MM drug resistance include molecular genetic abnormalities and metabolic reprogramming. 1q amplification is the most common secondary molecular genetic abnormality in MM. In recent years, there has been a growing body of reports on the role of lipid metabolism reprogramming in the onset and progression of MM drug resistance. The NR5A2 gene (located on chromosome 1q32), encoding the protein LRH-1. This protein is an important transcriptional regulator of lipid metabolism. This study aims to explore the role of NR5A2 in the occurrence and development of MM, as well as the relationship between lipid metabolism, ferroptosis, and MM cell proliferation and drug resistance. **Methods:** Data from whole exome sequencing (WES) revealing that high NR5A2 expression indicates a poor prognosis in MM patients. Protein and lipid metabolism data analysis was conducted to explore the downstream regulatory network of NR5A2, validated using CUT-Tag. ATP, malondialdehyde (MDA) staining, Fe2+ staining and reactive oxygen species (ROS) detection were employed to investigate the effects of NR5A2 on ferroptosis in HMCLs. **Results:** The decreased niacin flushing reactivity in MM patients suggests an imbalance in membrane phospholipid homeostasis. During the clonal evolution of MM, compared to MGUS and SMM, NDMM and RRMM exhibit a higher prevalence of amplifications/deletions. NR5A2

is significantly upregulated in MM patients with 1q+ compared to those without 1q amplification. Moreover, MM patients with high expression of NR5A2 exhibit poorer overall survival (OS) and progression-free survival (PFS). NR5A2 promotes proliferation and invasion of HMCLs. Proteomic analysis reveals the involvement of NR5A2 in phospholipid metabolism. NR5A2 over expression can suppress ferroptosis in HMCLs. CUT-Tag confirms that NR5A2 is an upstream transcription factor of MBOAT1 and MBOAT2. The NR5A2-MBOAT1/2 axis regulates phospholipid remodeling and suppresses ferroptosis in HMCLs. High expression of NR5A2 leads to resistance of HMCLs to dexamethasone. NR5A2 induces dexamethasone resistance in HMCLs by inhibiting ferroptosis. Inhibiting the expression of NR5A2 increases the sensitivity of HMCLs to dexamethasone. Co-culturing with polyunsaturated fatty acids (PUFA) promotes sensitivity of HMCLs to dexamethasone, and reverses the dexamethasone resistance caused by high expression of NR5A2. **Conclusions:** The orphan nuclear receptor NR5A2 regulates phospholipid remodeling via MBOAT1 and MBOAT2, inhibiting ferroptosis in HMCLs, promoting proliferation, and inducing resistance to dexamethasone in HMCLs. This study provides new insights into the pathogenesis of MM and offers novel therapeutic targets for MM treatment.

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EXCALIBER-RRMM: A Phase 3, Two-Stage Trial of Iberdomide, Daratumumab, Dexamethasone (IberDd) Versus Daratumumab, Bortezomib, Dexamethasone (DVd) in Patients With Relapsed/Refractory Multiple Myeloma

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Introduction: Trial in progress. New treatments (Txs) are needed to achieve deep and durable responses in relapsed/refractory multiple myeloma (RRMM). Iberdomide (IBER) is a novel, potent oral CELMoD™ agent with enhanced tumoricidal and immune-stimulatory effects compared with immunomodulatory drugs (IMiDs®). IBER has synergy with dexamethasone (DEX), daratumumab (DARA), and bortezomib (BORT) in vitro. In a phase 1/2 trial, IberDd demonstrated efficacy with a manageable safety profile in patients (pts) with RRMM (Lonial S, et al. HemaSphere 2021;5(S2):S187). The EXCALIBER-RRMM phase 3 trial (NCT04975997) will compare the efficacy and safety of IberDd with that of DVd in pts with early RRMM. **Methods:** This multicenter, open-label study will be conducted in 2 stages: in Stage 1, ≥ 200 pts will be randomized 1:1:1:1 to 1 of 3 IBER doses (1.0, 1.3, or 1.6 mg) + DARA and DEX or to the DVd arm to identify optimal IBER dose when combined with DARA + DEX; in Stage 2, ≈ 664 additional pts will be randomized 1:1 to IberDd at the selected IBER dose or to DVd, for efficacy and safety analyses (Stage 1 pts in IBER selected dose cohort and DVd arm to be also included). Pts will be stratified by number of prior Tx lines (1 vs 2), age (≤ 70 vs > 70 y), and ISS stage at study entry (I–II vs III). Primary efficacy endpoint is progression-free survival (PFS), which is defined as the time from randomization to progressive disease (PD) or death. The 3 planned interim analyses are: for IBER dose selection at end of Stage 1; and to examine PFS futility and superiority when ≈ 138 (30%) and ≈ 344 (75%) events, respectively, have been accumulated. Secondary endpoints include overall survival, duration of response, time to progression, overall response rate, measurable residual disease negativity rate, safety, and quality of life. Tx in the IberDd arm will consist of 28-day (D) cycles (C) with IBER on D1–21; 1800 mg subcutaneous (SC) DARA on D1, 8, 15, and 22 of C1–2, D1 and 15 of C3–6, and D1 of ≥ C7; and 40 mg oral DEX (20 mg in pts > 75 years of age) on D1, 8, 15, and 22. Tx in the DVd arm will consist of 21-D cycles for C1–8 and 28-D cycles for ≥ C9; 1800 mg SC DARA on D1, 8, and 15 for C1–3, D1 for ≥ C4; 1.3 mg/m^2 SC BORT on D1, 4, 8, and 11 for C1–8; and 20 mg oral DEX (10 mg in pts > 75 years of age) on D1, 2, 4, 5, 8, 9, 11, and 12 for C1–8. Tx will continue until confirmed PD, unacceptable toxicity, or consent withdrawal. Key eligibility criteria include age ≥ 18 y, 1–2 prior lines of antimyeloma Tx, partial response or better to ≥ 1 prior Tx, and documented PD during or after the last regimen. Prior anti-CD38 Tx is allowed only in Stage 2 (≤ 10% of pts). Enrollment began in June 2022 and is currently ongoing. Previously presented at ASCO 2023. **Results:** N/A **Conclusions:** N/A.

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Evaluation of Triple-Class Exposed (TCE) and Triple-Class Refractory (TCR) Myeloma Patients (pts) and Their Outcome: A Collaborative Study of the Argentine Group of Multiple Myeloma (GAMM)

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Introduction: Background: Multiple myeloma (MM) is the second most common hematologic malignancy. Over the past 20 years, several novel agents were approved and median patient survival has been prolonged. However, despite the introduction of novel agents in the upfront and relapsed treatment settings, MM remains incurable. Pts with relapsed and refractory multiple myeloma (RRMM) have a poor prognosis and limited treatment options after exposure to an immunomodulatory drug (IMiD), proteasome inhibitor (PI), and anti-CD38 antibody (mAb): TCE and TCR. Outcomes of real-world pts with TCE and TCR MM treated with standard-of-care (SoC) therapies are needed in low-income countries because data in this subgroup have not been reported yet. Aims: To understand the real-world outcomes of pts with RRMM to anti-CD38 mAbs, particularly those with TCE and TCR disease treated in Argentina. Furthermore, to describe the clinical characteristics, overall response rates (ORR), progression-free survival (PFS), and overall survival (OS). **Methods:** An observational, analytic, and retrospective study, including adult pts with RRMM to an anti-CD38 mAb-based index regimen after at least 4 weeks, among 22 centers from Argentina. Outcomes evaluated included ORR, PFS and OS after anti-CD38 mAb refractoriness, defined as T0. Data was compared between TCE and TCR groups. Statistical analysis was done with SPSS v.27 at p< 0.05. **Results:** We included 114 RRMM pts with a median age of 64 years at T0 and 49.5% were males. Risk groups included 35% ISS1, 38.8% ISS2, 26.2% ISS3, 9.9% high-risk by FISH, and 32.4% were unknown. Median line of treatments before T0 was 3. Next line of therapy was most commonly agents considered as SoC: PI/steroid (5/114, 4.38%), IMiD/alkylator (7/114, 6.14%), PI/alkylator (28/114, 24.5%), PI/IMiD (30/114, 26.3%), IMiD/steroid (4/114, 3.5%), polichemotherapy (11/114, 9.6%), anti-BCMA agents (5/114, 4,38%) and other treatments 21%. With a median of follow-up of 64.8 months (mo), the ORR was 61.4% with ≥ VGPR 28%. The median PFS and OS for the whole group after T0 was 11.1 and 13.5 mo, respectively. A significant higher median PFS and OS were observed on achieving ≥ VGPR (17.2 vs 6.8 mo, p=< 0.001; 34.7 vs 10.5 mo, p=< 0.001). 14 pts were TCE and 100 TCR. No differences were found in terms of PFS (6.2 vs 11.4 mo, p=0.686) and OS (7.5 vs 13.6 mo, p=0.424). 19 pts (16.6%) received anti-BCMA agents (5/19 at T0 and 14/19 at some point later) and a longer median OS (34.7 vs 11.3 mo, p=0.001) was observed. The main cause of death was progression of disease in 49/66. **Conclusions:** We presented the first RWD on TCE and TCR RRMM pts in Argentina. We observed in this preliminary study that pts relapsing on anti-CD38 mAb-containing regimens had poor outcomes when treated with SoC therapies. Achieving ≥ VGPR was associated with higher PFS and OS. Those who were treated with anti-BCMA agents at some point had significantly longer survival. Progression of disease was the main cause of death.

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Real-World Outcomes in Patients With Relapsed-Refractory Multiple Myeloma (RRMM) With Prior Proteasome Inhibitor and Lenalidomide Exposure in Sweden

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Introduction: The early use of immunomodulatory drugs (IMiD) such as lenalidomide (Len) in multiple myeloma (MM) has improved patient outcomes but also leads to an increased number of Len-refractory or intolerant patients in early lines with relapsed or refractory MM (RRMM). There is lacking data from the Nordics in the real-world clinical management and outcomes in these earlier lines of RRMM. **Methods:** In this single-center study, we have examined treatment patterns and survival outcomes by refractoriness to Len in RRMM patients with prior proteasome inhibitor (PI) and Len exposure at 1-3 prior lines (PL) of therapy (LOT) in Sweden. **Results:** Of patients with RRMM between January 2017 and May 2023, 266 unique patients were identified eligible at least one LOT. The median age of this cohort at relapse was 72.3 years, with 59.8% of male patients, and a median duration of 2.7 years since MM diagnosis. Among them, 25 % of patients were refractory to PI, and 43% were refractory to an IMiD. The majority of the patients (66%) had an ECOG (estimated from charts) scored 0 to 1. As inclusion criteria include multiple LOTs, 388 eligible observations were identified to report clinical outcomes.Among observations with evaluable outcomes, the proportion of 1, 2, and 3 PL were 32%, 43%, and 26%, respectively. The median overall survival (mOS) was 23 (95%CI: 15.9, 51.2) months, and real-world progression free survival (mPFS) was 9.8 (95%CI: 7.1, 13.1) months. mPFS was 14.0, 8.3 and 4.9 months at 1, 2, or 3 PL, respectively. For the cohort of observations which are Len-exposed non/not-yet-refractory (n=218), mOS was 30.5 (95%CI: 17.6, not evaluable N.E.) months and mPFS was 10.1 (95%CI: 8.2, 15.2) months, whereas for Len-refractory (n=166), the mOS and mPFS were 15.9 (95%CI: 9.9, 49.3) months and 7.4 (95%CI: 3.9, 15.1) months, respectively.The most frequent subsequential treatments after 1 PL are: Daratumumab (Dara) monotherapy (D-mono) (17%), PKd (14%) and Dara-Kd (11%), after 2 PL: D-mono (23%), Kd (12%) and Pd (11%), and after 3 PL: D-mono (26%) and Pd (11%). For the Len-exposed non/not-yet refractory group, the subsequent treatments after 1 PL are: D-mono (21%), Rd (19%) and Pd (10%), after 2 PL: D-mono (25%), Pd or Rd (14% for each regimen) and Kd (10%), and after 3 PL: Pd (33%) and D-mono (20%). **Conclusions:** To the best of our knowledge, this is the first study in Sweden reporting the treatment

pattern and outcomes of a difficult-to-treat RRMM cohort, with prior PI and Len exposure.Overall, this study shows that both PFS and OS of early line RRMM patients with previous Len-exposure in the population are short. Patients who are refractory to Len exhibit particularly unfavorable outcomes, highlighting a substantial unmet clinical need and the necessity to develop more efficacious and safe therapeutic options in RRMM treatment.

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Survival Analysis of Selinexor-Exposed Relapsed/Refractory Multiple Myeloma (RRMM) Treated with Chimeric Antigen Receptor T-Cell (CAR-T) Therapy: A Real-World Exploratory Analysis

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Introduction: Selinexor, an oral exportin 1 (XPO1) inhibitor, prevents the XPO1-mediated export of several tumor suppressor proteins (TSPs), leading to the accumulation of TSPs in the nuclei of malignant cells, and blocks protein translation of oncogenes that drive cell proliferation, ultimately causing cell cycle arrest and apoptosis. The quality and durability of responses from CAR-T therapy targeting B-cell maturation antigen (BCMA) vary, and treatment history may play a role. We employed real-world data to identify factors associated with progression-free survival (PFS) and overall survival (OS) in patients with RRMM previously exposed to selinexor who received CAR-T treatment. **Methods:** This retrospective cohort study reviewed medical records of patients who received selinexor prior to CAR-T therapy at two academic cancer centers in the United States - Icahn School of Medicine at Mount Sinai (ISMMS) and Cleveland Clinic Foundation (CCF). All patients received a selinexor-based regimen prior to CAR-T administration, and data were collected on response rates, duration of response (DOR), PFS and OS. Multivariate proportional hazards regression modelling was employed to compare the impact of selinexor exposure in the immediate prior line of therapy (LOT) on PFS and OS following CAR-T therapy. **Results:** The study consisted of 45 patients (27 from ISMMS and 18 from CCF), with a median age at MM diagnosis of 54 years. At the time of CAR-T infusion, patients from both institutions predominantly exhibited ISS stage I or II, ECOG Performance Status of 0 or 1, and triple-class exposure. CAR-T therapies used consisted of idecabtagene vicleucel (60%), ciltacabtagene autoleucel (35.6%), and BMS-986354 (4.4%). Only 24.4% of patients received selinexor as part of bridging therapy. Approximately 44.4% (20/45) of patients (11 patients at ISMMS and 9 patients at CCF) received selinexor immediately before CAR-T. Overall, 40/45 (88.9%) patients achieved a partial response or better, with a median DOR of 8.1 months (IQR: 2.9 to 39). At a median follow-up of 68 months post CAR-T therapy, median PFS and OS for the whole cohort were 8.0 and 35.9 months, respectively. The timing of the selinexor-based regimen relative to CAR-T was an independent variable that predicted survival as treatment with selinexor-based regimen in the LOT immediately prior to CAR-T therapy was associated with a 60% and 92% reduction in risk of disease progression (HR: 0.40 (95%CI: 0.14-1.09)) and death (HR: 0.08 (95%CI: 0.02-0.46)), respectively. **Conclusions:** When compared to those with a more distant exposure to selinexor, patients with RRMM treated with a selinexor-based regimen in the LOT immediately prior to CAR-T therapy experience improved survival outcomes. Further investigation with a larger real-world cohort including patients from other centers or a prospective clinical trial is warranted to confirm any survival benefit.

