MRD-driven strategy following IsaKRD induction in transplant-eligible NDMM: Primary endpoints of the phase 3 MIDAS trial.

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Background: The phase III IFM2020-02-MIDAS study (NCT04934475) evaluated a minimal residual disease (MRD)-driven consolidation and maintenance strategy following induction with isatuximab, carfilzomib, lenalidomide, and dexamethasone (IsaKRD) in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). Results from the IsaKRD induction phase have been previously published (Perrot et al., Blood, 2025). Here, we present the results from the MRD-driven consolidation phase of the trial. **Methods:** MIDAS is a multicenter, open-label, randomized phase 3 trial involving transplant-eligible patients aged 18-65 with NDMM. Patients achieving post-induction MRD negativity at a threshold of 10^{-5} by next-generation sequencing (NGS) were randomized to either 6 additional cycles of IsaKRD (Arm A) or autologous stem cell transplantation (ASCT) followed by 2 cycles of IsaKRD (Arm B), followed by lenalidomide maintenance. MRD-positive patients after induction (MRD $\geq 10^{-5}$) were randomized to either single ASCT plus 2 cycles of IsaKRD (Arm C) or tandem ASCT (Arm D) followed by isatuximab plus iberdomide maintenance. Randomization was stratified by cytogenetic risk and center for both comparisons, and by MRD negativity at 10^{-6} post-induction for the Arm A vs. Arm B comparison. The primary endpoint was MRD negativity at 10^{-6} (by NGS) prior to maintenance for both comparisons. **Results:** A total of 485 patients with post-induction MRD negativity were randomized to Arm A (n=243) or Arm B (n=242). The pre-maintenance MRD negativity rates at 10^{-6} were 84% in Arm A and 86% in Arm B (Odds Ratio [OR] 1.17, 95% confidence interval [CI] 0.64–2.76, p=0.64). Additionally, 233 MRD-positive patients (10^{-5}) were randomized to Arm C (n=109) or Arm D (n=124), with 19 patients (15%) not receiving the planned tandem ASCT. Pre-maintenance MRD negativity rates at 10^{-6} were 40% in Arm C and 32% in Arm D (OR 0.73, 95% CI 0.42–1.25, p=0.31). During the consolidation phase, 5 patients experienced disease progression (2 in Arm A, 0 in Arm B, 0 in Arm C, 3 in Arm D), and 2 patients died without progression in Arm A. No new safety signals were identified compared to the induction phase. The study is ongoing. With a median follow-up of 16.8 months in Arms A/B and 16.3 months in Arms C/D, sustained MRD negativity and progression-free survival (PFS) data are not yet available. **Conclusions:** After 6 induction cycles with IsaKRD, in patients who achieved MRD negativity at 10^{-5}, MRD negativity rates at 10^{-6} before maintenance were not significantly different between the transplant-based approach and IsaKRD consolidation alone, whereas in patients who do not achieve MRD negativity at 10^{-5}, tandem ASCT did not significantly improve MRD negativity rates at 10^{-6} before maintenance. Further follow-up, including sustained MRD negativity and PFS data, is needed to evaluate the long-term outcomes of this MRD-adapted strategy. Clinical trial information: NCT04934475. Research Sponsor: None.

Subcutaneous daratumumab (Dara) + bortezomib/lenalidomide/dexamethasone (VRd) with Dara + lenalidomide (DR) maintenance in transplant-eligible (TE) patients with newly diagnosed multiple myeloma (NDMM): Analysis of sustained minimal residual disease negativity in the phase 3 PERSEUS trial.

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Background: Minimal residual disease (MRD) negativity (neg) and sustained MRD neg are associated with longer survival and are strong prognostic clinical endpoints. PERSEUS (NCT03710603) evaluated subcutaneous Dara + VRd induction/consolidation (ind/consol) + DR maintenance (maint) vs VRd ind/consol + R maint in TE NDMM. DVRd significantly improved PFS, complete response or better rate (≥CR), and MRD neg rate. Nearly two-thirds of patients (pts) on DR maint could stop treatment (tx) after achieving sustained remission, leading to DVRd being recommended by NCCN as a preferred TE NDMM regimen. Here, we report the impact of sustained MRD neg status on PFS inPERSEUS. **Methods:** TE pts with NDMM age 18–70 years (y) were randomized 1:1 to DVRd (DVRd ind/consol + DR maint) or VRd (VRd ind/consol + R maint). The primary endpoint was PFS; MRD neg rate (MRD neg 10^{-5} and ≥CR) was a key secondary endpoint. Sustained MRD neg, assessed in the intent-to-treat population, was defined as confirmed MRD neg ≥12 months (mo) apart and without MRD positivity in between. Functionally high risk (FHR) was defined as disease progression ≤18 mo from tx initiation, excluding pre-progression deaths. **Results:** A total of 709 pts were assigned to DVRd (n=355) or VRd (n=354). At 47.5-mo median follow-up, ≥12-mo sustained MRD neg rates were higher overall with DVRd (64.8%; n=230) vs VRd (29.7%; n=105), and across clinically relevant subgroups, including age ≥65 y and high-risk cytogenetics. Similarly, ≥24-mo sustained MRD neg rates were higher with DVRd (55.8%; n=198) vs VRd (22.6%; n=80). Pts with ≥12-mo sustained MRD neg vs those without had improved 48-mo PFS rates regardless of tx arm (Table). DVRd vs VRd reduced FHR rates (3.1% vs 6.8%), and rates of FHR or pre-progression deaths were lower with DVRd vs VRd (5.4% vs 11.0%) in the first 18 mo. **Conclusions:** In TE NDMM, nearly two-thirds of pts treated with DVRd induction and DR maint achieved ≥12-mo sustained MRD neg, associated with >95% 48-mo PFS rate. Moreover, ≥24-mo sustained MRD neg rates with DVRd were 2.5 times as high as VRd, and FHR incidence was halved with DVRd vs VRd. Collectively, these data further support the PERSEUS regimen as standard of care for TE NDMM. Clinical trial information: NCT03710603. Research Sponsor: Johnson & Johnson.

	Achieved sustained (≥12 mo) MRD neg (10^{-5})			Without achieving sustained (≥12 mo) MRD neg (10^{-5})		
	DVRd (n=230)	VRd (n=105)		DVRd (n=125)	VRd (n=249)	
Median PFS, mo (95% CI)	NE (NE–NE)	NE (NE–NE)	HR=0.83 (95% CI 0.3–2.3) *P*=0.7149	NE (47.9–NE)	NE (45.3–NE)	HR=0.80 (95% CI 0.6–1.2) *P*=0.2489
48-mo PFS rate, % (95% CI)	95.3 (91.4–97.5)	94.2 (87.6–97.4)		60.3 (48.0–70.5)	54.9 (47.7–61.4)	

Hazard ratio, HR; NE, not estimable.
Median PFS and 95% CI are from Kaplan-Meier estimates.
P-value is from unstratified log-rank test.

Sustained MRD negativity in patients with newly diagnosed multiple myeloma treated with carfilzomib-lenalidomide-dexamethasone with or without isatuximab (phase III IsKia trial).