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Real-Life Outcomes in Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM) Treated With Carfilzomib- and/or Pomalidomide-Based Regimens in the LocoMMotion and MoMMent Studies

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Introduction: A pooled analysis from the prospective, non-interventional, multinational LocoMMotion (NCT04035226) and MoMMent (NCT05160584) studies demonstrated suboptimal outcomes in patients (pts) with TCE RRMM. The results also highlighted the lack of a single standard of care (SOC), with more than 100 different regimens used. The current analysis evaluates

outcomes in pts from LocoMMotion and MoMMent treated with carfilzomib- or pomalidomide-based regimens as observed during the period from 2019–2022, preceding the era of CAR-T cell therapies and bispecific antibodies. **Methods:** Data were pooled from LocoMMotion (clinical cut-off [CCO]: Oct 27, 2022; final data) and MoMMent (CCO: Aug 18, 2023). Both studies have similar designs. Eligible pts received ≥3 prior lines of therapy (LOT; LocoMMotion allowed < 3 prior LOT if pts were double refractory to a PI and IMiD), were TCE, had measurable disease and documented progressive disease since their last LOT, and had an ECOG performance status (PS) score of 0 or 1 at screening. All pts provided informed consent. The primary endpoint was overall response rate (ORR), evaluated per IMWG criteria by the same review committee in both studies. Continuous variables were summarized using descriptive statistics, and ORR was reported with 95% exact CIs. Time-to-event data were summarized by Kaplan-Meier methods. **Results:** The current pooled analysis includes 166 pts (LocoMMotion, n=131; MoMMent, n=35) treated with either a carfilzomib- or pomalidomide-based regimen. Median follow-up was 24.4 mo (range, 18.2–27.9). At baseline, median age was 69 years, 56.6% of pts were male, 74.7% had an ECOG PS of 1, and median time since diagnosis was 6.0 years. Pts received a median of 4 prior LOT (range, 2–12), 72.9% were triple-class refractory, and 11.4% were penta-drug refractory. 20 pts (12%) were refractory to both carfilzomib and pomalidomide. Overall, 36 unique carfilzomib- or pomalidomide-based regimens were used as SOC. The most common (≥5% of pts) were cyclophosphamide, pomalidomide, and dexamethasone (24.7%); carfilzomib + dexamethasone (20.5%); pomalidomide + dexamethasone (12.7%); and elotuzumab, pomalidomide, and dexamethasone (5.4%). ORR was 34.3% (95% CI, 27.2–42.1), median duration of response was 8.1 mo (95% CI, 5.2–11.1), median progression-free survival was 5.5 mo (95% CI, 4.4–6.0), median time to next treatment was 6.2 mo (95% CI, 5.3–7.2), and median overall survival was 15.3 mo (95% CI, 13.0–21.5). **Conclusions:** These results suggest that outcomes in pts with TCE RRMM remain poor despite the use of carfilzomib and pomalidomide. New therapies, such as CAR-T cell therapies and bispecific antibodies, are needed to address the remaining high unmet need for patients with TCE RRMM.

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ALLG MM26/D1/AMN009 Novel Combinations for Orphan Myeloma (NORM) Platform Study

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Introduction: In multiple myeloma (MM), patients with non-measurable disease, impaired renal function, extramedullary myeloma (EMM) or central nervous system (CNS) involvement are frequently excluded from clinical trials. In light of this, many of the novel agents have not been adequately studied in these subgroups, and these patients represent a group of unmet need. We have established a multi-arm platform trial to explore novel agents in these patient groups. **Methods:** The NORM platform is recruiting patients with relapsed/refractory MM (RRMM) after >1 prior line of therapy who meet the definition of one of the following disease strata: renal impairment (CrCl < 30ml/min) (stratum A); IMWG non-measurable disease (stratum B); EMM (stratum C) and CNS disease (stratum D). Novel therapies can be trialled across one or more strata. The primary objective is to determine efficacy of the novel agent/s in each stratum, defined as the proportion of patients who achieve >partial response (PR) as per IMWG, at any time up to cycle 4. In patients with non-measurable disease not assessable by IMWG (B), PET will be used for response assessment (Zamagni 2021). In CNS disease (D), primary CNS lymphoma response criteria will be utilised (Abrey 2005). Secondary endpoints include progression free and overall survival, safety and quality of life. In each stratum, efficacy will be investigated using a dual-criteria, Bayesian, Proof-of-Concept (PoC) approach (Neuenschwander 2011) with a minimally informative prior for the response rate. The prior probability of response will be updated when at least 10 patients have been followed for >4 cycles or have withdrawn prior to that. Domain-Specific Protocol Appendices will specify decision criteria that will be used to maintain or close treatment arms and guidelines for early publication of efficacy reports. Assessment of efficacy will be based on the percentiles of the posterior distribution for the overall response rate (ORR). The first combination trialled in NORM is selinexor, pomalidomide and dexamethasone (SPd) (Chen 2020). 40 patients will be recruited into Strata A, B and C and 20 patients into Stratum D. Accrual may be terminated early for PoC or futility. PoC for efficacy of SPd in a stratum will be claimed if 2 criteria are met: Stratum A or B, observed ORR ≥40% and posterior probability (PP) that the true ORR is ≥30%, given the data, is ≥0.90 and in stratum C or D, observed ORR ≥30% and PP(true ORR ≥20% | data) ≥ 0.90. Each stratum will be analysed separately. Any planned comparisons of strata and/or therapies will be pre-specified in appendices to the master protocol. **Results:** Accrual has commenced in Australia, South Korea, Taiwan and Singapore. **Conclusions:** The PoC platform study design allows rapid assessment of different novel therapeutic regimens, using one master protocol, in patient populations typically excluded from clinical trials. We aim to demonstrate efficacy and safety of available novel agents and combinations in these subgroups of MM patients.

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Primary Refractory Disease in Newly Diagnosed Multiple Myeloma: Incidence, Characteristics and Outcome From a Tertiary Care Cancer Centre in India

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Introduction: Primary Refractory Disease (PRD) in multiple myeloma is defined as either progressive disease (PD) or stable disease (SD) after 4 or 6 cycles of therapy. Despite improvements in the induction regimen used, a small proportion of patients don't respond and have poor outcomes. In this analysis, we look at their incidence, characteristics and outcomes. **Methods:** We did a retrospective observational analysis of patients with newly diagnosed multiple myeloma (NDMM) between July 1, 2022, to October 31, 2023. Statistical analysis was performed using SPSS v29.0 software. Demographic and baseline characteristics were reported using descriptive statistics. We compared PRD patients and primary responders for baseline characteristics, treatment given and outcomes by Univariate analysis using Chi-square and Unpaired t-tests followed by multivariate analysis using multiple linear regression. Kaplen Mayer analysis was used to calculate overall survival (OS). **Results:** A total of 162 patients were included for the analysis out of which 11 (6.8%) patients had PRD. On comparing the PRD patients with primary responders, the Median age at diagnosis for the patients was 60 years (Range- 45 to 70 years) and 55 years (range 30 to 85) respectively. For 135 (83.3%) patients that had R-ISS, it was stage I, II, and III in 1 (9.09%), 4 (36.3%), and 6 (54.54%) respectively for PRD while 16 (11.8%), 74 (54.8%), and 45 (33.3%) had stage I, II, and III disease, respectively among primary responders. Cytogenetic analysis showed 2 (18.2%) patients among PRD to have high-risk cytogenetics ((t4:14), t(16:16) and or Del17p) while among primary responders, 17 (10%) patients had high-risk features. 1q gain/amp was seen in 7 (63.6%) patients in PRD while 40 (23.5%) patients among primary responders. CRAB features were seen in 18(11.1%), 37(22.8%), 85 (52.5%), 143(88.3%) patients respectively among the whole cohort. The initial treatment given to PRD patients was VCd in 3(27.3%), and VRd in 8(72.7%) while the initial treatment in primary responders was VCd in 9 (6%), VRd in 133 (88.1%) patients. Death was reported in 3 (27.3%) in PRD patients while only in 6 (4%) in primary responders. Mean OS was 14.08 months in PRD patients. Among the various parameters analyzed by univariate analysis, 1q gain/amp and use of VCd were found statistically significant for PRD patients. Mortality was significantly higher in PRD patients as seen in Univariate analysis. On Multivariate Linear Regression analysis, 1q gain/amp and initial therapy of VCd were found statistically significant. **Conclusions:** This study highlights distinct clinical and genetic features associated with Primary Refractory Disease in multiple myeloma patients, emphasizing poorer prognosis and higher mortality in the subgroup. The proportion of patients having PRD is similar to the data reported in the West. It also highlights a need for tailored treatment and better assessment methods for PRD patients and a need for prospective trials for the same.

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Real World Outcomes with Elotuzumab-Based Therapies for Patients with Relapsed Refractory Multiple Myeloma (RRMM): A Mayo Clinic Experience

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Introduction: Elotuzumab (Elo) improved overall survival (OS) in combination with the immunomodulatory drugs (IMiDs) lenalidomide (R) and pomalidomide (P) in patients (pts) with RRMM in the ELOQUENT 2 and 3 trials, respectively. However, the efficacy of Elo-based regimens in RRMM pts that are triple class refractory (TCR), daratumumab (Dara)-refractory, IMiD-refractory and have received >3 prior lines of therapy (LOT) is poorly characterized. **Methods:** In this retrospective analysis, we aim to evaluate the real-world efficacy and the clinical outcomes of RRMM pts treated with Elo+ImiD+Dex regimens across the 3-site Mayo Clinic Cancer Center. **Results:** 135 pts were included in the analysis; 30 received ERd (3 LOT) and 105 received EPd (4 LOT). More EPd treated pts had undergone auto-transplant, were proteasome-inhibitor exposed, P-refractory, Dara-refractory and had extramedullary disease compared to pts treated with ERd ($p< 0.05$). The median (m) follow-up time for ERd and EPd treated pts was 20.5 and 52.8 months (mos), respectively. At 2 years 38.8% and 53.7% of pts had ongoing sustained response for EPd and ERd, respectively. The mPFS for pts treated with EPd was 4.8 mos and 17.28 mos for patients treated with ERd with no significant differences based on cytogenetic risk. The mOS for pts treated with EPd was 2.55 y and was 5.64 y for pts treated with ERd. For pts treated with EPd, the mPFS for TCR pts (n=52) was 4.3 mos compared to 5.04 mos for non-TCR pts (n=53), p=0.29. For pts treated with ERd, the mPFS for TCR pts (n=11) was 7.68 mos compared to 28.56 mos for non-TCR pts (n=19), p=0.20. For Dara-refractory pts, the m time from Dara-progression to start of ERd and EPd was 3 mos and 2.28 mos, respectively. Dara-refractory pts treated with EPd (n=94) received a m of 4 prior LOT and had a mPFS of 5.04 mos compared to non-Dara refractory pts (n=11) who received a m of 3 prior LOT and had a mPFS of 2.64 mos, p=0.84. Dara-refractory pts treated with ERd (n=18) received a m of 4 prior LOT and had a mPFS of 7.68

mos compared to non-Dara refractory pts (n=12) who received a m of 2 prior LOT and had a m PFS of 38.52 mos, p=0.015. EPd treated pts who received >3 prior LOT had a mPFS of 3.72 mos and a mOS of 14.16 mos and those who received ≤3 prior LOT had a mPFS of 5.04 mos and a mOS that was not reached (NR) (for OS, p=0.04). ERd treated pts who received >3 prior LOT had a mPFS of 5.16 mos and a mOS of 10.2 mos and those who received ≤3 prior LOT had a mPFS of 35.8 mos and a mOS that was NR (for OS, p< 0.001). Pts that were P-refractory and were treated with EPd (n=57) had an ORR of 28.7% and a mPFS of 3.72 mos. Pts that were R-refractory and treated with ERd (n=19) had an ORR of 52.3% and a mPFS of 23.64 mos. **Conclusions:** In this real-world analysis of Elo-based regimens in RRMM, pts receiving EPd were more heavily pretreated, and refractory compared to pts receiving ERd. Nonetheless, Elo+ImID+Dex regimens show clinical efficacy in Dara-refractory, IMiD-refractory, and TCR pt populations.

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Characterization and Management of Ocular Events in Patients Treated With Belantamab Mafodotin Plus Pomalidomide and Dexamethasone in the DREAMM-8 Study

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Introduction: DREAMM-8 (NCT04484623) demonstrated statistically significant and clinically meaningful progression-free survival (PFS) benefit in patients (pts) treated with belantamab mafodotin (belamaf) + pomalidomide + dexamethasone (BPd) vs bortezomib + pomalidomide + dexamethasone (PVd). Belamaf is associated with a risk of ocular events, which are generally reversible and manageable with dose modifications. Here we describe the management of belamaf ocular events in DREAMM-8. **Methods:** Starting dose of belamaf was 2.5 mg/kg IV (day 1 cycle 1) followed by 1.9 mg/kg Q4W (cycle 2 and onward). In addition to ocular adverse events (AEs), ocular examination findings were evaluated using the KVA scale and drove dose modifications. Dose delays or reduction in frequency to 1.9 mg/kg Q8W were permitted to manage ocular events. Further dose reductions to 1.4 mg/kg Q8W were permitted. **Results:** 155 pts were randomized to the BPd group and 36% remained on treatment with belamaf at DCO (29 Jan 2024). Median duration of follow-up was 21.78 mo (range, 0.03-39.23), and minimum follow-up in pts with ongoing treatment was 12.81 mo; median PFS was not reached (NR; 95% CI, 20.6-NR) with BPd and 12.7 mo (95% CI, 9.1-18.5) with PVd (HR, 0.52; 95% CI, 0.37-0.73; P< .001). In the BPd group, 150 pts received ≥1 dose of study treatment. While the majority of BPd-treated pts experienced an ocular event that led to dose interruption/delay (83%) or dose reduction (59%) of any component of treatment, discontinuations due to ocular events were low (9%). ≥1 ocular event (grade ≥2 per KVA) was observed in 87% (131/150) of BPd-treated pts. Of these pts, 120 of 131 (92%) continued belamaf on or after onset of the first event and received a median of 5 subsequent doses (range, 1-21), with 106 of 120 pts (88%) achieving partial response (PR) or better. The 14 pts (9%) who discontinued treatment due to ocular events did so after a median of 3 doses (range, 1-7) of belamaf, and 12 of them had a PR or better. Worsening of best-corrected visual acuity (BCVA) to bilateral 20/50 or worse at any point in the study from normal baseline (20/25 or better in ≥1 eye) was reported in 51 of 150 (34%) BPd-treated pts and 51of 137 (37%) BPd-treated pts who had normal BCVA at baseline. The first occurrence improved in 92% (47/51) of pts and BCVA recovered to normal (post hoc) baseline in 84% (43/51) by DCO. Of the BPd-treated pts who had normal BCVA at baseline (n=137), 16.8% (23/137) had bilateral worsening of BCVA to 20/50 or worse within the first 3 mo of treatment; the prevalence of BCVA declined in pts who remained on treatment and did not increase over subsequent 3-mo intervals. Additional analyses will be presented. **Conclusions:** Ocular events in BPd-treated pts were generally reversible and effectively managed by dose modifications. Pts were able to continue treatment and derive benefit. The rate of discontinuation due to these events was low.

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Real-World Treatment Patterns and Survival Outcomes of Patients With Relapsed/Refractory Multiple Myeloma (RRMM) Treated With a Selinexor-Containing Triplet-Based Regimen

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Introduction: Large cohort studies have demonstrated poor overall survival outcomes of approximately one year in RRMM with progression after treatment with proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies. Very few patients in these studies received selinexor in the next line of therapy (LOT), and its activity in triple-class exposed RRMM was not evaluated. This study analyzed real-world treatment patterns and survival outcomes of patients with RRMM treated with a selinexor-containing triplet-based regimen, particularly in the triple-class exposed setting. **Methods:** This longitudinal, retrospective cohort study used patient data from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. Patients were included if they had a chart-confirmed diagnosis of MM on or after January 1, 2011 through January 31, 2024 with evidence of receiving a National Comprehensive Cancer Network recommended selinexor-containing triplet regimen in the second line or later. Survival outcomes included real-world overall survival (rwOS). Descriptive statistics and time-to-event analysis via Kaplan-Meier method were employed. **Results:** Approximately 112 patients were eligible for inclusion in the analysis. Median age at index year was 69 years, 54% were male, and 72% had Eastern Cooperative Oncology Group performance status of 0 or 1. At initial diagnosis, 20%, 30%, and 29% of patients were International Staging System stage I, II, and III, respectively. High cytogenetic risk (defined as FISH del17p, t(4:14), or t(14:16)) was present in 27% of patients and standard risk in 36%. Median time from diagnosis to index date was 58 months, with 55% having prior stem cell transplantation and a median of 5 prior lines of treatment. Most patients had prior exposure to daratumumab (94%), lenalidomide (97%), bortezomib (96%), pomalidomide (83%), and carfilzomib (77%); 94.6% (106/112) of patients were triple class exposed. Selinexor-containing triplet regimens were selinexor + bortezomib + dexamethasone (47%), selinexor + carfilzomib + dexamethasone (25%), selinexor + pomalidomide + dexamethasone (18%), and selinexor + daratumumab + dexamethasone (9.8%). The median rwOS was 14.7 (95% confidence interval [CI]: 10.6, 20.9) months with a median follow up of 9.4 months. Stratification based on the index selinexor LOT showed longer rwOS for patients treated in 2 to 5L compared with 6L+ (16.4 months [95% CI: 11.7, NR] vs 13.4 months [95% CI: 7.7, 20.9]). **Conclusions:** In this retrospective analysis, treatment with a selinexor-containing regimen in a heterogeneous group of patients with triple-class exposed RRMM was associated with rwOS of greater than one year, which compares favorably with historical LocoMMotion and MAMMOTH study results. Selinexor-containing triplet regimens are a treatment choice that may be considered for inclusion as a benchmark comparison in future RRMM prospective cohort studies.

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Indirect Comparison of Linvoseltamab Versus Talquetamab for Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Management of patients (pts) with heavily pretreated multiple myeloma has advanced significantly with the availability of bispecific antibodies targeting BCMA or GPRC5D. In the absence of head-to-head trials, matching-adjusted indirect comparisons (MAICs) can provide insights into relative treatment efficacy and aid physician choice. We present results of unanchored MAICs to compare the efficacy of linvoseltamab and talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W in TCE RRMM. **Methods:** Pt-level data from LINKER-MM1 (linvoseltamab, 117 pts receiving 200mg in Phase 1/2, data cut-off [DCO] 1/2024, median follow-up [FU] 14.3 months [mo]) and published data from MonumenTAL-1 (talquetamab, QW: 143 pts, DCO 1/2023, FU 18.8 mo; Q2W: 145 pts, DCO 1/2023, FU 12.7 mo) were analyzed. Key prognostic factors were pre-specified based on a published literature review and physician grading; LINKER-MM1 pts were weighted to match MonumenTAL-1 on factors classified as most important by an international expert panel. A second set of MAICs matched all available pre-specified factors. Objective response rate (ORR), very good partial response or better (≥VGPR), complete response or better (≥CR), and minimal residual disease (MRD) negativity (- [at 10-5 threshold]) rates, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT) with linvoseltamab and talquetamab were compared. Odds ratios (ORs) for response endpoints and hazard ratios (HRs) for other endpoints with 95% confidence intervals (CIs) are reported. **Results:** Before matching, most prognostic factors were imbalanced. Differences existed in use of subsequent antimyeloma therapies (SAT): MonumenTAL-1 (46.9%, 135/288) vs LINKER-MM1 (29.9%, 35/117), and could not be adjusted in the MAICs. After matching, linvoseltamab (effective sample size [ESS]=86) showed significantly higher ≥CR rate (1.66 [1.12–2.46]), and longer PFS (0.44 [0.28–0.68]), TTNT (0.34 [0.22–0.52]), and DOR (0.32 [0.19–0.53]), numerically longer OS (0.97 [0.60–1.57]), identical ≥VGPR (1.00 [0.67–1.49]) and MRD[-] rates (1.00 [0.57–1.75]), and numerically lower ORR (0.82 [0.52–1.29]) vs talquetamab QW. After matching, linvoseltamab (ESS=73) showed significantly

longer DOR (0.54 [0.29–1.00]) and TTNT (0.40 [0.24–0.66]), numerically longer PFS (0.64 [0.39–1.05]) and higher ≥CR (1.31 [0.88–1.97]) and MRD[-] rates (1.13 [0.63–2.02]), and numerically lower ORR (0.87 [0.54–1.39]) ≥VGPR rate (0.88 [0.58–1.35]), and shorter OS (1.23 [0.71–2.14]) vs talquetamab Q2W. Results matching all available prognostic factors were consistent except the adjusted ≥CR rate and PFS were significantly better for linvoseltamab vs talquetamab Q2W. **Conclusions:** These results show better outcomes across several important efficacy endpoints for linvoseltamab vs talquetamab, highlighting its potential as a highly effective treatment option for TCE RRMM. Due to substantial differences in SAT use across trials, the OS comparison should be interpreted with caution.

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A Multicenter Observational Retrospective Study of Second-Line Treatment With Daratumumab–Bortezomib–Dexamethasone (DaraVd) in Multiple Myeloma (MM) Patients Refractory to Lenalidomide

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Introduction: Up-front use of lenalidomide (len) as maintenance therapy after ASCT or as continuous treatment in combination with other agents has become the gold standard for newly diagnosed MM patients (pts). The management of len-refractory (ref) pts at first relapse is challenging and requires careful evaluation of available treatment options. Daratumumab (Dara) - bortezomib (B) - dexamethasone (DaraVd) has been approved for RRMM after at least one prior line of therapy but few data were provided in pts ref to upfront len. **Methods:** We run a retrospective study to assess the outcomes of len-ref pts treated with DaraVd at first relapse in 9 Italian centers. **Results:** The baseline characteristics of 79 analyzed pts were representative of a general MM population, but median age (57 years) was lower. Pts with high-risk (HR) cytogenetics (t(4;14) and/or t(14;16) and/or del17) were 16 (27%) at diagnosis, and 7 (29%) at relapse (data available in 24 pts only). Toxicity-related B dose-reduction occurred in 39 pts (49.4%); 27 (44%) pts delayed a median of 1 dose of Dara (range 1-5), mostly for infections. At least one grade ≥2 adverse event (AE) occurred in 67 (85%) pts. 73 pts started with IV Dara, 6 with SC, with 14% of infusion related reactions (IRR) (grade 1-2). Most common AEs were hematological (72%), infections (30%, 8% grade 3, 1% grade 5), pneumonia (14%) and asthenia (38%). Peripheral neuropathy rate was 58% (46 pts), 8% of grade 3. Three pts discontinued for toxicity. Overall response rate (ORR) was 86% (61% ≥VGPR). With a median follow-up of 25 months (mos), median PFS and OS were 15 and 47 mos, respectively. The dose and duration of previous len exposure did not influence PFS, which was favorably affected by the absence of amp1q (p=0.04), BM plasma cells < 60% (p=0.003), absence of extramedullary disease (p=0.009) and a best response ≥VGPR (p< 0.001) or ≥CR (p=0.012). In a multivariate model, a response ≥VGPR was confirmed to be independently associated to PFS (HR=0.08, p< 0.001, 95% CI 0.018-0.359), with a median of 26 vs 7 mos. **Conclusions:** In len-ref pts, second line DaraVd was manageable and safe. PFS was shorter than in the general population (27 mos), except for pts with ≥VGPR, but two-fold longer than previously reported in the CASTOR study (7.8 mos), regardless of the number of prior lines of therapy. Overall, DaraVd remains an alternative option for len-ref pts at first relapse, especially for those ineligibles to receive pomalidomide-or carfilzomib-based regimens.

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Efficacy of Belantamab Mafodotin + Bortezomib + Dexamethasone (BVd) Compared to Alternative Regimens in 2L+ Relapsed/Refractory Multiple Myeloma (RRMM): A Network Meta-analysis of Randomized Trials

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Introduction: Belantamab mafodotin (belamaf) is an antibody-drug conjugate targeting B-cell maturation antigen. The phase III DREAMM-7 study (NCT04246047) evaluated belamaf with bortezomib (V)+dexamethasone (d; BVd) vs daratumumab (D)+Vd (DVd) in patients with RRMM who had ≥1 prior line of therapy (2L+). BVd improved the primary endpoint of progression-free survival (PFS) vs DVd (hazard ratio [HR] 0.41, [95% confidence interval {CI} 0.31–0.53], P< 0.00001), with a median PFS (95% CI) of 36.6 months (28.4–not reached) vs 13.4 months (11.1–17.5), respectively. Median overall survival (OS) was not reached in either arm (HR 0.57, 95% CI 0.40–0.80, P< 0.0005). Overall response rate (ORR [95% CI]) favored BVd over DVd (82.7% [77.4–87.3]

vs 71.3% [65.3–76.8]). Indirect comparisons are needed to evaluate the relative efficacy of BVd compared with other regimens for early RRMM. **Methods:** Randomized controlled trials (RCT) of adults with RRMM in 2L+ who had disease progression on/after most recent therapy were identified in a systematic literature review (2008–January 2024). RCTs included only those trials that evaluated PFS, OS, or ORR in a regimen approved/likely to be approved by the US Food and Drug Administration/European Medicines Agency, or which were of interest for health technology assessment. For PFS, OS, and ORR, trials were linked together by the treatment(s) they shared to form connected networks of evidence, and a Bayesian network meta-analysis (NMA) was conducted. Trials/regimens that weren't part of the connected evidence networks were excluded from the NMAs. **Results:** The connected evidence networks comprised a total of 13 RCTs (including DREAMM-7) for PFS and ORR, and 11 RCTs for OS (ARROW/GEM KyCyDEX trials did not report OS). All regimens compared to BVd included a proteasome inhibitor 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. The PFS/ORR networks included an alternative dosage of Kd. PFS of BVd was the longest of all therapies included in the fixed-effect NMA, with notable PFS HRs (95% credible interval [CrI]) including 0.38 (0.24–0.60) vs DKd, 0.42 (0.26–0.68) vs IsaKd, and 0.41 (0.31–0.54) vs DVd. HRs for PFS were 0.13–0.42, and were statistically significant, favoring BVd. OS was longer for BVd than the other regimens, with notable HRs (95% CrI) including 0.67 (0.39–1.12) vs DKd, 0.67 (0.37–1.18) vs IsaKd and 0.57 (0.40–0.81) vs DVd. HRs for OS were 0.39–0.67, and the 95% CrIs were under 1 except for 4 comparisons (BVd vs CyVd, EVd, IsaKd, and DKd). Odds ratios (95% CrI) for ORR consistently favored BVd over the other regimens and ranged from 1.12 (0.42–2.97) vs CyKd to 7.47 (2.49–22.65) vs CyVd. **Conclusions:** In the absence of any direct RCTs comparing BVd, this NMA indicated BVd offers the highest PFS, OS, and ORR of the included proteasome inhibitor-based regimens for 2L+ RRMM.

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Subcutaneous Administration of Isatuximab by an On-Body Delivery System (OBDS) in Multiple Myeloma Patients: Results of a Nurse Survey

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Introduction: Intravenous (IV) isatuximab (Isa) in combination with pomalidomide-dexamethasone (Pd) is approved for the treatment of relapsed/refractory multiple myeloma (RRMM) patients. Results of a Phase 1b study (NCT04045795) in RRMM showed safety and efficacy of SC Isa plus Pd comparable to IV Isa plus Pd, with excellent local tolerability and no infusion reactions with OBDS administration. We report here results of an ad-hoc nurse survey conducted to gather nurses' perceptions and experiences with subcutaneous (SC) Isa administration via the investigational OBDS in patients with MM. **Methods:** From 8Dec23 to 3Jan24, 12 registered nurses, who participated in trials at clinical sites in Australia, France, Germany and Spain, were invited to complete an online, native-language survey, assessing delivery modalities and predefined nurse-vetted lists of advantages and potential disadvantages with SC Isa treatment via OBDS, based on their experience. Data were combined and presented in percentages. **Results:** Of the 12 nurses who completed the survey (100% response rate), 75% had experience with administration of Isa via OBDS and 100% with patient monitoring. All nurses expressed confidence in SC administration using the OBDS; 100% indicated a preference for treatment delivery by OBDS vs IV administration and 90% a preference for SC administration using the OBDS vs manual syringe push of high-volume antibody formulations. All respondents found it easy to learn and administer treatment with the OBDS and agreed that use of the OBDS improved efficiency at their centers. Main advantages identified for HCPs in using the OBDS were hands-free delivery (100% of respondents), reduced physical burden (100%), facilitated patient management (100%), controlled delivery (92%), no needle exposure (92%), and labor saving (92%). Main advantages for patients, as perceived by the nurses, included short duration of treatment (100%), no needle visibility (100%), a generally well-tolerated and painless SC injection via OBDS (83%), and potential for at-home treatment (100%). Extent of drug delivered not clear in case of interruption (83%) and need to press/hold a button to pause injection (67%) were agreed upon as potential disadvantages for HCPs; risk of allergy to the adhesive tape (50%) was reported as a potential disadvantage for patients, although no interruptions or allergy were observed in 581 administrations via OBDS in the Phase 1b study (IMS 2023; P-306). 92% of nurses indicated that they were comfortable with monitoring ending 1 to 2 hours after start of first injection (based on the different trial protocols) and 100% with monitoring until end of injection for subsequent administrations. **Conclusions:** Findings from this nurse survey show a high level of confidence and preference for SC Isa treatment delivery using a hands-free OBDS vs IV administration, due to its ease of use, tolerability, and time savings, suggesting its applicability in routine clinical practice.