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Background: The phase III IsKia trial assessed the efficacy and safety of isatuximab-carfilzomib-lenalidomide-dexamethasone (IsaKRd) as pre-ASCT induction and post-ASCT consolidation vs KRd. The rate of measurable residual disease (MRD) negativity was significantly higher in IsaKRd vs KRd patients (pts) after both induction and consolidation (Gay et al. ASH 2023). Here we report the rates of 1-year sustained (sust)MRD negativity and findings about the light consolidation phase. **Methods:** Transplant-eligible NDMM pts aged <70 years were enrolled. IsaKRd pts received 4 full-dose IsaKRd induction cycles, MEL200-ASCT, 4 full-dose IsaKRd consolidation cycles and, thereafter, 12 28-day light consolidation cycles [Isa 10 mg/kg IV on days (dd) 1, 15; K 56 mg/m^2 IV dd 1; R 10 mg PO daily dd 1–21; d 20 mg PO dd 1, 15]. Pts in the KRd arm received the same KRd schedule used in the other arm. MRD was tested by NGS in all pts who achieved ≥VGPR. 1-year sustMRD was defined as 2 sequential MRD-negative evaluations at least 1 year apart. Analyses were based on the ITT principle (pts with missing MRD data or who did not achieve VGPR were considered as MRD positive). The data cut-off was Jul 22, 2024. **Results:** 151 vs 151 pts were randomly assigned to the IsaKRd vs KRd arms. Pt characteristics were well balanced: 43% vs 41% had R2-ISS stage III/IV disease; 9% vs 11% had ≥2 high-risk cytogenetic abnormalities [CA; including del(17p), t(4;14), t(14;16), 1q+]. The median follow-up was 35 months (IQR 32–38). In the ITT analysis, the MRD negativity rates at the 10^{-5} cut-off after full-dose consolidation were 77% vs 67% (OR 1.67; p=0.049) with IsaKRd vs KRd; the rates of 10^{-5} 1-year sustMRD after light consolidation were 66% vs 59% (OR 1.36; p=0.21). The MRD negativity rates at the 10^{-6} cut-off after full-dose consolidation were 67% vs 48% (OR 2.29; p<0.001) with IsaKRd vs KRd; the rates of 10^{-6} 1-year sustMRD after light consolidation were 52% vs 38% (OR 1.82; p=0.012). The 10^{-6} 1-year sustMRD negativity advantage with IsaKRd was retained in all subgroups. In particular, the 10^{-6} 1-year sust MRD negativity rates were: 62% vs 20% in pts with ≥2 high-risk CA (OR 6.3, 95% CI 1.11–35.66) and 47% vs 35% in pts with R2-ISS III/IV (OR 1.62, 95% CI 0.77–3.41). During light consolidation, in the IsaKRd vs KRd arms, the main grade 3–4 hematologic AEs were neutropenia (17% vs 18%) and thrombocytopenia (2% vs 3%); the main grade 3–4 non-hematologic AEs included infections (8% vs 5%), gastrointestinal (4% vs 4%) and vascular AEs (3% vs 1%); discontinuation for toxicity occurred in 3% vs 2%; treatment-related deaths were 2 (1 cerebral ischemia, 1 pulmonary embolism) vs 0. **Conclusions:** The addition of isatuximab to KRd induction-consolidation and the prolonged light consolidation significantly increased the rates of 10^{-6} sustMRD negativity in NDMM pts, including those with high-risk disease. Clinical trial information: NCT04483739. Research Sponsor: Sanofi; Amgen.

7503 Oral Abstract Session

Randomized, multi-center study of carfilzomib, lenalidomide, and dexamethasone (KRd) with or without daratumumab (D) in patients with newly diagnosed multiple myeloma (NDMM): The ADVANCE clinical trial.

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Background: The use of modern combination therapy in NDMM patients delivers deep and durable treatment responses independent of transplant status. In the current ADVANCE study (NCT04268498), patients were randomly assigned to receive 8 cycles of carfilzomib-lenalidomide-dexamethasone with or without daratumumab (DKRd vs KRd). Transplants were offered to patients who were minimal residual disease (MRD) positive after 8 cycles. All patients transitioned to lenalidomide maintenance. Primary endpoint was MRD negativity 10^-5 by NGS after up to 8 cycles of combination therapy. **Methods:** 306 NDMM patients were randomly assigned 1:1 to receive 8 cycles (28-day cycles) of either DKRd or KRd (D: 1800 mg SC, days 1, 8, 15, and 22 (C1-2), days 1 and 15 (C3-6), day 1 (C7-8); K: 20/56 mg/m2 IV, days 1, 8, and 15; R: 25 mg days 1-21; d: 40/20 mg). Stem cell collection was encouraged after 4 cycles for eligible patients. After completion of cycle 8, patients were evaluated for MRD (ClonoSEQ). Transplant was reserved for MRD-positive patients (post C8). MRD-negative patients transitioned to lenalidomide 10 mg maintenance (D1-21/28). Sustained MRD status was monitored annually. Key eligibility included NDMM with ECOG PS 0-2 and adequate organ function, independent of transplant status. The study was monitored and approved by an independent data safety monitoring committee. **Results:** At 2nd prespecified analysis (data cutoff 01/15/25) demographics and disease characteristics were well balanced and included: median age 62 y/o (range: 35-76), Hispanic: 23%, Black: 11%, ISS 2-3: 39%, ECOG PS 2: 6%, and high-risk cytogenetics: 35%. The primary endpoint of MRD negativity at 10^-5 by NGS was significantly higher in the DKRd arm compared to the KRd arm (59% vs 36%, adjusted OR=2.5, 95%CI: 1.5-4.2; P<0.0007). EFS, PFS and OS data are currently immature, however, at 32.7 months median follow-up, PFS events included one death in each arm, PD 4 vs 5%, and 86 vs 79% were progression-free and censored in the DKRd vs KRd arms, respectively. Overall, 98% had an adverse event (AE) with hematologic AEs occurring in 15 vs 24%; cardiac AEs: 13 vs 16%; gastrointestinal AEs: 68 vs 72%; infections: 61 vs 53%; acute kidney injury: 1 vs 4%; vascular disorders: 6 vs 2% with DKRd vs KRd, respectively. Serious AEs occurring in >1% included: febrile neutropenia: 2 vs 2%; pyrexia: 5 vs 2%; chest pain: 0 vs 3%; non-cardiac chest pain: 2 vs 0%; pneumonia: 3 vs 10%; sepsis: 2 vs 0%; COVID-19: 2 vs 0%; wound infection: 2 vs 0%; hip fracture: 2 vs 0%; infusion reaction: 2 vs 0%; back pain: 2 vs 0%; syncope: 2 vs 0%; acute kidney injury: 0 vs 3%; and dyspnea: 2 vs 0%, with DKRd vs KRd, respectively. **Conclusions:** In this large randomized, multicenter investigator-initiated trial for NDMM, treatment with DKRd (59%) compared to KRd (36%) showed a significant, 2.5-fold higher MRD negativity rate with no new safety concerns. Updated EFS, PFS and OS results will be presented at the meeting. Based on these results, DKRd should be a new standard for most NDMM patients receiving initial KRd-backbone therapy. Clinical trial information: NCT04268498. Research Sponsor: U.S. National Institutes of Health; P30CA240139; Janssen; Amgen.

Elranatamab in combination with daratumumab and lenalidomide (EDR) in patients with newly diagnosed multiple myeloma (NDMM) not eligible for transplant: Initial results from MagnetisMM-6 part 1.

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Background: Elranatamab (ELRA), a BCMA-CD3 bispecific antibody, induced deep and durable responses with a manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM). MagnetisMM-6 (NCT05623020) is a phase 3, open-label, randomized study evaluating the efficacy and safety of ELRA in combination with lenalidomide (R) ± daratumumab (DARA) (EDR or ER) vs DARA + R + dexamethasone (DRd) in pts with transplant-ineligible (TI) NDMM. Part 1 of the study evaluates the optimal dose of EDR or ER in pts with RRMM or NDMM to determine the recommended phase 3 dose for part 2. Initial results from part 1 dose level G (DLG) are presented. **Methods:** In DLG, eligible pts had TI (age ≥65 or age <65 years with comorbidities impacting the possibility of transplant) NDMM, measurable disease, ECOG ≤2, and adequate liver, renal and bone marrow function. Pts received subcutaneous (SC) ELRA with a priming regimen followed by ELRA 76 mg SC every 4 weeks (Q4W) on cycle (C) 1 day (D) 1; DARA 1800 mg SC weekly (D1, D8, D15, D22 in C1-C2), every 2 weeks (D1, D15 in C3-C6), and Q4W (D1 in C7+); and oral R 25 mg daily on D1-D21 in 28-day cycles. Endpoints assessed in DLG include safety and preliminary efficacy. **Results:** A total of 37 pts were enrolled in DLG; 34 received EDR. The median age was 75.0 years (range, 67-83); 37.8% were male; 86.5% were White, 13.5% Asian. Four patients (10.8%) had R-ISS stage III disease, 9 (24.3%) had ≥50% baseline bone marrow plasma cells, 1 (2.7%) had ECOG=2, none had EMD, and 9 (24.3%) were frail according to the simplified IMWG frailty score. At data cutoff (Dec 23, 2024), the median follow-up was 4.6 months (range, 1.2-6.2); treatment was ongoing in 33 pts. TEAEs were reported in 97.3% (G3/4 94.6%) of pts, hematological TEAEs in 78.4% (G3/4 70.3%), and infections in 64.9% (G3/4 18.9%). The most frequent TEAEs (any grade ≥25% or G3/4 ≥10%) are shown in the Table. CRS occurred in 62.2%, all ≤G2; 1 case of G2 ICANS was reported. There was one G5 candida pneumonia. Overall, 36 out of 37 pts are responders with 2 pending confirmation as of DCO. The confirmed ORR (95% CI) by investigator was 91.9% (78.1-98.3), 81.1% with VGPR or better. In pts enrolled ≥4 months before the DCO (n=23), confirmed ORR was 95.7% (78.1-99.9), all with VGPR or better. **Conclusions:** In pts with TI NDMM, EDR demonstrated a manageable safety profile consistent with the known toxicities of components. High response rate and early responses were observed. Enrollment in dose level H evaluating the ER combination is ongoing. Updated safety and efficacy data with a longer follow-up will be presented. Clinical trial information: NCT05623020. Research Sponsor: Pfizer.

TEAEs, %	Any grade	G3/4
Neutropenia, incl. neutrophil count decreased	70.3	67.6
CRS	62.2	0
Pyrexia	35.1	0
Anemia, incl. hemoglobin decreased	32.4	16.2
Injection site reaction	29.7	0
Nausea	27.0	0
Thrombocytopenia, incl. platelet count decreased	13.5	10.8
Asthenia	16.2	10.8

First-in-human study of JNJ-79635322 (JNJ-5322), a novel, next-generation trispecific antibody (TsAb), in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Initial phase 1 results.

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Background: Bispecific antibodies (BsAbs) have begun to transform outcomes in MM. Emerging data suggest that targeting two MM antigens with T-cell redirection may overcome tumor heterogeneity and acquired resistance to further improve clinical outcomes. JNJ-5322 is a next-generation TsAb dually targeting BCMA and GPRC5D via T-cell redirection, comprising novel binding domains, including low affinity CD3, selected in vitro to enhance on-tumor effects and reduce off-tumor impact. We report first results from an ongoing phase 1 study of JNJ-5322 (NCT05652335). **Methods:** Dose escalation/expansion cohorts enrolled measurable RRMM pts previously exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody. Escalating fixed Q2W or Q4W SC doses (0.4–300 mg) were explored, including 100 mg Q4W, the putative recommended phase 2 dose (RP2D). Pts received 1 step-up dose (SUD) (5 mg) prior to receiving the 100 mg Q4W dose, allowing faster full dose initiation and attenuation of cytokine release syndrome (CRS) risk. Adverse events (AEs) were graded by CTCAE v5.0; CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Overall response rate (ORR) was assessed by IMWG criteria. **Results:** As of Jan 15, 2025, 126 pts received JNJ-5322 (36 at 100 mg Q4W); median follow-up (mFU) 8.2 mo. Median age 64 yrs; median 4 prior lines of therapy; 100% triple-class exposed (56% refractory); 31% high-risk cytogenetics; 23% had prior anti-BCMA/-GPRC5D therapy (77% naïve). The putative RP2D was identified as 100 mg Q4W. Overall, 99% of pts had ≥1 AE, most commonly CRS (59%; all grade [gr] 1 [45%]/2 [14%]; no gr ≥3), nail AEs (gr 1/2 56%), taste AEs (gr 1/2 56%), neutropenia (48%; gr 3/4 41%), and non-rash skin AEs (47%; gr 3/4 1%). Overall, 16% had weight decreases (no gr ≥3), 16% had rashes (no gr ≥3), 2% had ICANS (all gr 1), and 75% had infections (gr 3/4 28%). 5 pts had dose-limiting toxicities. 4 pts died due to AEs. In response-evaluable pts, ORR was 86% (75% ≥VGPR) at the RP2D (n=36), and 73% (66% ≥VGPR) overall (n=124). ORR was 100% (89% ≥VGPR) at the RP2D among pts naïve to anti-BCMA/-GPRC5D therapies (n=27), and all patients remain in response (mFU 8.5 mo). Median time to first response was 1.2 mo. **Conclusions:** In the largest data set for a next-generation dual antigen T-cell redirecting TsAb, the first clinical data for JNJ-5322 showed a 100% ORR at the putative RP2D in anti-BCMA/-GPRC5D naïve patients, with convenient Q4W dosing. Tolerability appeared improved, including lower incidence and severity of GPRC5D-associated AEs vs anti-GPRC5D BsAbs and manageable gr 3/4 infection rates. CRS was mostly gr 1 (no gr ≥3 CRS) using 1 SUD. First data with JNJ-5322 suggest a paradigm shift, offering ORRs similar to CAR-Ts but as an off-the-shelf therapy intended for outpatient dosing. Clinical trial information: NCT05652335. Research Sponsor: None.

Isatuximab (Isa) subcutaneous (SC) via an on-body delivery system (OBDS) vs Isa intravenous (IV), plus pomalidomide and dexamethasone (Pd) in relapsed/refractory multiple myeloma (RRMM): Results of the randomized, non-inferiority, phase 3 IRAKLIA study.

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Background: IV Isa-Pd is approved to treat RRMM patients (pts) based on the ICARIA-MM study. A Phase 1b study showed safety and efficacy of Isa SC via an OBDS, an investigational wearable bolus injector, plus Pd, in RRMM pts. Isa SC offers shorter duration, fixed dose and smaller administration volume. Here, we report results of the IRAKLIA trial (NCT05405166); Isa SC vs IV + Pd in RRMM pts, the first Phase 3 myeloma trial reporting the use of an OBDS. **Methods:** This multicenter, open-label study enrolled pts aged ≥18 years with ≥1 prior line of therapy (LOT). Pts were randomized 1:1 to Isa SC (1400 mg) or Isa IV (10 mg/kg) weekly in Cycle (C)1, then every 2 weeks + P (4 mg/day, Day [D]1–21) + d (40 mg [20 mg if age ≥75 years] weekly). Pts had 4-week cycles until progression, unacceptable toxicity or patient request. Co-primary endpoints were overall response rate (ORR; non-inferiority [NI] margin of 0.839) and Isa trough level (C_{trough}) at steady state (predose at C6D1; NI if lower limit of 90% CI of geometric mean ratio ≥0.8). **Results:** 531 pts (SC n=263; IV n=268 [4 not treated]) were randomized. Baseline characteristics were balanced (median age 66 years; median 2 prior LOT). After median 12 months follow-up, ORR was 71% (SC arm) and 71% (IV arm; relative risk [95% CI] = 1.008 [0.903–1.126]; lower CI > NI margin). Mean (SD) C_{trough} at C6D1 was 499 (259) μg/mL for SC and 340 (169) μg/mL for IV. C_{trough} geometric mean ratio (90% CI) was 1.532 (1.316–1.784); lower CI > NI margin. Co-primary and all 4 key secondary endpoints including pt experience are in the Table. Grade ≥3 treatment-emergent adverse events occurred in 82% (SC) and 76% (IV) of pts; with treatment discontinuation rates of 8% and 9%. Injection site reactions (ISRs) occurred in 4% (11/263) of the SC arm and in 19 (0.4%) of 5145 SC injections (all Grade 1–2). 99.9% of OBDS injections were completed without interruption. **Conclusions:** IRAKLIA met its co-primary endpoints, showing efficacy and pharmacokinetic NI between Isa SC vs IV + Pd. No new safety signal besides a low ISR incidence was observed, showing excellent Isa SC tolerability. Far fewer infusion reactions and higher pt satisfaction were also noted for SC vs IV. Efficacy and safety are comparable to Isa IV in ICARIA-MM. These results support potential use of Isa SC delivered via the OBDS, designed to improve pt experience and practice efficiency. Clinical trial information: NCT05405166. Research Sponsor: Sanofi.