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Successful Pregnancy Outcome and CR 4 Transplant in a Patient of Multiple Myeloma

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Introduction: Multiple myeloma is a disease of elderly, but young myeloma is not rare in India. Though infertility is a major concern with ASCT, Women with childbearing age group has successful pregnancy outcome post-transplant. Here we report a case of young myeloma with 2 successful pregnancy outcomes. **Methods:**

we retrospectively collected the data from hospital information system (HIS) **Results:** A 44 years old female, who initially presented to our department in 2009 with severe backache and fatigue which was present since a year. She also had history of previous two MTP in view of non-viable fetus and history of spontaneous abortion of twin pregnancy. Initial lab analysis were suggestive of severe anemia (hemoglobin 8g/dl) and further work-up revealed the presence of M band of 5.7 g/dl and monoclonal IgG kappa immunoglobulin was detected by serum immunofixation electrophoresis while bone marrow examination showed 60% atypical plasma cells. Thus diagnosis of Multiple myeloma was confirmed and she was initiated on VAD chemotherapy regime (V=Vincristine, A=Adriamycin, D=Dexamethasone). After 6 cycles, complete remission was achieved and she was shifted to Thalidomide-dexamethasone maintenance followed by single agent thalidomide. In January 2012 she presented with amenorrhea for 3 months, pregnancy was confirmed on ultrasonography and no anomalies were detected in the fetus. As patient opted to continue with pregnancy, thalidomide was stopped and she was followed up at regular intervals. Her disease continued to be in remission during her pregnancy. At 37 weeks of gestation, she had spontaneous vaginal delivery and delivered a normal healthy female baby. She was thus put on close follow up after delivery and her disease continued to be in remission for next five years. In 2017, she again presented with severe anemia and was found to have relapse of Multiple myeloma. She was treated with bortezomib-thalidomide-dexamethasone, VGPR was attained and subsequently thalidomide maintenance was continued. In 2019, her disease again relapsed for which she was initiated on carfilzomib-pomalidomide-dexamethasone and VGPR was attained after 5 cycles. On both the previous occasion, she did not opt for autologous transplant. In June 2022, she again presented with severe anemia and a 3 rd relapse of multiple myeloma was Confirmed. Cytogenetics revealed ultra-high-risk features with detection of IgH rearrangement, TP53 deletion, gain 1q, deletion 1p. She was started on carfilzomib-pomalidomide-dexamethasone, after 6 cycles VGPR was attained which was then consolidated with autologous transplantation. Currently, she is day+350 post HSCT and continues to be in complete remission with MRD negative. **Conclusions:** Infertility is a major concern by ASCT, for reproductive age group. Late ASCT can be considered for young female with myeloma.

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Characteristics, Treatment and Outcome of Patients with Extramedullary Multiple Myeloma or Plasma Cell Leukemia: A Real-World Monocentric Analysis

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Introduction: During the last decade, the prognosis of multiple myeloma (MM) has markedly improved with new treatment options, including next-generation immunotherapeutics. However, MM remains incurable and difficult-to-treat patient groups remain with unfavorable outcome. Soft tissue extramedullary disease (EMD) and plasma cell leukemia (PCL) are representing a clinically high-risk disease where prospective or systematic data on disease course are still very limited leading to significant uncertainty in treatment options. Here, we report our tertiary center experience of patients with EMD and/or PCL, including CNS involvement. **Methods:** We conducted a retrospective study at the University Medical Center Hamburg-Eppendorf. MM pts with radiologically confirmed EMD or confirmed PCL in peripheral blood smear were assessed. PCL was defined with > 20% plasma cells detected in the peripheral blood smear. Data were retrieved from the electronic health records. The cutoff date for follow-up was 31.03.2024. Data concerning pts‘ characteristics, treatment regimens, and outcome variables were analyzed using descriptive statistics. OS and progression-free survival (PFS) were analyzed using Kaplan-Meyer estimates. **Results:** To date, 57 pts with EMD and/or PCL were included in this retrospective analysis, with initial diagnoses from 2002 to 2024. Median age of pts at initial diagnosis was 58 years (y) (IQR, 50-66y). 18 pts (32%) were female, 39 pts (68%) were male. 42 (74%) pts had EMD, 10 (18%) PCL, and 5 (9%) pts EMD+PCL. CNS involvement was the most frequent EMD location occurring in 7 (15%) pts, cutaneous involvement in 6 (13%) pts, and liver involvement in 5 (11%) pts, respectively. Most pts developed EMD (34 pts, 72%) or PCL (9 pts, 60%) at first or further relapse(s). High-risk cytogenetic aberrations at initial diagnosis were identified in 19 (37%) of 52 evaluable pts. International Staging System at initial diagnosis showed stage II in 18 pts (37%) and stage III in 20 pts (41%) of 49 evaluable pts. Overall, pts received more than 30 different treatment regimens. 20 pts received next-generation immunotherapeutics, including CAR T cell therapy and bispecific antibodies. Median OS for pts with EMD at initial diagnosis was 31 mo, and 26 mo from the occurrence at relapse. Median OS for pts with PCL at initial diagnosis was 22.4 mo, and 4.4 mo from the presence at relapse. **Conclusions:** Despite novel treatment options, pts with EMD or PCL still show poor survival outcomes and have an unmet need for new treatment options. With more than 30 different treatment regimens the individual difficult treatment situation but also the lack of systematic data for this difficult-to-treat pt group is reflected. Therefore, prospective studies have a clear unmet need to elucidate optimal management strategies for pts with EMD or PCL.

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Characteristics of Patients and Management of Ocular Adverse Events After Treatment With Belantamab Mafodotin (Belamaf) in Relapsed/Refractory Multiple Myeloma (RRMM): A Real-World Study in Europe

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Introduction: Belamaf is a B-cell maturation antigen-targeted antibody-drug conjugate previously available in the US/EU as a monotherapy for RRMM. Due to the potential for ocular adverse events (OAEs), patients (pts) had eye exams. This EU study examined real-world (RW) evidence on use, effectiveness and safety of belamaf, including management of OAEs. **Methods:** This multinational, non-interventional study included pts with RRMM who received belamaf per approved labeling. The primary objective was to characterize pt demographics and disease characteristics. A key secondary objective was characterization of OAEs, including timing of eye exams and management of OAEs using dose reduction/delay. Other outcomes included treatment discontinuation and effectiveness. **Results:** The 2nd interim analysis (Dec 1, 2023) included 77 pts with >1 administration of belamaf across Italy, Norway, Austria, Spain, Belgium, Germany and Greece. Mean age at diagnosis was 64.0 y (>75 y: n=32, 42%); 56% were female (n=43). Median time from MM diagnosis to 1st belamaf dose was 79.7 mo. Most pts (79%) had >4 prior lines of therapy, which included immunomodulatory agents (99%), proteasome inhibitors (99%), and anti-CD38 monoclonal antibodies (97%); 92% were at least triple-class refractory (missing data: 8% pts). Baseline (pre-index–index date) comorbidities included cardiac disease (32 [42%]), vascular disorders (26 [34%]) and eye diseases (20 [26%]; ongoing [13]: glaucoma, 3 [4%], cataract, 7 [9%] and other, 4 [5%]). Overall, 45 pts (58%) had OAEs, including keratopathy (33 [43%]), change in best corrected visual acuity (6 [8%]), blurred vision (4 [5%]), corneal erosion (4 [5%]) and dry eye (1 [1.3%]). OAEs emerged in 21 pts after 1 belamaf dose, 15 after 2 doses, 6 after 3 doses, 2 after 4 doses and 1 after >5 doses, with keratopathy in 15, 12, 5 and 1 pt after 1 dose (mild: 40%; moderate [mod]: 53%; severe [sev]: 7%), 2 doses (mild: 17%; mod: 50%; sev: 33%), 3 doses (mod: 60%; sev: 40%) and 4 doses (mod: 100%), respectively. Duration of OAEs ranged from 20–260 d; resolution data may be missing if changes to OAEs occurred after data cutoff. Eye exams occurred prior to doses 1, 2, 3 and 4 in 79% (61/77), 77% (49/64), 66% (29/44) and 86% (24/28) of pts, respectively, and in 93% (42/45), 86% (36/42), 81% (25/31) and 96% (22/23) of pts with >1 OAE, respectively. Based on label guidance, OAEs were managed with dose holds in 23 (29%) and dose reductions in 13 pts (17%); 43 pts discontinued treatment, with 7 due to OAEs (mod: 5, sev: 2). Median duration of treatment was 4.2 mo, and 56 pts (73%) had >4 mo of follow-up. Median RW progression-free survival was 3.9 mo. **Conclusions:** OAEs in pts with RRMM receiving belamaf were managed per label guidance with ophthalmic monitoring and dose holds/reductions. Frequency of OAEs was lower than clinical trials (CT), eye exams were less frequent, and many pts continued belamaf while having an OAE. This analysis indicates RW effectiveness and safety of belamaf were consistent with CT data.

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Carfilzomib, Lenalidomide and Dexamethasone (KRD) Therapy Post Autologous Stem-Cell Transplantation (ASCT): Real-World Data in Multiple Myeloma Patients Eligible for Second ASCT

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Introduction: In recent years, treatment options for patients with multiple myeloma (MM) have expanded considerably, providing physicians more choices. For transplant-eligible patients at relapse, salvage autologous stem-cell transplantation (ASCT) is an effective treatment option. One of the most effective regimens currently used for relapsed MM is carfilzomib, lenalidomide, dexamethasone combination (KRD). Evidence suggests that this regimen may be effective in first-line patients when administered as induction before and consolidation after ASCT. Currently, there is a lack of data on the use of KRD in combination with salvage ASCT for treating relapsed MM. **Methods:** In this single-center study, we retrospectively analyzed all patients (≥18 years) who underwent salvage ASCT combined with KRD as induction before and consolidation after salvage ASCT. We compared treatment outcomes with a matched control group of patients treated with salvage ASCT with induction other than KRD. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. **Results:** KRD group included 27 patients: 14 (52%) men, 13 (48%) women; median age 57 years (range 38-66); median ISS 2 (1-3); high-risk genetic abnormalities (t(4;14), t(14;16), t(14;20), del(17p), del(1p) or gain(1q)) were found in 12 (44%) patients; a hyperdiploid karyotype in 6 patients. For first-line treatment, 12 (44%) KRD patients received immunomodulatory (IMiD)-based treatment; 15 patients received IMiD+proteasome inhibitors(PI)-based treatment. Patients received KRD as second-line treatment following ASCT +- KRD consolidation. In the KRD group median time from first ASCT to KRD start was 45 months (range 28-97 months). After KRD+ASCT treatment, 25 (92.6%) patients reached very good

partial response (VGPR) or better response (while before second ASCT >=VGPR was 20/27 (74%)). KRD group's PFS median was 37.00 months (95% CI not reached; 2-year survival – 82.0%) and OS median was not reached (two occurred deaths were related to disease progression).Control group consisted of 30 patients: 15 men and 15 women; median age 57 years (range: 40-67 yrs); median ISS 2 (1-3). For first-line and second-line control group patients received IMiD-based or IMiD+PI-based treatment + ASCT. In the control group, before second ASCT, the >=VGPR rate was 19/30 (63%), and after second ASCT – 22/30 (73.3%). Control group's PFS and OS medians were 28.00 months (95% CI 23.87-32.13) and 51,00 months (95% CI 44.07-57.93). Although the KRD group had better survival rates, the difference between the groups was not statistically significant (PFS p=0.223; OS p=0.449). Compared to ASPIRE study results (where KRD group PFS was 26.3 months), our results are favorable, prolonging PFS by almost 11 months. **Conclusions:** KRD combined with salvage ASCT is an effective regimen, and no new safety challenges were observed in our cohort. Further investigation is warranted.

P-423

Salvage Autologous PBSC Transplantation for tMDS and AML Leads to Remission and Long-Term Disease Control

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Introduction: Multiple myeloma patients are often treated with induction chemotherapy, autologous peripheral blood stem cell (PBSC) transplantation, then maintenance therapy with lenalidomide for disease control. This process improves progression-free and likely overall survival but can result in the development of a therapy related myeloid neoplasm (TMN) typically myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). Survival for those with a TMN is short (~13 months). Over the past 7 years, 5 patients with a TMN who could not undergo allogeneic transplantation were treated with a salvage autologous PBSC transplant using banked stem cells collected prior to their initial transplant. Outcomes for these patients are reported. **Methods:** Five patients with a history of multiple myeloma and a TMN were treated with melphalan 140-200 mg/m2 and the re-infusion of banked stem cells. All patients had either tMDS requiring transfusion support (3 patients) or AML (2 patients). **Results:** All patients engrafted neutrophils and platelets within 21 days. No patient required further transfusion support after this time. One patient succumbed from relapsed multiple myeloma 14 months after transplantation without evidence of MDS. Two patients remain in CR from the TMN and multiple myeloma after 17 months and 7 years respectively. One patient has residual MDS 6 years later with a TMN that lost two adverse cytogenetic features but that no longer requires transfusion support. The final patient recovered normal hematopoiesis but is only 1 month post transplantation. **Conclusions:** The development of a TMN is a devastating event in patients with multiple myeloma after a PBSC transplantation. A salvage second PBSC using stored autologous peripheral blood stem cells after melphalan conditioning has resulted in durable hematopoietic recovery, long-term disease-free outcomes, improved quality of life and in one case a cure of disease. This approach should be considered in these patients.