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

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

7507 Oral Abstract Session

Long-term (≥5 year) remission and survival after treatment with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 patients (pts) with relapsed/refractory multiple myeloma (RRMM).

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Background: CARTITUDE-1 evaluated cilta-cel in pts with heavily pretreated RRMM who historically have an expected median progression-free survival (PFS) of <6 months (mo) and median overall survival (OS) of ~1 year (y). At 33.4 mo median follow-up, median PFS was 34.9 mo, and median OS was not reached (36-mo OS rate, 62.9%; Lin et al, ASCO 2023). We report OS, ≥5 y progression-free outcomes, and safety with a median study follow-up of 60.3 mo. **Methods:** Pts in CARTITUDE-1 received a single cilta-cel infusion. Correlative analyses were performed utilizing drug product, baseline, and postinfusion samples. Pts are followed for progression, survival, and safety in a 15-y follow-up study, CARTinue (NCT05201781), with pt evaluations per local standard of care (reported annually at a minimum). **Results:** Of 97 pts treated, 32 (33.0%) remain alive and progression free for ≥5 y after cilta-cel, without further MM treatment. For these 32 pts, prior to enrollment in CARTITUDE-1, median time from start of last line of therapy (LOT) to progression was 4.0 mo (range, 0.7–48.6). Among the 32, median age was 60 y (range, 43–78), median number of prior LOT was 6.5 (range, 3–14), 23.3% had high risk cytogenetics, 12.5% had extramedullary disease (EMD), 90.6% were triple-class refractory, and 46.9% were penta-drug refractory. Baseline characteristics of pts who were progression free for ≥5 y, including those with high-risk cytogenetics and EMD, were comparable to pts with progressive disease (PD) within 5 y. Compared with pts who had PD within 5 y, biomarkers significantly associated with ≥5 y progression free status included a higher fraction of naïve T cells in the drug product, lower neutrophil to T cell ratio, higher hemoglobin and platelets at baseline, and higher effector-to-target ratio (Cmax to sBCMA at baseline). At Cmax, these pts also had significantly higher CD4 central memory CAR+ T cell subsets and CAR+ T cells that were positive for the activation markers CD38, CD25, and PD-1. Data were collected on a subset of pts from a single center where local serial MRD assessments were performed. All 12 pts at this center who were progression free for ≥5 y were MRD negative at 10^{-6} and imaging negative by PET/CT yearly for 5 y. Overall, at 60.3 mo median follow-up in CARTITUDE-1 (N=97), median OS was 60.6 mo (95% CI, 41.9–NE). With continued follow-up, 3 additional pts reported a second primary malignancy (1 of which was acute myeloid leukemia; onset, 2.8 y after infusion). No new cases of movement and neurocognitive disorders were reported. **Conclusions:** The median OS for pts enrolled in CARTITUDE-1 was 5 y, and 33% of pts remain progression free for ≥5 y following a single cilta-cel infusion. These data provide the first evidence that cilta-cel is potentially curative in pts with RRMM. Clinical trial information: NCT03548207, NCT05201781. Research Sponsor: None.

Safety and efficacy data from Nexicart-2, the first US trial of CAR-T in R/R light chain (AL) amyloidosis, Nxc-201.

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Background: No FDA approved treatments exist for relapsed/refractory (RR) AL Amyloidosis. Chimeric antigen receptor T-cell (CAR-T) is a novel approach to treating RR AL Amyloidosis. In this study, we report safety and efficacy data from NEXICART-2, the first U.S. clinical trial of any CAR-T in RR AL Amyloidosis. **Methods:** NEXICART-2 (NCT06097832) is a single-arm, multi-site U.S. Phase 1b/2 dose escalation and expansion trial of autologous BCMA-targeted CAR-T NXC-201 in RR AL Amyloidosis. It will enroll 40 patients (pts) with a 6 patient safety run-in, that has now completed. Pts must have been exposed to bortezomib and anti-CD-38 antibody with persistent or relapsed disease. Lymphodepletion was with fludarabine and cyclophosphamide. The primary endpoint is complete hematologic response (CR) rate (Palladini. 2012). **Results:** 7 pt (4 F, 3 M), median age 66 years (range: 56-82) were included. Median follow-up 97 days (range 7-209). Median prior lines 4 (range: 2-9); including 4(57%) with prior autologous stem cell transplant; 6/7 had gain 1q. Median dFLC at enrollment were 5.4 mg/dL (range: 2.4-12.1). 57% (4/7) had cardiac involvement (Mayo stage I (N =2), II (N=4) and IIIa (N=1) with median NT-proBNP 909 pg/mL (range: 146 – 2,532)); 2/7 had New York Heart Association (NYHA) class II heart failure, 5/7 class I. 2 pts had kidney involvement, with 4.5 and 10.0gm of proteinuria in 24h. 3 pts received 150 million and four 450 million CAR+T cells. CRS was observed in 5 pts (grade 1 (N=4), grade 2 (N=1)); onset day 1 (N=3) or 3 (N=2), lasting $<$24 hours following 1 dose of tocilizumab in all pts. No pt had neurotoxicity. Adverse events included neutropenia (grade 3 (N=3), grade 4 (N=2). 1 pt with pre-existing stage 4 chronic kidney disease prior to enrollment had Grade 4 acute on chronic kidney injury. There was no febrile neutropenia, treatment-related infections, cardiac toxicity, and no deaths. All pts (7/7, 100%) normalized pathological disease markers after NXC-201. Pts 1, 2, 4, 5, 6, 7 normalized FLCs at median 7 days (range 7-14) following NXC-201, all with reduction of dFLC to $<$1 mg/dL. Pts 1, 2, 4, 5, 6 had MRD negativity in bone marrow by flow cytometry (10^{-6} sensitivity) at day 25 or 26 (Pt 7 was not MRD evaluable as of the cut-off date). Pt 3 had a renal organ response per AL criteria (reduction in albuminuria) and resolution of the m-spike 15 days following NXC-201 (0.79g/dl at enrollment). As of the data cutoff, all pts are in VGPR/CR, with no relapses recorded. Improvement in NYHA class from II to I occurred in 1 pt 14 days following NXC-201 treatment. 15 pts are expected to have been treated at presentation time. **Conclusions:** In this first reported U.S. CAR-T clinical trial experience in RR AL Amyloidosis, we demonstrate that NXC-201 can be given safely and resulted in rapid and deep hematologic responses in all pts treated. Our data suggests that the novel anti-BCMA CAR-T NXC-201 may become a valuable treatment option for RR AL pts. Clinical trial information: NCT06097832. Research Sponsor: Immix Biopharma; MSK Cancer Center Support Grant/Core Grant (P30 CA008748).

7509 Rapid Oral Abstract Session

Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) for high-risk (HR) newly diagnosed multiple myeloma (NDMM): First-time report of the full cohort of transplant-eligible (TE) patients in the GMMG-CONCEPT trial.

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Background: Patients (pts) with HR NDMM have shown impaired survival outcomes even in the era of modern combination therapies. Establishing Isa-KRd in an intensified first-line regimen, the Phase II CONCEPT trial (NCT03104842) aimed at improving outcomes for HR NDMM pts for whom clinical trials had long been missing. **Methods:** The prospective, multicenter, academic Phase II CONCEPT trial has 2 parallel treatment arms according to transplant-eligibility. Adult NDMM pts with HR disease, defined as ≥1 HR cytogenetic aberration (CA) (del(17p), t(4;14), t(14;16), ≥3 copies 1q21) in combination with ISS stage II/III were included. All pts received Isa-KRd induction (6 cycles), intensification (HD-MEL+ASCT [TE pts; arm A] or 2 cycles Isa-KRd [non-TE pts; arm B]), 4 cycles Isa-KRd consolidation and 2 years Isa-KR maintenance. Primary endpoint is minimal residual disease (MRD) negativity (NGF, 10^{-5}) at the end of consolidation, tested against the null hypothesis MRD-neg rate ≤50% (TE pts); key secondary endpoints include survival times (PFS, OS). The trial recruited in 2 phases: 2017-2020 (TE+TNE; 1st cohort) and 2021-2022 (TE only; 2nd cohort), with a switch in carfilzomib application implemented in 2021 (1x weekly instead of 2x weekly). Interim results of the 1st cohort have been shown before. Here, we report for the first time the final analysis on the primary endpoint from the full cohort of TE pts. **Results:** 219 TE pts (and 26 TNE pts) were included and dosed. At data cut-off (9 Jan 2025), 66 pts were still on treatment. Median age of TE pts was 60 years (range, 31-73) with 119 and 100 showing ISS II and III. Del(17p) and gain1q were the most common HRCA (40.6% and 46.6%) and 35.6% had ≥2 HRCA. The trial met its primary endpoint with an MRD-neg rate after consolidation of 73.2% in the MRD-analysis population (153/209; 10 not assessable). Further analyses confirmed the benefit across different CA subgroups. Overall, 58.4% reached MRD-neg ≥CR, 86.8% reached MRD-neg at any time. 64.8% and 40.6% retained ≥1-year- and ≥2-year-sustained MRD-neg. With a median follow-up (mFU) of 42 mo (0-85.5 mo), mPFS for TE pts was 69.7 mo, while mOS has not been reached. For TNE pts (mFU 60 mo), mPFS and mOS have not been reached. Reaching and remaining in MRD-neg state led to a significant PFS benefit (*hr* 0.16 [0.08;0.32], time-dependent Cox regression). Carfilzomib 1x weekly resulted in fewer K discontinuations than 2x weekly dosing (0.6% and 4.8%, TE pts), with more dose reductions in the 1x weekly dosing (9.5% and 5.5%, TE pts). **Conclusions:** The full CONCEPT cohort represents the largest prospective trial cohort of purely HR NDMM pts reported so far. Isa-KRd resulted in unprecedented rates of MRD-neg., sustained MRD-neg. and survival supporting the use of Isa-KRd as a standard-of-care regime in this hard-to-treat population. Clinical trial information: NCT03104842. Research Sponsor: University Medical Center Hamburg-Eppendorf; Sanofi; Amgen; BMS/Celgene.

7510 Rapid Oral Abstract Session

Linvoseltamab (LINVO) + bortezomib (BTZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): First results from the LINKER-MM2 trial.

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Background: LINVO, a BCMA×CD3 bispecific antibody, has shown high efficacy and generally manageable safety in triple-class exposed (TCE: anti-CD38 Ab + immunomodulatory drug [IMiD] + proteasome inhibitor [PI]) pts with RRMM. PIs such as BTZ have direct anti-MM activity and may enhance LINVO activity by improving immune function. We report safety and preliminary efficacy data from dose escalation and expansion in the LINVO + BTZ cohort of the phase 1b, open-label LINKER-MM2 trial (NCT05137054). **Methods:** Eligible pts were ≥18 yrs with RRMM that progressed after ≥3 lines of therapy (LoT), or ≥2 LoT if either TCE or double-class refractory (IMiD + PI). Prior BTZ was allowed if previously tolerated and ≥6 months (mos) had elapsed since last exposure. BTZ-refractory pts were allowed during dose escalation. Treatment (tx) began with LINVO alone (Cycle [C] 0: 2 step-up doses [5 and 25 mg] and ≥1 full dose [dose level [DL] 1 = 100 mg or DL2 = 200 mg]) before initiating standard dose BTZ (1.3 mg/m^2 twice weekly over 21-day cycles) at C1. LINVO was given once weekly (QW) in C1–4, then Q3W thereafter. BTZ dosing could be switched to QW after C3 and ended after a total of 8 cycles. Dexamethasone premedication was limited to C0–1. Primary endpoints were dose-limiting toxicities (DLTs; dose-finding portion) and incidence/severity of tx-emergent AEs (TEAEs). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). **Results:** As of Sept 30, 2024, 22 pts had received tx (DL1: n=6; DL2: n=16). Median follow-up duration was 6.3 mos (range 1–21), with 55% of pts still receiving tx. Median age was 68.5 yrs (range 45–77), 68% were male, 23% had ISS stage III, and 55% had extramedullary or paraskeletal disease. Median prior LoT was 3 (range 2–9), including 86% of pts with TCE and 41% with triple-class refractory disease; 59% were refractory to ≥1 PI (9% BTZ-refractory). Among evaluable pts, ORR was 79% (11/14; DL1 80% [4/5]; DL2 78% [7/9]). The 6-month DOR rate was 90% (95% CI 47–99) and 6-month PFS rate was 79% (95% CI 47–93). PK analysis found LINVO concentrations were not affected by addition of BTZ. The most common TEAEs were neutropenia (any Grade [Gr] 59%; Gr 3–4 45%), thrombocytopenia (50%; 36%), and cytokine release syndrome (55%; 0%). ICANS was reported in 4 pts (all Gr 1–2 with onset during step-up dosing). Infections were reported in 82% of pts (Gr 3–4 36%); 1 pt died of pneumonia ≤30 days after last dose before start of combination tx. One DLT occurred at DL2 (Gr 3 CMV colitis on day 48; resolved with tx delay and ganciclovir). **Conclusions:** LINVO + BTZ induced high response rates, with encouraging early DOR and PFS, in a population that was mostly PI-refractory. Safety was consistent with the known profile of each drug, and risk of Gr 3–5 infection was similar to LINVO monotherapy. These data will inform LINVO combination strategies for earlier LoT. Clinical trial information: NCT05137054. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Heterogeneity in the expression of GPRC5D between patients with multiple myeloma.

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Background: G-protein-coupled receptor class C group 5 member D (GPRC5D) is a protein inducible by all-trans retinoic acid with expression levels that vary depending on cellular differentiation. This protein receptor is targeted by several therapeutic modalities including chimeric-antigen receptor T-cell therapy (CAR-T), T-cell engagers (TCEs) and antibody-drug conjugates (ADCs). However, our understanding of GPRC5D expression levels in multiple myeloma cells and patient-to-patient heterogeneity remains limited. We investigated the expression levels of GPRC5D in the plasma cells of patients with multiple myeloma and compared its level of expression with those of CD38, CD138 and BCMA (TNFRSF17). **Methods:** Plasma cells from the bone marrow aspirates of 290 patients with multiple myeloma were enriched using CD138 column. RNA was extracted from the CD138 enriched population and sequenced by next generation sequencing (NGS) using a targeted RNA panel of 1600 genes. The RNA expression levels of various genes were quantified and expressed as transcript per million (TPM). **Results:** There was significant variation in the expression of GPRC5D between myeloma samples. The median and standard deviations for CD38, CD138, BCMA, and GPRC5D were 89 and 113, 69 and 134, 58 and 132, and 10 and 166, respectively. There was significant correlation ($P < 0.00001$) between CD38, CD138 and BCMA. However, there was no correlation between the levels of GPRC5D and CD38 (R=-0.05, P= 0.4), CD138 (R=0.3, P= 0.6) or BCMA (R=0.1, P=0.02). Ten samples (3%) had zero TPM expression of GPRC5D despite relatively high CD138 (between 33 TPM and 487 TPM). The ratio of GPRC5D: BCMA varied from 0 to 39 with one sample with an exceptionally high ratio of 459 due to very low BCMA with high CD138 due to anti-BCMA therapy. **Conclusions:** Analysis of these data suggests that unlike BCMA, there is a significant patient-to-patient heterogeneity in GPRC5D expression. GPRC5D expression levels show a wide variation with approximately 3% of patients showing an absence of GPRC5D expression. Clinical trials exploring anti-GPRC5D therapy should consider measuring GPRC5D expression levels and potentially explore other therapies that may induce its increased expression given our findings. Research Sponsor: None.