NURSING SYMPOSIUM ORAL PRESENTATIONS

NSO-01

The Real World Experience of the Incidence, Assessment, and Management of Oral Adverse Events and Weight Loss With Talquetamab Leading to the Development of an Assessment Tool

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Introduction: Talquetamab is a T-cell redirecting bispecific antibody that targets a novel antigen, GPRC5D, on myeloma cells and CD3 on T cells. Data from the MonumenTAL-1 study in patients with relapsed/refractory multiple myeloma (RRMM) support efficacy of talquetamab with overall response rates >71%. Talquetamab is associated with a distinct group of GPRC5D-related adverse events (AEs) including oral AEs (dysguesia, dysphagia, and dry mouth). Oral AEs can limit a patient's intake and lead to weight loss. These particular AEs can greatly effect a patient's quality of life and treatment adherence. Here we aim to describe the real world experience (RWE) of the incidence, presentation, and management of oral AEs and weight loss in patients receiving talquetamab. **Methods:** This retrospective study analyzed data from all RRMM patients who were treated with commercial talquetamab at our center beginning August 31, 2023. Patients who received talquetamab as a part their therapy were identified through the pharmacy's database. Data was abstracted from electronic medical records and data on treatment administration, disease profiles, and toxicities were collected. **Results:** As of May 25, 2024, data from 47 patients was analyzed. Patient race consisted of 47% White, 38% Black and Hispanic, and 4% Asian. Overall, 100% of patients experienced at least one oral toxicity. Among patients with oral toxicity, 98% of patients experienced any grade dysguesia, 61% dry mouth, and 11% dysphasia. One patient discontinued treatment due to oral AEs. Out of the patients who completed at least 3 cycles (N23), 57% of patients had any grade weight decrease of which 69% were grade 1 and 23% were grade 2. Management of oral AEs consisted of dexamethasone/nystatin swish and spit three times a day, artificial saliva, and nutritional consultation for weight management. **Conclusions:** Our RWE from a heterogeneous patient population demonstrates a higher incidence of dysgeusia and weight loss than the MonumenTAL-1 study. Grading the severity of oral AEs was a limitation in this study due to inconsistencies in documentation across practitioners and a lack of a standardize assessment tool for dysgeusia. Based on symptoms observed in our practice we have developed the Sinai dysgeusia evaluation tool (SiDET) that can

identify the impact of dysgeusia and can be applied to evaluate the effectiveness of interventions for dysgeusia and determine if dose adjustments are warranted. Understanding real word incidence of oral toxicities is needed for practical guidance in patient education and symptom management to ensure successful administration and adherence of talquetamab.

NSO-02

An Advanced Practice Provider Consult Clinic is Feasible to Evaluate Patients With Monoclonal Gammopathy of Undetermined Significance (MGUS) And Plasma Cell Disorders (PCDs)

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Introduction: Advanced practice providers (APs) are vital in outpatient clinics in the United States, which continues to extend internationally. Access to specialized hematology/oncology (hem/onc) evaluation of monoclonal gammopathy of unknown significance (MGUS) for clinical significance is critical to patients experiencing unexplained symptoms. However, a lack of provider access can delay a correct diagnosis. With a standardized initial workup and additional training, APs are well-suited to fill this access gap. Thus, we report our experiences to improve patient access to a standardized specialty evaluation of MGUS and collaborative efforts to expedite diagnosis and treatment if necessary. **Methods:** Since 2/2014, outpatient APs with at least 2 years of experience in hem/onc were deemed eligible to see new MGUS patient (pt) consults independently. A standardized procedure and diagnostic algorithms were developed with input from physicians and APs based on international guidelines for the initial workup of patients with MGUS, anemia, or suspected amyloidosis. This algorithm created a care path for all providers to follow in the organization to standardize the initial workup of MGUS. Pts were scheduled to see the AP using the central hem/onc consult schedulers, who reviewed internal and external consult requests for patients who met the criteria for MGUS. APs were required to consult with a physician if any patient had a confirmed monoclonal protein and "red flag" symptoms of hypercalcemia, renal insufficiency, anemia, polyneuropathy, suspicion of amyloidosis, POEMS, demyelinating polyneuropathy, lymphoma, or other hematologic conditions. At our center, two tumor boards were established to collaboratively discuss complex cases in 2018 (PCD) and 2021 (MGUS) and provide education. **Results:** From 1/2014-3/2024, 1,466 unique pts were identified as seen by the AP for an initial consultation of MGUS based on the ICD-10 diagnosis code. All pts were referred for evaluation of MGUS either externally (ext), internally (int), or as a new patient with whom an MGUS or PCD provider had not seen within 2 years. From the initial 5 yrs from 1/1/2014-1/1/2019, 338 patients were seen by 2 APs referred ext (n=29) int (n=268) or new (n=41). For the 5 yrs from 1/2/2019-3/1/2024, 1128 patients were seen by 4 APs referred ext (n=78) int (n=904), new (n=118). An additional 28 patients were seen by a remote virtual visit. From the 398 pts seen in the initial 5-yr period, 1128 is a 183.42% increase. Additional outcomes will be reported later. **Conclusions:** An AP consult clinic is feasible for evaluating patients with MGUS. A standardized workup and collaborative tumor board format allows a team approach to patient care and a forum to discuss best practices in diagnosing and managing MGUS and PCD. Expanding the initial consult model to other APs allowed an exponential increase in patient visits to manage increased patient volumes. Future analyses should focus on the role of virtual visits in this patient population.

NSO-03

Validation of the Steroid Symptom Questionnaire Multiple Myeloma (SSQ-MM) with Concurrent Symptom and Quality of Life Measurement (EORTC QLQ-C30 and MY20)

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Introduction: Steroids, typically included in treatments for multiple myeloma (MM), are associated with significant side-effects. We developed the 20-item Steroid Symptom Questionnaire Multiple Myeloma (SSQ-MM) as a patient-reported outcome measure (PROM) to enable monitoring and management of steroid effects. In pilot testing it demonstrated high levels of feasibility, acceptability, and internal consistency. Here we its further psychometric evaluation. **Methods:** Multi-centre cross-sectional study of 140 MM patients taking dexamethasone as part of treatment >4-mnth since diagnosis recruited from five haematology centres in Australia. Participants completed the SSQ-MM, EORTC QLQ-C30 and MY20 PROMs. The SSQ-MM was repeated 1-week later. Internal consistency reliability was tested with Cronbach's alpha >0.8 for individual patient decision-making. Test-retest using intraclass correlation coefficient >0.7 evaluated SSQ-MM stability reliability. Construct validity was tested with factor analysis and spearman ρ rank-order correlation coefficients for similar domains between the PROMs (high, r > 0.7; moderate, r 0.3-0.7; low, r < 0.3). **Results:** Participants were aged between 38-89yrs (Mean: 69.7, SD: 9.9), 54% male, with an average 4.5yrs since diagnosis (range 4mths to 22yrs). Average dexamethasone dose was 26mg weekly (range 4-80), or 84mg per cycle (range 12-180) and participants had completed an average of 4.0 (SD: 3.0) prior lines of treatment. Internal consistency reliability was high: Cronbach's alpha 0.84, and test-retest indicated SSQ-MM stability (ICC: 0.846). Factor analysis supports a total score reflecting overall symptom bother associated with steroids. Moderate positive correlations were observed between SSQ-MM total scores and MY20 symptom and treatment side-effect scores (r = .466 and .682) providing evidence towards

construct validity. Frequently reported symptoms were disturbed sleep 127/140 (90.7%), fatigue 113/140 (80.7%), and fragile skin/easy bruising 109/140 (77.9%). Patients typically experienced 10 symptoms concurrently (range, 0-19) with four symptoms rated severe (range, 0-12), including: disturbed sleep 91/140 (65 %), fatigue 68/140 (48.6%), and fragile skin/easy bruising 60/140 (42.9%). Longer time since diagnosis (r=0.239; p=0.005), female gender (r=0.194; p=0.022) and higher ECOG (r=0.169; p=0.048) were associated with higher SSQ-MM total scores. Our descriptive findings highlight Social/Role functioning is impacted by steroid use, which in other studies has been shown to correlate with lowered overall QOL. Fatigue, pain, dyspnoea were reported as high; these are consistently the highest reported symptoms reported across MM studies at each phase of disease. **Conclusions:** This study provides evidence in support of the validity and reliability of the SSQ-MM. It is suitable for clinical use to detect steroid toxicity and improve treatment outcomes for MM patients and for use in research settings to assess the impact of steroids in MM.

NSO-04

Evaluation of Clinical Outcomes and Toxicities in Multiple Myeloma Patients Receiving Commercial Talquetamab

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Introduction: Talquetamab (talq) is a GPRC5D bispecific antibody approved for treatment of patients (pts) with multiple myeloma (MM) who have received 4 lines of therapy including an anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulatory agent. In addition to plasma cells, GPRC5D is expressed on keratinized tissue and tongue papillae making these areas vulnerable to toxicity including dysgeusia, skin changes, and onychomadesis previously reported in ~ 50-70% of pts (Chari, A., et al 2022, NEJM). These adverse events (AEs) may decrease the quality of life of pts receiving talq. Subsequently a guideline for the prophylaxis and management of talq AEs was developed by a multidisciplinary team for use at MD Anderson Cancer Center in an effort to avoid and/or quickly identify and manage dermal, nail, and oral talq toxicities by initiating early interventions for prophylaxis and treatment including, lotions, nail strengtheners/oils and zinc supplementation among others. **Methods:** A retrospective chart review to characterize dermal, nail, and oral toxicities of pts with MM who received talq between 11/2023 - 5/2024 for > 28 days was performed using the aforementioned guidelines. AEs were graded using CTCAE v4.03. **Results:** 30 pts who received talq were considered evaluable and included in the analysis. Eighty-two percent experienced skin toxicity, 79% dysgeusia, and 75% dry mouth. Among 22pts with skin AEs, 72% had palmar-plantar erythema, 36% dry skin, and 27% rash. 99% of pts experienced >1 skin toxicity with the majority being Gr 1 except for Gr 2 palmar-plantar erythema (30%) and rash (9%). Onychomadesis occurred in 51.7% of pts of which 85% were Gr 1 and 13.3% Gr2. Dysgeusia was reported by 79.3% of pts among which Gr1 was noted in 77%, Gr 2 in 18%, and Gr 3 in 5%. 22 pts had dry mouth; the majority were Gr 1 (95.5%) or Gr 2 (4.5%) toxicities. 6 pts had dysphagia including 83.3% Gr1 and 16.7% Gr 2 toxicity. Among pts who experienced skin, oral or nail toxicities only 2 required a subsequent treatment delay. Among all pts, 44% had baseline zinc deficiency with a median level of 61.5 mcg/dL (range 60-106 mcg/dL). Further analysis to evaluate median time to onset of toxicities, management strategies, and association with therapeutic response will be presented. **Conclusions:** While most patients reported skin, oral, and nail toxicities during therapy w/ talq, the majority of AEs were < Gr 2 in severity. Only 2 patients required treatment delays and no patients discontinued therapy due to oral, skin or nail associated adverse events. Further investigation of the effect of prophylaxis and early intervention for talq-related AEs with optimization of these measures warrant further study in patients receiving treatment with talquetamab.

NSO-05

Recommendations for Infection Screening and Prophylaxis for Bispecific Antibodies in Myeloma: A Single Center Analysis

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Introduction: Multiple myeloma (MM) is associated with an increased risk of infections. The risk of infections is variable and related to tumor burden, underlying comorbidities, and treatments used. Three bispecific antibodies (BsAbs), teclistamab-cqyv (Tec), elranatamab-bcmm (Elra), and taqluetamab-tgvs (Talq), have been granted accelerated approval by both the FDA and EMA for the treatment of patients with relapsed/refractory multiple myeloma (RRMM). In the clinical trials for approval, patients that were treated with BsAbs had significantly higher rates of infection. Infectious complications related to the use of BsAbs are not well described. Recommendations for infectious screening and prophylaxis can be variable; therefore, we implemented an institutional protocol to screen all BsAbs patients for infections and the use of prophylactic antimicrobials. **Methods:** All patients receiving BsAbs at our institution received antiviral prophylaxis and pneumocystis jiroveci pneumonia (PJP) prophylaxis at the initiation of therapy. Monthly IVIG was started on cycle 2 of therapy (after the step-up dosing). CMV viral load was monitored on day 1 of each cycle. We conducted a pooled analysis that included all BsAbs used in MM at our institution (Tec, elra, talq). We assessed the frequencies of grade 3-4 neutropenia (absolute neutrophil count < 1.0× 103/mL), infections, CMV reactivation, and hypogammaglobulinemia.

Results: From 9/1/2023 until 3/31/2024, 142 patients received BsAbs treatment at our institution. Median age for BsAbs was 68 years, 50% were male, 47% were African American, and patients had received a median of 5 prior LOT. 39% of patients had received prior BCMA therapy. Overall, 30% of patients treated with BsAbs experienced an infection during therapy. Of the 142-patients treated 25% had CMV reactivation; no patients were admitted for CMV treatment or complications. Infection rates were lowest in patients treated with taqluetamab (23% all cause infections and 16% CMV reactivation) compared to teclistamab (30% infections and 22% CMV reactivation) and elranatamab (45% infections and 55% CMV reactivation). 60% of patients were receiving concomitant monthly IVIG. Grade 3 neutropenia (ANC < 1000) occurred 57% in patient treated with teclistamab, 44% with taqluetamab and 41% with elranatamab. One patient developed zoster and no patients develop PJP. **Conclusions:** In our analysis the prevalence of all grade infections was 30% which is lower than reported in the clinical trials that led to approval of BsAbs for MM. The routine monitoring of CMV allowed for early diagnosis and management resulting in no hospitalizations or death associated with CMV. Under our protocol BsAbs dose frequency was decreased in a treatment response which likely helped with immune reconstitution resulting in fewer infections. The implementation of antimicrobial prophylaxis and IVIG infusions may decrease the risk of infectious complications and should be added to institutional protocols.

NSO-06

Protocol for Outpatient Administration of Multiple Myeloma Bispecific Antibodies Step-Up Dosing

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Introduction: Teclistamab (Tecvayli®), elranatamab (Elrexfio™), and taqluetamab (Talvey™) are T-cell redirecting bispecific antibodies (BsAbs) that gained accelerated approval for the treatment of patients with relapsed/refractory multiple myeloma (RRMM) who have been treated with 4 prior lines of therapy (LOT) by FDA and with 3 prior LOT by EMA. All 3 BsAbs have a REMS program due to the risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The package inserts support hospitalization to receive the initial step-up doses for CRS and ICANS monitoring. In an effort to transition administration of BsAbs to outpatient (OP) setting, thereby minimizing hospitalization and reimbursement burdens, we implemented an institutional protocol to deliver step-up and target doses in the OP setting. **Methods:** Eligible patients must stay within 30 minutes of the Immediate Care Center (ICC) and have a 24-hour caretaker until 48 hours after the receipt of the target dose of the BsAb. Patients did not qualify for OP step-up dosing if they had known significant disease burden, circulating plasma cells, prior history of CRS or ICANS or poor performance status. Step-up doses were administered on days 1, 4 and 8 of the step-up dose cycle preceded by acetaminophen, diphenhydramine, and dexamethasone before each dose. All patients received prophylactic tocilizumab prior to dose #2 per institutional protocol. From initiation of step-up dose #1 until 48-hours after the target dose, patients monitored temperature every 8 hours or in the setting of new CRS symptoms, and for signs of ICANS. If fever or neurologic change occurred, patients took dexamethasone 20 mg, diphenhydramine 50 mg and acetaminophen 650 mg and were instructed to present to the ICC for toxicity assessment and management. **Results:** From 9/1/2023 to 3/31/2024, 41 patients received OP BsAb step-up dosing. During the same time, 42 patients received inpatient BsAb. The median age for OP BsAb was 62 years (range, 38-81), 54% were male, 44% were African American, and patients had received a median of 4 prior LOT (range, 3-9). Overall, 6 patients (15%) experienced CRS (four grade 1, one grade 2 and one grade 3) and 1 patient (2%) experienced ICANS (grade 1). Three patients (7%) required hospitalization for toxicity management (1 for grade 3 CRS and grade 1 ICANS, 1 for grade 2 CRS, and 1 for grade 1 CRS). The median time of hospitalization was 7 days (range, 6-15). The other 3 patients were treated with tocilizumab in the ICC and discharged home with symptom resolution. All patients recovered from CRS and ICANS without additional toxicity. **Conclusions:** Implementation of this OP protocol to administer BsAbs is feasible and minimized the risk of CRS, ICANS and hospitalizations for step-up dosing. The low incidence of CRS (14%) and ICANS (3%) with prophylactic tocilizumab and premeds and the low hospitalization rates make this appealing for selected RRMM patients and likely can be adopted to larger practices.

NURSING SYMPOSIUM POSTER PRESENTATIONS

NSP-01

Nursing Considerations for Young Adults with Multiple Myeloma, an Institutional Review

Carrie Bellerive[1], Charlotte Wagner[1], Kelley Julian[1], Tiffany DeHemmer[1], Emily Doxey[1], Samuel Shewan[1], Steven Bleak[1], Meghan Vigil[1,2], Linsday Maxwell[1,2], Eliza Parkin[1,2], Amandeep Godara[2], Brian McClune[2], Douglas W. Sborov[1], Mary Steinbach[1,2]

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Introduction: Multiple myeloma (MM) commonly affects older adults, with a median diagnosis age of 69. Younger adults with MM (YA MM) face a shortened life expectancy along with significant impacts on career, fertility, and quality of life. Understanding and tailoring supportive care for this group is crucial to improving outcomes.Our insitute analyzed data from YA MM patients to identify areas for improvement. **Methods:** Patient data was exported from the EHR and included patients under 50 diagnosed with MM or plasma cell leukemia.Patients diagnosed with amyloid,MGUS, or SMM were excluded.The presence of t(4;14), t(14;16), t(14;20), del(17p), p53 mutation, 1p deletion, or 1q21 defined high-risk cytogenetic disease. Data regarding referral to supportive care services were

analyzed. Specifically, social work notes were reviewed for mentions of distress, financial toxicity, transportation needs, or survivorship support. **Results:** We identified 155 YA MM patients, of which 37% were female. The majority (72%) were aged 41-49 years, with very few (2%) < 30 years. Most patients (59%) had standard-risk disease, 19% had high risk, and the rest were undefined. Nearly half (42%) sought social security disability. Referrals included: reproductive counseling (15%), fertility preservation (9%), pain specialists (23%), wellness center (17%), physical therapy (28%), nutrition counseling (5%), financial counseling (8%), sleep medicine (8%) and psychiatric care (2%). Social work referrals included counseling on Advance Directives (3%), depression, anxiety, or distress (7%), and transportation assistance (19%). **Conclusions:** YA MM patients in our cohort are predominantly male and fall within the age range of 41-49 years, with a significant proportion having standard-risk disease. This aligns with existing literature on YA MM patients. Many patients sought disability services, underscoring the disease's severe impact on the daily functioning and financial stability in this population.In general, referrals for reproductive counseling, physical therapy, nutrition support, pain management, and psychiatric care were low. Areas of improvement for comprehensive care for the YA MM population include proactively assessing risks for impaired fertility, promoting the completion of medical power of attorney and living wills, and increasing awareness and referrals for psychiatric care and counseling services early on in the MM disease course, to more robustly address the psychological impacts of the disease. In addition, implementing referrals to AYA-specific support groups align with the NCCN AYA guidelines.This retrospective review may lead to missing information, potential selection bias, and possible data entry errors, which are limitations. YA MM patients encounter unique challenges that necessitate a multidisciplinary approach to care. Enhancing early awareness and timely referrals to appropriate support services can significantly improve this vulnerable cohort's quality of life and overall well-being.

NSP-02

Real World Experience of Talquetamab Administration and the Prevalence and Management of Associated Dermatological Toxicities

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Introduction: Talquetamab is a T-cell redirecting bispecific antibody that targets a novel antigen, GPRC5D, on myeloma cells and CD3 on T cells. Data from the MonumenTAL-1 study in patients with relapsed/refractory multiple myeloma (RRMM) support efficacy of talquetamab with overall response rates >71%. Talquetamab is associated with a distinct group of GPRC5D-related adverse events (AEs) including dermatologic (skin and nail) AEs. Here we describe the presentation and management of dermatologic AEs in patients treated at a single center. **Methods:** This retrospective study analyzed data from all RRMM patients who were treated with commercial talquetamab at our center beginning August 31, 2023. Patients who received talquetamab as a part their therapy were identified through the pharmacy's database. Data was abstracted from electronic medical records and data on treatment administration, disease profiles, and toxicities were collected. **Results:** As of May 25, 2024, data from 47 patients was analyzed. Patient race consisted of 47% White, 38% Black and Hispanic, and 4% Asian. Overall, 70% of patients experienced at least one dermatological AE. Skin related AEs were further evaluated into hand/foot exfoliation, pruritus, and dryness. Among patients with skin related AEs, 62% of patients experienced any grade dryness, 26% pruritus, and 30% hand/foot exfoliation. Thirty percent of patients experienced a nail event. No patients discontinued treatment due to dermatological AEs. Management of dermatologic AEs included use of a heavy moisturizer for general dryness; ammonium lactate 12% lotion twice daily (BID) for hand and foot peeling; loratadine 10-mg oral tablet daily for 3-5 days post-dose and triamcinolone 0.1% cream BID for pruritus, injection site reaction, and rash; and use of nail hardeners, topical vitamin E oil, and triamcinolone 0.025% ointment for nail thinning and peeling. **Conclusions:** Our real world experience from a heterogeneous patient population demonstrates a high prevalence of dermatological AEs. Grading the severity of dermatological AEs was a limitation in this study due to inconsistencies in documentation across practitioners and warrants a more unified approach to documenting and grading AEs. Talquetamab is an effective therapy for patients with RRMM. Skin and nail AEs are common but manageable with no discontinuations at our institution. Appropriate management, education, and supportive care ensures patients can stay on treatment to receive optimal benefit from talquetamab.

NSP-03

Real-world Experience in Treating MM and Amyloidosis Patients with Teclistamab and Talquetamab in the Private Setting in the UK

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Introduction: The commencement of a new therapeutic regimen, hitherto confined to clinical trials in the UK, instigates both anticipation and challenges in the management of associated side effects and patient expectations. At present we have a cohort of 20 patients whom have started these new BioSpecifics treatments. The cohort exhibited an average age of 63 years at the commencement of the treatment. The patient distribution included 13 males and 7 females, all diagnosed with MM and AL for an average duration of six years. This study was undertaken with the principal objective of examining patient knowledge about these novel drugs, with focus on understanding how the treatment information was delivered, retained, and understood. Administering these novel drugs comes with challenges in providing clear and accurate information to patients whilst ensuring its accessibility and understanding. For our group of patients, the information was provided via clinic appointments with the consultants, 1:1 nurse conversation, and

through support group. A survey was created to assess patient comprehension and their preferred methods of receiving the information necessary to provide informed consent to commence these treatments. **Methods:** Collection from the patient electronic health records (EPIC). An online, questionnaire designed by the authors via Microsoft Forms. This questionnaire surveyed MM/AL patients who received these novel drugs (undergoing survey). **Results:** The survey will be sent to all MM and AL patients that continue to visit our centre who have received treatment here with Teclistamab and Talquetamab. If we consider past surveys we have undertaken and bearing in mind the small number of patients and their frequent monitoring, we anticipate a high participation rate of >80%. Since the first treatment commenced very recently in April 2023, and with a continued increase in patients starting these drugs, we expect to add more patients by the time the survey is completed. Although we haven't yet collected the data, our survey will take place from start of July 2024 ongoing, and data will be analysed prior to September 2024. **Conclusions:** Although we don't have results, we anticipate that this analysis offers a distinct opportunity to investigate the administration of these new drugs outside the confines of clinical trials, namely how the patients received the pre-treatment information and their preferred education method. The survey will analyse whether patient comprehension, and retention of information was sufficient to prepare them for treatment admission and if education was sufficiently delivered, as well as an insight into the quality and understanding of education provided regarding treatment side effects. As the landscape of treatment options broadens and life expectancy increases for this patient group, there is a discernible need for tailored and specialized care.

NSP-04

Patient Perceptions When Receiving Talquetamab for Triple Class Exposed Relapsed/ Refractory Myeloma: A Thematic Analysis

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Introduction: Talquetamab is a bispecific T cell antibody targeting GPRC5D/ CD3 and is approved for patients with relapsed and refractory multiple myeloma (RRMM). Whilst it has significant efficacy, patients experience on target off tumour toxicities affecting the mouth, skin and nails. Quality of life (QOL) data is limited to the MonumenTal 1 trial with global and myeloma specific patient reported outcomes. We therefore aimed to characterise the real world patient experience to improve the quality of our service. **Methods:** Qualitative semi-structured interviews were performed at a single time point on a sub-group of patients with RRMM treated with Talquetamab through a named patient programme at a single institution between July 2023- May 2024. Interviews were performed by a Clinical Nurse Specialist (CNS) with questions centred around experiences of treatment, support received, aspirations of patients before being treated and effect on quality of life. Data was analysed using a Braun and Clarke's thematic analysis approach from recordings of telephone or in person interviews. Themes were generated and grouped prior to analysis. **Results:** 9 patients participated in interviews (5 male, 4 female; 6 White, 2 Black, 1 Asian) at a median of 9 months from treatment.Themes identified included physical side effects, effects on QoL and psychological effects. 33% reported that Talquetamab had improved their quality of life and 45% felt that the treatment gave them hope for the future and might improve their overall outcomes. 33% found the subcutaneous administration convenient, allowing them to continue with their usual activities of daily living.Common side effects identified included nail changes (89%) dysgeusia (67%), skin changes (89%) and weight loss (45%), similar to trial reported outcomes. 67% of patients felt that the supportive therapy received concomitantly with Talquetamab ameliorated symptoms. 56% of patients experienced anxiety around social events due to difficulty eating, and 33% developed low mood due to physical effects. 22% of patients felt socially isolated due to changes in their physical appearance, whilst 22% felt they would benefit from better dietician support.Overall, patients felt they received adequate support from clinicians and in particular the CNS teams which significantly improved their overall experience. 67% of patients felt they had received appropriate information prior to commencing Talquetamab but 33% did not feel prepared for the side effects. **Conclusions:** Talquetamab was able to bring hope and improve QOL in patients with no other treatment options. Side effects were a major reported theme; however supportive medications and particularly CNS input were beneficial to coping strategies. This data serves to highlights the needs for patients receiving Talquetamab.

NSP-05

Are Participants of Myeloma Trials Representative of the Patient Population? Audit Data From a Large Haematology Centre in the UK

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Introduction: Multiple myeloma (MM) is a haematological malignancy characterised by clonal proliferation of plasma cells. Despite advancements in treatments, data suggests disparities in outcomes for patients diagnosed with MM relative to socioeconomic status and ethnicity. Disparities in access to clinical trials has also been demonstrated relative to these factors. Multiple myeloma disproportionately affects people from Black ethnic backgrounds. However, patients participating in clinical trials, including those leading to approval of new therapies, are disproportionately white. This underrepresentation raises concerns about the generalisability of trial findings. There are currently no large data sets published from the UK demonstrating trial participation of MM patients. This study aimed to assess whether patients with MM are fairly represented in clinical trials, within the context of a large research hospital in the National Health System (NHS) in England. **Methods:** An audit of retrospective data from an Electronic Health Record system for MM patients treated at a single site between February 2020 &

November 2023 was performed. Patients who received standard of care (SOC) treatment were compared to those treated on a clinical trial. Statistical analysis was performed with RStudio v4.3. **Results:** Our dataset included 1,059 patients, of which 16% were treated in a clinical trial. Logistic regression analysis of sex and ethnicity showed white patients were 2.5 times more likely to participate in a clinical trial than non-white patients ($p< 0.001$). No significant differences were observed relative to sex (odds ratio=1.02, p=0.92). Median age was comparable between SOC (63 years, IQR: 56-70) and trial cohorts (63 years, IQR: 56-69). Index of Multiple Deprivation was slightly greater for trial patients (7, IQR: 4-9) compared to SOC patients (6, IQR: 3-8), suggesting patients participating in a clinical trial may be more affluent. **Conclusions:** Findings support existing literature that patients recruited to MM clinical trials may not be reflective of the patient population. The observation of these issues for patients treated within the NHS demonstrates this issue may persist in countries with free access to healthcare. Underrepresentation in clinical trials is a concern as it may lead to results that are not generalisable to the broader patient population, ultimately compromising patient safety and outcomes.

NSP-06

Self-Administration of Subcutaneous Bortezomib in the Home Setting: A Feasibility Study

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Introduction: Bortezomib-based regimens for patients with multiple myeloma (MM) are administered in cancer day units (CDU), requiring repeated travel to the hospital once or twice weekly. In addition to high health care costs associated with therapy, travel adds to the financial and treatment burden experienced by the individual and family. Patients and carers in regional New South Wales Australia, reported anxiety provoked by frequency of hospital visits, waiting times, travel and parking. This study examined the feasibility, safety and acceptability of a new model of care (MOC) enabling patients to self-administer subcutaneous (SC) bortezomib at home, supported by guidelines, educational resources, competency tools, telehealth tools, and safety protocols. **Methods:** Twenty-three MM patients participated in a prospective mixed-methods study. Patients or caregivers underwent an education period and competency assessments before home administration. Patients were observed self-injecting on day 1 of each subsequent cycle to monitor technique, receive any intravenous therapy, and dispense medications including remaining bortezomib for the cycle. Subsequent injections were monitored via telehealth. Patient experiences were explored through patient reported experience measures, CDU appointment survey and a MOC survey. Semi-structured interviews were conducted with 8 patients. Costs were analysed for bortezomib manufacture, time burden data, chair time and staffing. Pre- and post- Self-Injection Assessment Questionnaires (SIAQ) were completed at baseline, week 1 and week 4. Safety and efficacy were evaluated using pathology results and self-injection adverse event (AE) reports. Neuropathy assessment was completed using PRO-CTCAE items and FACT- NTX13. Staff acceptability was explored using a survey. **Results:** Patients ranged from 50 – 87 years, with 81% male and 57% on their first line of therapy. Twenty-one patients completed the study. SIAQ satisfaction scores showed significant improvement over time (baseline vs T1, $p = 0.0046$; vs T4, $p = 0.0139$). The only AE reported was a needle-stick injury during self-injection. The self-administration model required 30 minutes of the patient's time per week compared to 1-3 hours in the CDU. Interviews revealed that the self-administration program significantly improved patients' daily lives, with time savings the most frequently reported benefit. Cost analysis indicated higher expenses for CDU-administered bortezomib ($308 per cycle) compared to self-administration ($216 per cycle). **Conclusions:** Self-administration of SC bortezomib is a safe and feasible option for patients with MM in a regional setting. There is a high level of satisfaction from patients and carers. This model reduced the treatment burden, allowing patients and families to dedicate more time to meaningful activities and rest. The comprehensive design of the MOC is potentially transferable and adaptable to other drugs and tumour streams.