RNA Expression Levels (TPM)

Variable	Median	Lower Quartile	Upper Quartile
CD38	89	63	135
CD138	69	44	134
BCMA	58	35	106
GPRC5D	10	2	50

Spearman Correlations

Pair of Variables	R	t(N-2)	p-value
CD38 & CD138	0.362809	6.60727	0.0000000
CD38 & BCMA	0.383742	7.05224	0.0000000
CD138 & BCMA	0.63282	13.86974	0.0000000
CD138 & GPRC5D	0.028007	0.47548	0.6348020
CD38 & GPRC5D	-0.045081	-0.76583	0.4444070
BCMA & GPRC5D	0.138314	2.37004	0.0184450

Belantamab mafodotin plus lenalidomide/dexamethasone in newly diagnosed intermediate-fit & frail multiple myeloma patients: Long-term efficacy and safety from the phase 1/2 BELARD clinical trial.

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Background: We report the long-term safety & efficacy results of a novel, extended dosing schedule of belantamab mafodotin (belamaf) combined with Lenalidomide & Dexamethasone (Rd), in transplant-ineligible newly diagnosed Multiple Myeloma patients (pts). **Methods:** Phase 1/2 BelaRd trial (NCT04808037) Part 1 evaluated the safety/tolerability of belamaf 2.5/1.9/1.4 mg/kg plus Rd & established a recommended phase 2 dose (RP2D) of 1.9 mg/kg Q8W, extended to Q12W for Ocular Adverse Events (OAEs, Best Corrected Visual Acuity [BCVA] change from baseline & keratopathy). Dosing was led by ophthalmologist-assessed OAEs. In Part 2 RP2D is assessed in 2 groups: Dosing in Group A is guided as in Part 1 & in Group B by Vision-Related Anamnestic (a 9-question tool on pt-reported ocular symptoms & their impact on daily functioning) & ≥Gr3 OAEs. Safety/efficacy results from both Parts of the trial are presented. **Results:** Of Part 1 pts (n=36; median age: 72.5; male: 53%), 25 (69%) are ongoing & 11 (31%) discontinued (8 [22%] due to fatal events; 1 [3%] progressive disease; 2 [6%] withdrew consent). 17%/75% of pts had stage I/II disease per R-ISS & 8% high-risk cytogenetics (HRC). At a median follow-up (FU) of 36.2 months, Overall Response Rate (ORR) was 100%. Meaningful BCVA decline (Snellen <20/50) was recorded in 12% & Gr2/≥Gr3 keratopathy in 12%/3% of ocular exams. Median time to resolution was 1.9/1.1 months for ≥Gr2 BCVA/keratopathy OAEs, respectively. The most common (≥10%) Gr≥3 non-ocular AEs were fatigue, diarrhea, rash, COVID-19, pneumonia & insomnia. Of Part 2 pts (n=30; median age: 75; male: 67%), 22 (73%) are ongoing & 8 (27%) discontinued (6 [20%] due to fatal events; 1 [3%] progressive disease; 1 [3%] withdrew consent). 27%/63% of pts had stage I/II disease per R-ISS & 17% had HRC. At a median FU of 19.7 months, ORR was 96.7%. Meaningful BCVA decline was recorded in 27% & Gr2/≥Gr3 keratopathy in 9%/<1% of ocular exams. Median time to resolution of ≥Gr2 OAEs was 1.75 months. The most common Gr≥3 non-ocular AEs were fatigue & rash. The 12/24/36-months Time to Progression rates for all 66 pts were 98.2%/98.2%/94.4% (table 1). **Conclusions:** As has also been shown in the DREAMM-7/-8 studies,-belamaf exhibits substantial clinical activity, with rapid, deep & durable responses in an unfit pt population, with only 2 PDs observed after a median of ~2 years FU. Only a few high-grade OAEs were recorded, that resolved quickly & no new safety signals were observed. Moving forward, the BelaRd combination, with the extended belamaf dosing schedule, warrants further investigation in larger pt numbers. Clinical trial information: NCT04808037. Research Sponsor: None.

Time to progression (TTP) rates in the overall population (66 pts).

	TTP rate in % (95% CI)
12 months	98.21 (87.99-99.75)
24 months	98.21 (87.99-99.75)
36 months	94.44 (77.81-98.70)

CI: Confidence Interval.

7513 Rapid Oral Abstract Session

Linvoseltamab (LINVO) + carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Initial results from the LINKER-MM2 trial.

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Background: LINVO, a T-cell redirecting BCMA×CD3 bispecific antibody, has demonstrated high efficacy and generally manageable safety in triple-class exposed (TCE: anti-CD38 Ab + immunomodulatory drug [IMiD] + proteasome inhibitor [PI]) pts with RRMM. Combination treatment (tx) with CFZ, a potent second-generation PI, may enhance clinical activity via rapid cytoreduction and complementary immunostimulatory mechanisms like immunogenic cell death and antigen spreading. We report safety and preliminary efficacy from dose escalation in the LINVO + CFZ cohort of the phase 1b, open-label LINKER-MM2 trial (NCT05137054). **Methods:** Eligible pts were ≥18 years with RRMM that progressed after ≥3 lines of therapy (LoT), or ≥2 LoT if either TCE or double-class refractory (IMiD + PI). Prior CFZ was allowed if previously tolerated and ≥6 months had elapsed since last exposure. CFZ-refractory pts were allowed during dose escalation. Tx began with LINVO alone (Cycle [C] 0) consisting of 2 step-up doses (5 mg and 25 mg) and 2 full doses (dose level [DL] 1 = 100 mg or DL1b = 150 mg) before initiation of CFZ (20/56 mg/m^2 on days 1, 2, 8, 9, 15, 16) at C1. LINVO was given once weekly (QW) in C1–4, and Q2W thereafter. CFZ dosing could be switched to QW after C2. Dexamethasone premedication was limited to C0–1. Primary endpoints were dose limiting toxicities (DLTs) and tx-emergent adverse events (TEAEs). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). **Results:** As of Sep 30, 2024, 18 pts were treated at DL1 (n = 12) or DL1b (n = 6). Median duration of follow-up was 16.9 (DL1) and 7.7 months (DL1b), with 67% and 83% of pts still receiving tx, respectively. Median age was 68 years (range 53–79), 50% were male, 6% had ISS stage III, 50% had extramedullary or paraskeletal disease, and 17% had high-risk cytogenetics. Median prior LoT was 3 (2–6), including 83% of pts with TCE and 33% with triple-class refractory disease. Among evaluable pts, ORR was 91% at DL1 (10/11; ≥VGPR 91%) and 100% at DL1b (6/6; ≥VGPR 80%). Median DOR was not reached at either DL. For DL1, the PFS rate was 91% (95% CI 51–99) at 6 months and 73% (95% CI 37–90) at 12 months. No PFS events had occurred at DL1b. PK analysis found LINVO concentrations were not affected by addition of CFZ. The most common TEAEs were neutropenia (any Grade [Gr] 78%; Gr 3–4 61%), thrombocytopenia (61%; 39%), and cytokine release syndrome (61%; Gr ≥3 0%). One pt experienced ICANS (Gr 1). Infections were reported in 89% of pts (Gr ≥3 44%). One DLT was observed at DL1, Gr 4 thrombocytopenia in the setting of tumor lysis syndrome, from which the pt recovered and afterward resumed tx. **Conclusions:** LINVO + CFZ induced a high rate of deep and durable responses with a safety profile consistent with the individual drugs, supporting further development. Enrollment at 200 mg LINVO in combination with CFZ is ongoing. Clinical trial information: NCT05137054. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7514 Rapid Oral Abstract Session

Phase 1, first-in-human study of ISB 2001: A BCMAxCD38xCD3-targeting trispecific antibody for patients with relapsed/refractory multiple myeloma (RRMM)—Dose escalation (DE) results.

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Background: MM remains an incurable disease and resistance mechanisms are emerging. ISB 2001, a first-in-class trispecific T cell engager, redirects cytotoxic T cells to BCMA and/or CD38-expressing myeloma cells. By simultaneously targeting two TAA, ISB 2001 enhances avidity binding to tumor cells in vitro, hence potency, while the distal positioning of the CD38 vs CD3 binders minimizes CD38-related off-tumor adverse events. **Methods:** We report data from the DE portion of a Phase 1 study of ISB 2001, assessing safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) in RRMM patients (pts) exposed to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 therapies and refractory or intolerant to established therapies. Prior BCMA-targeted and/or T-cell directed therapies were allowed. ISB 2001 was administered weekly subcutaneously (SC) in 28-day cycles, with initial step-up doses on Days 1 (15μg/kg) and 4 (variable). DE utilized an accelerated titration design (initial 3 cohorts with single-patient dosing) followed by a standard 3+3 design. DLTs were evaluated in the first 28 days. After DE, the study will proceed with Part 2 (dose expansion) to confirm safety and select the recommended Ph2 dose under FDA Project Optimus. **Results:** As of January 13, 2025, 24 pts were treated with ISB 2001 across 8 dose levels (5–1800 μg/kg) with a median follow-up of 6 months (range: 2–12). DL9 (2700 μg/kg) is last dose level and currently enrolling. Among 24 pts, median age was 66 years; 58% male, 83% white with a median of 6 prior lines of therapy (range: 3-11). All pts were triple-exposed, 17/24 (71%) penta-exposed, and 3/17 penta-refractory (18 %). No DLT, adverse events (AE) leading to treatment discontinuation or deaths occurred. Serious AEs were reported in 8 (33%) patients. Drug related Grade (Gr) 3-4 AEs were seen in 13 (54%) pts. CRS was reported in 17 (70.8%) patients, primarily Grade 1–2, with a median onset of 3 days and a median duration of 2 days. No neurologic AEs or ICANs. The Overall Response Rate (ORR) was 75% across all 8 doses, including stringent CR (sCR) 13%, CR 13%, VGPR 38%, PR 13%. Responses were observed from dose level as low as 50 μg/kg (MRD-neg, sCR) with an ORR of 82% at doses ≥50 μg/kg. Median time to response was 36 days. ISB 2001 showed near dose-proportional PK, a half-life >10 days, and consistent T-cell activation, supporting its mechanism of action. **Conclusions:** ISB 2001 was well tolerated with manageable CRS, no ICANS and demonstrated robust anti-myeloma activity in heavily pretreated RRMM pts (NCT05862012). Full clinical data, including PK and PD results from the dose-escalation portion of the study, will be presented at the conference. Clinical trial information: NCT05862012. Research Sponsor: IGI.

7515 Rapid Oral Abstract Session

Minimal residual disease (MRD) negativity (neg) in patients (pts) with relapsed or refractory multiple myeloma (RRMM) treated with belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd): Analysis from the DREAMM-8 trial.

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Background: In DREAMM-8 (NCT04484623), BPd demonstrated a statistically significant, clinically meaningful benefit to progression-free survival (PFS) vs PVd in pts with RRMM who received ≥1 prior line of treatment including lenalidomide. MRD neg has been shown to be a predictor of PFS and overall survival (OS) in MM. We assessed efficacy outcomes by MRD status. **Methods:** Ptswere randomized (1:1) to BPd or PVd. The primary endpoint was independent review committee (IRC)–assessed PFS; OS, duration of response, and MRD status determined by next-generation sequencing with 10^{-5} sensitivity threshold was assessed in pts with complete response or better (≥CR) every 6 mo until progressive disease. Post hoc subgroup analyses of PFS and OS were conducted based on IRC-assessed response (≥CR or ≥VGPR) and MRD-neg status using Kaplan-Meier method; CIs were estimated using Brookmeyer-Crowley method. **Results:** 302 pts were randomized to BPd (n=155) or PVd (n=147). As previously reported (median follow-up, 21.8 mo), more pts with BPd had CR-based MRD neg vs PVd (37/155 [24%] vs 7/147 [5%]). A similar trend was seen in pts with ≥VGPR; 50/155 pts (32%) had VGPR-based MRD neg with BPd vs 8/147 (5%) with PVd. In the DREAMM-8 trial, MRD neg was associated with improved efficacy outcomes (Table). Pts with CR-based MRD neg had a lower risk of disease progression or death compared with pts without MRD neg (PFS HR, 0.14; 95% CI, 0.06-0.32; Table); median was NR overall and in each treatment arm (HR [BPd vs PVd], 0.90; 95% CI, 0.10-7.76). MRD neg pts had a lower risk of death (OS HR, 0.18; 95% CI, 0.07-0.49). In all pts who did not have CR-based MRD neg, pooled median PFS was 14.0 mo (95% CI, 11.1-18.6 mo; BPd, 19.6 mo; PVd, 10.2 mo; HR [BPd vs PVd], 0.67; 95% CI, 0.47-0.94), and the pooled 18-mo PFS rate was 46% (95% CI, 39%-52%; BPd, 52%; PVd, 39%). Median OS was NR overall, 33.0 mo (95% CI, 23.7-NR) with BPd and NR with PVd; 18-mo OS rate was 69% (95% CI, 63%-75%; BPd, 72%; PVd, 67%). **Conclusions:** Consistent with previous reports, MRD neg was associated with a robust benefit in PFS and OS, highlighting the significance of a greater response depth. Pts with BPd achieved a 5-fold improvement in CR-based MRD neg vs PVd (24% vs 5%). Pts who did not achieve CR-based MRD neg had a clinically meaningful benefit in PFS with BPd vs PVd. Clinical trial information: NCT04484623. Research Sponsor: Funding statement: This study sponsored by GSK. Editorial support provided by Nucleus Global and funded by GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

	MRD neg			Non-MRD neg		
MRD status (≥CR), n	**Pooled (44)**	**BPd (37)**	**PVd (7)**	**Pooled (258)**	**BPd (118)**	**PVd (140)**
Median PFS (95% CI), mo	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)	14.0 (11.1-18.6)	19.6 (13.5-NR)	10.2 (8.4-17.1)
18-mo PFS rate (95% CI), %	93 (79-98)	91 (75-97)	100 (100-100)	46 (39-52)	52 (42-62)	39 (30-48)
18-mo OS rate (95% CI), %	93 (80-98)	92 (76-97)	100 (100-100)	69 (63-75)	72 (62-79)	67 (59-74)

Daratumumab plus bortezomib, lenalidomide, and dexamethasone (DVRd) in patients with newly diagnosed multiple myeloma (NDMM): Subgroup analysis of transplant-ineligible (TIE) patients in the phase 3 CEPHEUS study.