NSP-07

Patient Reported Outcome Measures in Routine Haematology Cancer Care: A Scoping Review

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Introduction: Background: Haematological cancers can have devastating effects on patients' physical, emotional, and psychosocial health. With improvements in therapies, patients are living longer. There is growing evidence to support the use of Patient Reported Outcome Measures (PROMs) in capturing cancer care sequel as they measure a patient's perception of their own health status and needs through validated tools. While PROMs are widely adopted in oncology, it is felt that uptake in haematology remains limited in routine clinical care. Objective: This scoping review seeks to explore and identify the utility of PROMs in routine haematology clinical practice and to understand the extent and type of evidence in relation to benefits of PROMs to patients. **Methods:** This review was conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews and the Preferred Reporting Items for Systematic Reviews and Meta analysis scoping review model for organising information. **Results:** Initial searches identified 10,071 papers, 110 full texts were reviewed and 14 papers that met the final inclusion criteria were included in the review. Over 20 individual outcome measures were identified that fell into the following categories: accessibility and usability, self-efficacy, shared decision making and implementation. **Conclusions:** The studies focused on the perceived benefits of adopting PROMs within routine haematology care: the choice of PROM, acceptability and usability, motivation for use, patient and health care professionals'

experience of using PROMs, the stated value of the PROM and implementation advice. However, there are limited published studies supporting how PROMs can be meaningfully adopted into the routine care for people with haematological cancer to impact clinical and patient outcomes. Implications for Practice: While numerous validated PROMs exist, there is a pressing need for the application of implementation science methodologies in integrating PROMs into routine care for hematologic cancer patients, to enhance the quality of care delivered.

NSP-08

UK Pharmacist Prescribing Practice: Results of UKMS Pharmacy Survey

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Introduction: Haematology services in the UK are under increasing pressure due to increased demand and difficulties in recruiting haematologists. In addition, there has been a significant increase in the number of drugs approved in myeloma with the majority of these continued until progression. The British Society of Haematology Annual Scientific meeting 2023 highlighted workforce issues and the use of allied healthcare professionals to deliver novel models of care to address this. The UKMS (UK Myeloma Society) Pharmacy group conducted a survey to understand the extent and nature of pharmacist prescribing within the UK myeloma setting **Methods:** Pharmacist Independent Prescribers (PIPs) working within Myeloma clinics in the UK, were invited to complete an MS (Microsoft™) Forms survey (31 questions), exploring the scope and nature of their practice including barriers and enablers. Several questions were "select all that apply". **Results:** 27 PIPs responded. All respondents worked in NHS (National Health Service) trusts. The mean duration of time worked in the myeloma outpatient setting was 3.4 years (range < 1-10). Training: all respondents are qualified PIPs. Additional training undertaken included communication skills (22%), ordering imaging (11%), clinical skills (11%) and in-clinic training (7%). Clinic models: various models have been implemented; these included consultant-led (n=20), pharmacist-led (n=8) and joint nurse and pharmacist clinics (n=2). Consultation type varied with respondents reporting undertaking telephone reviews, face to face or a combination of both. Clinic capacity: most respondents are carrying out one clinic per week with frequency ranging between less than weekly to more than 3 clinics per week. The mean number of patients reviewed in each clinic was 7.1 (range 2 to 14). Clinical activity: 19 respondents reviewed all patients irrespective of the treatment regimen. 7 reviewed follow-up patients on treatment, 13 reviewed follow-up patients on or off treatment and 2 also reviewed new patients. Other roles undertaken included delivering bad news (56%), consenting patients for systemic anticancer therapy (SACT) (22%), completing Blueteq requests (30%) treatment break forms (37%), attending MDT (74%) and counselling patients on SACT (93%). Barriers: Of those who experienced barriers, the most common number of barriers faced was two (1-5). The most commonly cited barrier was "lack of room capacity" (n=7) followed by "no allocated time in job plan" and "no funding to backfill pharmacy role" (n=6). Only 2 PIPs cited a "lack of clinical engagement" as a barrier. **Conclusions:** Pharmacists are an integral part of the Myeloma Outpatient MDT reviewing and prescribing for a wide range of patients and undertaking extended roles. Reassuringly, clinician engagement is more commonly an enabler rather than barrier to PIPs working in clinic. This demonstrates that, with appropriate investment and training, specialist pharmacists can expand capacity within myeloma clinics.

NSP-09

The 5E Management Program: A Holistic Approach to Enhancing Recovery and Satisfaction in Multiple Myeloma Patients

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Introduction: Multiple myeloma (MM) is a malignant disease characterized by plasma cell proliferation, leading to significant morbidity and mortality. The 5E management program, an innovative rehabilitation model, has been introduced to improve patient outcomes through a comprehensive care approach. This program includes Encouragement, Education, Exercise, Employment, and Evaluation, aiming to establish positive cognitive patterns and promote effective disease management and health behaviors.The study aimed to evaluate the impact of the 5E management program on the clinical outcomes, psychological well-being, and satisfaction levels of MM patients. **Methods:** A total of 220 MM patients admitted between January 2017 and December 2022 were randomly assigned to either the observation group (110 patients) receiving the 5E management program or the control group (110 patients) receiving conventional care. The 5E program involved daily empowerment education during hospitalization and continuous support via WeChat groups post-discharge. Health education was personalized and multifaceted, enhancing patient understanding and engagement in their treatment. **Results:** The 5E management program significantly reduced the average length of hospital stay from 16.2 days to 11.8 days (P=0.025). The incidence of complications such as pulmonary infections, fractures, and lower extremity deep vein thrombosis was markedly lower in the 5E group compared to the control group (P=0.005). Anxiety and depression scores were significantly reduced in the 5E group post-intervention (P=0.018). Patient satisfaction with nursing care was higher in the 5E group (P=0.021). Additionally, physician satisfaction with nursing work was significantly higher in the 5E group (99.1%) than in the control group (88.4%) (P=0.013). Patient satisfaction with nursing work was also significantly higher in the 5E group (98.5%) compared to the control group (86.2%) (P=0.001). **Conclusions:** The 5E management program offers a comprehensive and effective approach to the care of MM patients, leading to improved clinical outcomes, reduced hospital stays, lower complication rates, and enhanced satisfaction.

NSP-10

Improving Diagnosis of Myeloma in the UK: The Power of Multidisciplinary Collaboration

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Introduction: For many individuals the journey to a myeloma diagnosis is not straightforward and often delayed compared to other cancers. In the UK, the median interval from initial symptom presentation to diagnosis is 163 days, with 31% of myeloma patients diagnosed via an emergency route. These diagnostic delays, present in both primary and secondary care settings, are associated with more advanced disease and poorer patient outcomes. Seven years ago, Myeloma UK established an early diagnosis steering committee to lead and facilitate the collaborative efforts required to tackle late diagnosis. **Methods:** The Myeloma UK Early Diagnosis Steering Committee is comprised of an expert panel including consultant haematologists, immunologists, clinical scientists, clinical nurse specialists, general practitioners (GPs), and academic researchers. The committee's overarching goals are to raise awareness, provide education, and enhance the consistency of current practices. **Results:** In both primary and secondary care, knowledge about the appropriate diagnostic tests, access to rapid diagnostics and interaction between the clinicians and laboratory teams when significantly abnormal results are found, are key in reducing diagnostic delays. For GPs, we developed a Myeloma Diagnostic Tool: Guidance for Primary Care that lays out the signs and symptoms of myeloma and the tests to request. It uses a traffic light system to guide GPs on the interpretation of test results and referral. A survey reported that, thanks to the tool, 95% of GPs felt more confident recognising the signs of myeloma and 87% more confident in interpreting myeloma test results. Other educational initiatives created by the group for GPs were a guide on myeloma, MGUS and related conditions, an MGUS patient diary and an e-learning module on monitoring MGUS. To disseminate the above resources, GP information packs were sent out across the UK - targeting practices with a higher percentage of black patients and highlighting the inequalities experienced by black patients in the cover letter. Considering the whole diagnostic pathway, anecdotal evidence suggested inconsistent laboratory practice for diagnosing myeloma, confirmed by a survey conducted through the committee in 2017. Consequently, the laboratory best practice sub-group developed a monoclonal gammopathy laboratory tool which set out guidelines for laboratory staff. In 2023, we collaborated with the Association for Laboratory Medicine on an international audit. The results highlighted areas of good practice and areas for improvement. These findings benchmark current practice and a planned future audit will be used to assess the impact of the laboratory tool. **Conclusions:** Collaboration between Myeloma UK and various expert groups has produced a wide array of respected educational resources and practical tools, a few of which are highlighted above. This multidisciplinary approach is invaluable in addressing complex issues that can lead to a delayed diagnosis of myeloma.

NSP-11

Predictive Factor for Higher Level of Preferences for Cure and Survival in Myeloma

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Introduction: Studies have shown that myeloma treatment decision preferences and risk tolerance vary between patients, with preference patterns differing by certain patient characteristics. **Methods:** We conducted a secondary analysis of our database on preferences for cure and survival and examined sociodemographic features that are correlated with higher level of preference for cure and survival among patients with symptomatic myeloma. One hundred seventy-four (N = 174) patients diagnosed with MM within the network of International Myeloma Foundation online patient support groups across the United States were included in this secondary data analysis. **Results:** The sample is homogeneous in terms of race (mostly white) and marital status (most were partnered or married), which precluded these factors from the analysis. We hypothesized that younger age, higher income, and higher education level will be strong factors for higher preference for cure and overall survival based on preliminary findings from a prior study. We created dichotomous groupings for age, income, and educational level to gain statistical power to detect differences between two groups. The grand mean scale score for the entire sample was 7.47 (SD=1.83). The adjusted score of the less than bachelor's degree group was 8.26 (95% CI = 7.58–8.94) while the adjusted score for the bachelor's degree or higher was 7.28 (95% CI = 6.94–7.61). We found that this difference is substantial given the difference between groups is more than half of a standard deviation difference in terms of the outcome, and the less educated group is .43 SD above the grand mean. Post-hoc tests showed neither of these adjusted scores is statistically significant from the grand mean but there is a significant association between less than bachelor's education level and higher cure/survival preferences scores (p=0.01). **Conclusions:** A bachelor's degree and higher were more likely to score lower on the 5-item scale than their less educated counterparts. Age and income were found to have no impact on cure and survival preferences. These novel findings merit additional research to strengthen their generalizability.

NSP-12

The Impact of an Advanced Clinical Practitioner Role in Myeloma on Service at a Tertiary Haematology Centre: An Exploratory Case Study Analysis

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Introduction: Although well established in other countries, the advanced clinical practitioner (ACP) role remains a relatively new role in the UK (Mann et al 2023). The variation in role was

further explored in a recent national review, recommending it become a regulated level of practice within the UK (The Nursing and Midwifery Council 2024). A key benefit of the role is that of enhancing capacity and capability within multiprofessional teams (Evans et al 2020). A high level of critical thinking and the ability to make complex, safe, autonomous decisions is essential (Woodman 2022). In order to do this it is important that the ACP is working to their full potential within their scope of practice (Hook and Walker 2020). In 2019, the first trainee ACP post was implemented locally in one of the largest haematological centres in the UK. This study aimed to review the impact of the role on patient flow and capacity whilst understanding the perceptions of clinical and non-clinical roles within the myeloma specialism around the role of the ACP. **Methods:** A single centre study collected data over a period of 12 months quantifying outpatient appointments conducted by the ACP. In addition an electronic questionnaire was developed. Questions were aimed at identifying frequency of contact with the ACP, understanding of the role and perceptions of the impact of the role on service delivery. Target participant groups included Consultants, Registrars, Physician Associates, Clinical Nurse Specialists, ward nurses and administrative staff. Data was analysed using thematic analysis. **Results:** The ACP reviewed a total of 615 patients in the outpatient setting over a 12 month period, 100 of which were new referrals with suspected myeloma or MGUS. 16 survey responses were received (40% completion rate). Responses were categorised via thematic analysis in to 7 identified themes – support, continuity, safety, enhanced capacity, clinical skills, service development and knowledge. 93.75% of respondents worked directly or indirectly with the advanced clinical practitioner. 93.75% of respondents felt they understood the advanced clinical practitioner role, however responses largely focussed on clinical skills with only 3 respondents exploring non clinical aspects of the role (research, education and leadership). **Conclusions:** The role of the advanced clinical practitioner has proven to be of significant value in supporting patient care (Fowler 2018). This study suggests that locally the role has had a significant impact on capacity and patient flow, providing support to the wider multidisciplinary team. The work highlights the benefit of the advanced clinical practitioner role in myeloma, however it is proposed that further education is needed amongst the multidisciplinary team to ensure full understanding of the role.

LATE BREAKING ABSTRACTS

OA-63

Daratumumab + Bortezomib/Lenalidomide/Dexamethasone in Patients With Transplant-ineligible or Transplant-deferred Newly Diagnosed Multiple Myeloma: Results of the Phase 3 CEPHEUS Study

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Introduction: Daratumumab (DARA) has improved overall survival (OS) in 3 frontline regimens and was the first anti-CD38 monoclonal antibody approved in newly diagnosed multiple myeloma (NDMM). For transplant-ineligible (TIE) NDMM, the MAIA regimen (DARA + lenalidomide/dexamethasone [D-Rd]) is a standard of care (SOC), with a median OS of 7.5y. For transplant-eligible NDMM, the PERSEUS regimen (subcutaneous DARA [DARA SC] + bortezomib/lenalidomide/dexamethasone [D-VRd]

then D-R maintenance) has shown significant progression-free survival (PFS) benefit vs SOC. The CEPHEUS study evaluated the addition of DARA SC to VRd vs VRd in NDMM patients (pts) who are TIE or for whom transplant was not planned as initial therapy (transplant deferred). Here we report for the first time the results of the CEPHEUS study. **Methods:** Pts were aged ≥18y with TIE or transplant-deferred NDMM. All pts received eight 21-day cycles of VRd, followed by 28-day cycles of Rd until progressive disease (PD). Patients randomized to D-VRd received DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) given QW in Cycles 1-2, Q3W in Cycles 3-8, and Q4W in Cycles 9+ until PD. The primary endpoint was overall minimal residual disease (MRD)-negativity (neg) rate (10^{-5}), among pts achieving complete response or better (≥CR). Secondary endpoints included ≥CR rate, PFS, and sustained MRD-neg rate (≥12 months [mo]). **Results:** 395 pts were randomized 1:1 (D-VRd, n=197; VRd, n=198). Median age was 70 (range, 31-80) y; 28.1% had ISS stage III disease; 13.2% had high-risk cytogenetics (t[4;14], t[14;16], or del[17p]). At a median follow-up of 58.7 mo, the overall MRD-neg rate was 60.9% for D-VRd vs 39.4% for VRd (OR, 2.37; 95% CI, 1.58-3.55; P< 0.0001). PFS was significantly improved with D-VRd vs VRd (HR, 0.57; 95% CI, 0.41-0.79; P=0.0005). Median PFS was not reached for D-VRd vs 52.6 mo for VRd; estimated 54-mo PFS rates were 68.1% vs 49.5%. ≥CR rate was 81.2% with D-VRd vs 61.6% with VRd (P< 0.0001) and sustained MRD-neg rate was 48.7% vs 26.3% (P< 0.0001). OS trended in favor of D-VRd (HR, 0.85; 95% CI, 0.58-1.24); HR was 0.69 (95% CI, 0.45-1.05) in a sensitivity analysis censoring deaths due to COVID-19. Median treatment duration was 22 months longer for D-VRd (56.3 mo) vs VRd (34.3 mo). Addition of DARA did not affect relative dose intensity of VRd. TEAEs were consistent with known safety profiles for DARA and VRd. Grade 5 TEAE rates adjusted for treatment exposure were comparable for D-VRd and VRd (0.39 vs 0.31 per 100 pt-mo). **Conclusions:** In pts with TIE or transplant-deferred NDMM, DARA SC + VRd significantly improved PFS vs VRd, reducing the risk of progression or death by 43%. D-VRd significantly increased overall MRD negativity, ≥CR rate, and sustained MRD negativity. These data, coupled with PERSEUS, demonstrate the consistent benefit of DARA + VRd vs VRd, and support DARA quadruplet therapy, with or without transplant, as a new SOC for NDMM.

OA-64

Belantamab Mafodotin in Combination with VRd for the Treatment of Newly Diagnosed Transplant Eligible Multiple Myeloma Patients: Results from the Phase II, Open Label, Multicenter, GEM-BELA-VRd Trial

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Introduction: GEM-BELA-VRd is a phase II, open label, multicenter, non-randomized single arm clinical trial evaluating belantamab mafodotin (belamaf) plus bortezomib, lenalidomide, and dexamethasone (VRD) in transplant-eligible newly diagnosed multiple myeloma (TE NDMM) patients (pts). The preliminary analyses of safety and efficacy after 4 cycles (cy) of induction were encouraging (González-Calle V et al. ASH, 2022). Here we report the results after all pts have completed 1 year of maintenance (1 yr-maint). **Methods:** 50 pts were recruited. Treatment consisted of 6 induction cy with VRd (Q4W) and belamaf 2.5 mg/kg iv (Q8W), followed by autologous stem cell transplant (ASCT). Patients also receive 2 consolidation cy with VRd (Q4W) and belamaf (at 2.5mg/kg Q8W) and maintenance with R until progression/toxicity and belamaf (Q8W) for 2 yrs (at 2.5 and 1.9 mg/kg after protocol amendment). Primary endpoint was safety (incidence of adverse events (AEs) [CTCAE v. 4.0]). Main key secondary endpoints were overall response rate (ORR), complete response rate (CR) and minimal residual disease negativity (MRD neg) rate. Cut-off date: June 1, 2024. **Results:** Median age was 56 years (27-75). Most of pts had MM Ig G kappa (64%), ECOG 0 (66%) and ISS I (64%). Besides, 12% had high LDH and 15% paraskeletal plasmacytomas. Ocular AEs were the most frequent. Among the patients with normal best correct visual acuity (BCVA) at baseline (20/25 or better), a decrease in the BCVA to 20/50 or worse occurred in 18/43 pts (41.9%) in induction; 8/43 (18.6%) in consolidation; and 11/43 (25.6%) in 1yr-maint. Blurred vision improved in all patients prior to ASCT (12 wks from last dose of belamaf). Only 1 pt had decrease of BCVA to 20/200 (2.3%), during 1yr-maint. Most common non-ocular G≥3 AEs were hematological and infections. Incidence

of G≥3 neutropenia and thrombocytopenia were 18 and 16%, during induction, and 28% and 8% during 1yr-maint, respectively. The incidence of G≥3 infections was 30% in induction, 16% in consolidation and 14% within 1yr-maint. The most common type was respiratory. In the ITT population (n=50), best ORR was 96%, sCR/CR rate improved overtime: 36% after induction; 56% after ASCT; 70% after consolidation and 82% after 1yr-maint. For those evaluable patients, MRD neg rate was 28/46 (60.9%) after induction; 29/42 (69.0%) after ASCT; 32/38 (84.2%) after consolidation and 31/34 (91.2%) after 1-yr maint. With a median follow-up of 28.5 m (18.8-37.6), 4 pts progressed, at 7, 26, 28 and 34 months with 2yr-TTP of 96% and 2yr-PFS of 78%. Eight pts died, 5 from infections (4 Covid and 1 sepsis), 1 early gastrointestinal toxicity, 1 disease progression and 1 unknown reason. **Conclusions:** Belamaf-VRD resulted in manageable eye-related AEs, expected hematological toxicity and respiratory infections, also due to the impact of the COVID -19 pandemic during trial recruitment. Besides, this combination was effective with a deepening of the response over time in TE NDMM.

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Overall Survival (OS) With Ciltacabtagene Autoleucel (Cilta-cel) Versus Standard of Care (SoC) in Lenalidomide (Len)-Refractory Multiple Myeloma (MM): Phase 3 CARTITUDE-4 Study Update

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Introduction: A single cilta-cel infusion significantly improved progression-free survival (PFS; hazard ratio [HR], 0.26 [protocol-specified weighted analysis]; P< 0.0001) vs SoC in patients (pts) with len-refractory MM after 1–3 prior lines of therapy at 16-month (mo) median follow-up in CARTITUDE-4. We report longer-term data, including updated prespecified OS analysis at 34-mo median follow-up. **Methods:** Pts were randomized to cilta-cel or SoC (pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]). Pts assigned to cilta-cel underwent apheresis, bridging therapy (PVd or DPd), lymphodepletion, and cilta-cel infusion (target dose, 0.75 × 106 CAR+ viable T cells/kg). The primary endpoint was PFS. Key secondary endpoints, tested hierarchically, were complete response (CR) or better, overall response, overall minimal residual disease (MRD) negativity (10–5), OS, and time to worsening on the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) total symptom score. **Results:** 419 pts were randomized (cilta-cel, n=208; SoC, n=211). Median OS was not reached (NR, 95% CI, not estimable [NE]–NE) with cilta-cel or SoC (95% CI, 37.75 mo–NE) (HR, 0.55; 95% CI, 0.39–0.79; P=0.0009); 30-mo OS rates were 76% and 64%, respectively. OS benefit across prespecified subgroups was generally maintained. Median PFS was NR with cilta-cel (95% CI, 34.50 mo–NE) and 11.79 mo (95% CI, 9.66–14.00) with SoC; 30-mo PFS rates were 59% and 26%, respectively. The ≥CR rate was 77% vs 24%, the overall response rate was 85% vs 67%, and the overall MRD-negativity rate was 62% vs 18% with cilta-cel vs SoC, respectively. Median duration of response was NR (95% CI, NE–NE) with cilta-cel and 18.69 mo (95% CI, 12.91-23.72) with SoC. Median time to symptom worsening based on MySIm-Q was NR (95% CI, NE–NE) with cilta-cel and 34.33 mo (95% CI, 32.20–NE) with SoC (HR, 0.38; 95% CI, 0.24–0.61; P< 0.0001). In the safety set (cilta-cel, n=208; SoC, n=208), 97% of pts in each arm had grade (gr) 3/4 treatment-emergent adverse events (TEAEs); cytopenia was the most common. Treatment-emergent infections occurred in 63% and 76% of pts in the cilta-cel and SoC arms, respectively (gr 3/4, 28% vs 30%). Hematologic second primary malignancies occurred in 7 pts (3%) in the cilta-cel arm (myelodysplastic syndrome, n=4 [2 progressed to acute myeloid leukemia {AML}]; AML, n=1; peripheral T-cell lymphoma, n=2) and 1 pt (< 1%) in the SoC arm (Epstein-Barr virus–associated lymphoma). There were 50 and 82 deaths in the cilta-cel and SoC arms, respectively, of which 21 and 51 were due to progressive disease. **Conclusions:** At ~3 years of follow-up, cilta-cel significantly extended OS, reducing the risk of death vs SoC by 45%, and significantly improved quality-of-life measures vs SoC. Collectively, these data continue to support the overall benefit-risk profile of cilta-cel vs SoC in pts with len-refractory MM as early as after first relapse.

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Isatuximab, Plus Bortezomib, Lenalidomide, and Dexamethasone (VRd) for Newly Diagnosed Multiple Myeloma (NDMM) Transplant-ineligible Patients: Frailty Subgroup Analysis of IMROZ

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Introduction: Isatuximab (Isa) is an anti-CD38 monoclonal antibody that induces myeloma cell death via multiple mechanisms. In the phase 3 IMROZ study (NCT03319667) in transplant-ineligible (Ti) NDMM patients (pts), Isa in combination with VRd significantly improved progression-free survival (PFS) and induced deep and sustained responses. However, frail Ti NDMM pts often have worse outcomes. Here we present a post-hoc subgroup analysis of IMROZ across frail and non-frail subgroups. **Methods:** IMROZ is a global, phase 3, open-label study investigating an initiation phase with Isa-VRd followed by a maintenance phase with Isa-Rd (n=265) vs VRd followed by Rd (n=181) in Ti NDMM pts aged ≤80. Intravenous (IV) Isa was given 10 mg/kg QW in cycle 1, then Q2W, and Q4W from cycle 18. Both arms received recommended doses of subcutaneous V, oral R, and oral/IV d. Primary endpoint was PFS; key secondary endpoints included complete response or better (≥CR), minimal residual disease negativity (MRD-) in pts with CR, and safety. Frailty scores at baseline were calculated based on age, modified Charlson Comorbidity Index, calculated using medical history at baseline, and Eastern Cooperative Oncology Group performance status; pts with frailty score of 0/1 were considered non-frail, and scores ≥2 were frail. **Results:** Using the above frailty score, 29% of pts were frail (28% Isa-VRd; 32% VRd), and 70% non-frail (72% Isa-VRd; 67% VRd) pts, 1% missing. The median treatment duration was 31.5 months and 23.7 months in frail Isa-VRd and VRd pts respectively, vs 55.2 and 36.6 months in non-frail pts. Median relative dose intensity of Isa was similar across subgroups (≥92%). After a median follow-up of 59.7 months, Isa-VRd led to significantly improved PFS vs VRd in both subgroups — frail pts HR=0.584 (95% CI: 0.340–1.004; p=0.0516); non-frail pts HR=0.593 (95% CI: 0.403–0.873; p=0.008). Improved rates of ≥CR (frail, 61.6% vs 50.9%; non-frail, 79.9% vs 71.1%) and MRD- (10-5 by next generation sequencing) (frail, 50.7% vs 22.8%; non-frail, 60.3% vs 54.6%) were seen with Isa-VRd vs VRd. TEAEs leading to definitive discontinuation in Isa-VRd vs VRd occurred in 29.2% vs 35.1% of frail pts, and 20.7% vs 22.3% of non-frail. In frail pts, grade ≥3 upper respiratory tract infection occurred in 2.78% vs 5.26% of Isa-VRd and VRd pts (p=0.654), while pneumonia occurred in 36.1% vs 28.1% (p=0.351). **Conclusions:** Isa-VRd followed by Isa-Rd led to significantly improved PFS and response rates in both frail and non-frail pts, consistent with the results of the IMROZ intent-to-treat population. No new safety signals of frail pts were observed. **Funding:** Sanofi.

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Real-world Prevalence and Multi-omic Analysis of t(11;14)-Positive Multiple Myeloma: Final Analysis from the MEDICI Study

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Introduction: Multiple myeloma (MM) is characterized by complex cytogenetic abnormalities and diverse genomic subtypes that can determine disease course and treatment response. t(11;14)-positive MM is a distinct subset of MM with a unique biology that makes it highly susceptible to BCL-2 inhibition. The underlying biology and real-world (RW) prevalence of t(11;14)-positive MM remains to be fully investigated. Here, we present the final analysis (FA) from the global, noninterventional MEDICI study (NCT04721002), which evaluated RW t(11;14) status and associated disease and genomic characteristics in newly diagnosed MM (NDMM) and relapsed/refractory MM (RRMM). **Methods:** Bone marrow (BM) aspirates of patients (pts) aged ≥18 y with MM who provided informed consent were collected at diagnosis and/or disease relapse and subjected to plasma cell enrichment (PCE)

before fluorescence in situ hybridization (FISH), next-generation RNA sequencing before differential gene expression analysis (GEA), and whole-exome sequencing (WES). The primary objective was to evaluate t(11;14) prevalence in NDMM/RRMM using interphase FISH with PCE. The primary endpoint was t(11;14) status of the earliest BM sample collected. **Results:** At the October 31, 2023 cutoff, 525 pts (306 NDMM; 219 RRMM) were enrolled. Median age was 66.0 y, and most pts were male (55.4%) and White (74.5%); 3.2% of pts were Black. ECOG PS was ≤2 in 83.2% of pts, and ≥3 in 2.9%. Disease was ISS stage I in 31.6% of pts, stage II in 23.8%, and stage III in 25.0%. FISH testing was evaluable in 498/525 pts (94.9%), of which only 12 (2.4%) samples had an indeterminate result. t(11;14) prevalence was 22.1% (95% CI: 18.5–26.0) in MM, 18.8% (14.5–23.7) in NDMM, and 27.0% (21.0–33.7) in RRMM. Distribution of t(11;14) across lines of therapy was 18.8% (14.5–23.7) in 1L, 27.4% (16.9–40.2) in 2L, and 28.7% (21.6–36.6) in 3L+. Distribution of t(11;14) across disease stage was 24.1% (17.6–31.5) in stage I, 20.0% (13.3–28.3) in stage II, and 21.3% (14.4–29.6) in stage III. Whole transcriptome sequencing was evaluable in 487/525 (92.8%) pts. Differential GEA confirmed significant CCND1 (cyclin D1) overexpression in t(11;14)-positive vs -negative disease (NDMM, P=9.22e-18; RRMM, P=1.15e-22). The apoptotic sensitizer PMAIP1 (NOXA) was significantly overexpressed in t(11;14)-positive vs -negative disease (NDMM, P=1.02e-06; RRMM, P=1.18e-07). While BCL2 expression was similar between t(11;14)-positive vs -negative NDMM (P=.6313) and between t(11;14)-positive RRMM vs NDMM (P=.0632), BCL2 was significantly overexpressed in t(11;14)-positive vs -negative RRMM (P=4.78e-07). Increased levels of BCL-2 inhibitor resistance indicators were observed in t(11;14)-positive RRMM vs NDMM (BCL2A1, P=.0049; KRAS signaling pathway, P=.0039). WES will be presented. **Conclusions:** MEDICI FA showed an overall RW t(11;14) prevalence of 22.1% in MM. Multi-omic analyses revealed increased genomic heterogeneity in t(11;14)-positive RRMM vs NDMM, which may harbor additional resistance mechanisms.