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Background: After readout of the PERSEUS and CEPHEUS trials, daratumumab-based therapy + VRd is emerging as the standard of care in NDMM treatment. In CEPHEUS (NCT03652064), DVRd improved minimal residual disease negativity (MRD neg) and progression-free survival (PFS) vs VRd in patients (pts) with TIE or transplant-deferred (TD) NDMM. As transplant deferral is not a common clinical pathway in many regions, here we report a post hoc analysis of DVRd efficacy in TIE pts. **Methods:** CEPHEUS enrolled pts with TIE or TD NDMM, ECOG performance status (PS) 0–2, and an International Myeloma Working Group (IMWG) frailty score of 0 or 1. Pts were randomized (1:1) to DVRd or VRd. In this analysis, the primary endpoint of overall MRD neg rate (MRD neg at 10^{-5} and complete response or better [≥CR]), and key secondary endpoints, including PFS and sustained MRD neg (confirmed MRD neg ≥12 months [mo] apart without MRD positivity in between) were assessed in the CEPHEUS TIE population. **Results:** Of 395 pts, 289 were TIE (DVRd, n=144; VRd, n=145). TIE population baseline (BL) characteristics were generally well balanced between DVRd vs VRd. In the TIE vs intent-to-treat (ITT) population, median age was older (72 vs 70 years [y]), and a higher percentage of pts were intermediate fit per IMWG criteria (41.2% vs 35.2%). In TIE pts, overall MRD neg rate at 10^{-5} was 60.4% for DVRd and 39.3% for VRd (odds ratio [OR] 2.37; 95% CI 1.47–3.80; $P<0.0001$); at 10^{-6}, it was 45.8% vs 26.9% (OR 2.28; 95% CI 1.40–3.73; $P=0.001$). Sustained MRD neg rate (10^{-5}) was 46.5% vs 27.6% (OR 2.27; 95% CI 1.39–3.70; $P=0.0010$). Overall ≥CR rate was 80.6% vs 61.4% (OR 2.73; 95% CI 1.71–4.34; $P<0.0001$). At 58.7-mo median follow-up, median PFS was NR for DVRd and 49.6 mo for VRd, and the 54-mo PFS rate was 69.0% vs 48.0% (HR 0.51; 95% CI 0.35–0.74; $P=0.0003$); OS favored DVRd vs VRd (HR 0.66; 95% CI 0.42–1.03; after censored for deaths due to COVID-19, HR 0.55; 95% CI 0.34–0.90). Treatment effect was generally consistent across subgroups (Table). Safety profile was consistent with ITT and the known profile for daratumumab subcutaneous and VRd. **Conclusions:** In CEPHEUS TIE pts, the ≥CR rate was 80.6% and overall MRD neg rate (10^{-5}) was 60.4%, with ~50% of pts sustaining MRD neg for ≥1 y. Nearly 70% of pts were alive and progression free at 4.5 y. These subgroup data reinforce the strong efficacy of DVRd in the TIE population. Clinical trial information: NCT03652064. Research Sponsor: Johnson & Johnson.

	MRD neg (10^{-5}) rate, %				Median PFS, mo			
BL characteristic	**DVRd**	**VRd**	**OR**	**95% CI**	**DVRd**	**VRd**	**OR**	**95% CI**
ISS stage I	66.0	41.7	2.72	1.20–6.17	All not estimable	60.6	0.58	0.30–1.12
II	59.3	43.9	1.86	0.88–3.96		49.4	0.41	0.21–0.77
III	55.0	30.0	2.85	1.14–7.15		33.6	0.61	0.31–1.19
Cytogenetic risk High	50.0	50.0	1.00	0.28–3.57		31.7	0.82	0.33–2.03
Standard	62.9	38.7	2.68	1.54–4.64		60.6	0.54	0.33–0.86
ECOG PS 0	57.7	43.9	1.75	0.82–3.73		60.6	0.33	0.16–0.69
≥1	62.0	36.4	2.85	1.56–5.22		47.2	0.63	0.40–0.99

Isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) in newly diagnosed multiple myeloma (NDMM): Outcomes in patients with 1q21+ status in the phase 3 IMROZ study.

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Background: Gain or amplification of 1q21 (1q21+, ≥3 copies) is a chromosomal abnormality often detected in MM that can negatively affect prognosis by its involvement in resistance to therapy and MM progression. Results from the global, randomized Phase 3 IMROZ study (NCT03319667) demonstrated significant progression-free survival (PFS) benefit with Isa-VRd followed by Isa-Rd compared with VRd followed by Rd, along with deep and sustained responses, in transplant-ineligible patients (pts) with NDMM. To evaluate efficacy of combination treatment with Isa-VRd/Isa-Rd vs VRd/Rd in NDMM pts with 1q21+ status, we analyzed clinical outcomes (PFS, overall response, minimal residual disease negativity [MRD−]) for 1q21+ pts in the IMROZ study. **Methods:** In IMROZ, 446 pts were randomized 3:2 to receive Isa-VRd (n=265) in the initiation phase followed by maintenance with Isa-Rd vs VRd (n=181) followed by Rd. 1q21+ status was assessed by FISH (30% cutoff) and prespecified as ≥3 copies (gain=3, amplification >3). Isolated 1q21+ was defined as presence of 1q21+ and absence of high-risk chromosomal abnormalities [HRCAs; del(17p), t(4;14), t(14;16)]. MRD data by NGS were reported at 10^{-5} sensitivity threshold. **Results:** Overall, 35.9% and 38.7% of pts had 1q21+ status in the Isa-VRd and VRd arms, respectively (23.8% and 26.0% with gain(1q21), 12.1% and 12.7% with amp(1q21); 7.2% and 8.3% also had ≥1 HRCA). Treatment with Isa-VRd significantly prolonged PFS vs VRd in 1q21+ pts (with or without HRCA) and in pts with isolated 1q21+ (see Table) and led to higher rates of complete response (CR) and MRD−. A substantially greater proportion of pts with 1q21+ or isolated 1q21+ achieved MRD− CR and sustained MRD− for ≥12 months with Isa-VRd than with VRd. Data for gain(1q21) and amp(1q21) will be presented. **Conclusions:** Results from our analysis of outcomes in 1q21+ pts in the IMROZ trial demonstrate consistent PFS benefit with Isa-VRd vs VRd, as reported in the overall study population. Benefit was observed regardless of 1q21+ or isolated 1q21+ status.These findings are in line with similar analyses done with Isa-pomalidomide-dexamethasone and Isa-carfilzomib-dexamethasone in Phase 3 studies. Clinical trial information: NCT03319667. Research Sponsor: Sanofi.

	1q21+		Isolated 1q21+[a]		Standard risk[a]	
	Isa-VRd	VRd	Isa-VRd	VRd	Isa-VRd	VRd
n (%)	95 (35.9)	70 (38.7)	75 (28.3)	55 (30.9)	207 (78.1)	140 (77.4)
mPFS, mo (95% CI)	NR (NR–NR)	39.13 (22.93–48.95)	NR (NR–NR)	43.01 (20.60–59.70)	NR (NR–NR)	53.91 (43.01–NR)
PFS HR (95% CI)	0.407 (0.253–0.653) *p*=0.0002		0.369 (0.213–0.642) *p*=0.0004		0.517 (0.363–0.737) *p*=0.0003	
ORR %	95.8	85.7	96.0	81.8	97.5	100
≥CR %	76.9	60.0	78.7	52.7	72.5	79.4
MRD− %	63.2	41.4	65.3	40.0	58.9	40.7
MRD− CR %	62.1	38.6	64.0	36.4	55.6	37.9
Sustained MRD− ≥12 mo %	51.6	22.9	50.7	23.6	45.4	22.9

[a]Absence of del(17p), t(4;14) and t(14;16). NR, not reached.

Disease response at apheresis and association with long-term outcomes following CAR-T cells for relapsed/refractory multiple myeloma (RRMM).

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Background: The two approved BCMA-targeted CAR-T products, cilta-cel and ide-cel, have significant efficacy in RRMM, but are not considered curative. Initial studies in ≥4th line RRMM required progressive disease (PD) at time of enrollment and T cell apheresis. We hypothesized that using CAR-T cells as a planned consolidation strategy (i.e. in patients (pts) with stable or responsive disease on their current therapy) may lead to lower toxicity and better long-term disease control. **Methods:** We conducted a retrospective review of all RRMM pts receiving commercial CAR-T cells at the University of Pennsylvania from 6/1/21 to 4/30/24, with at least 6 months of follow-up. Intent for consolidation was retroactively assigned by chart review. Kaplan-Meier methodology was used to determine PFS and OS. **Results:** We identified 149 pts for analysis, with a median follow-up of 14.4 months (mos). Median prior lines was 6 and 81% of pts were triple class-refractory; 46% had high-risk cytogenetics, 26% had extramedullary disease, and 17% had prior BCMA-directed therapy. Pts received either cilta-cel (54%) or ide-cel (46%), and 95% received bridging therapy. CAR-T cells were intended as planned consolidation in 51 pts (34%); of these, 36 (71%) had ≥PR at time of apheresis. For consolidation vs non-consolidation groups, this translated into greater depth of response post-CAR-T cells (≥VGPR, 86% vs. 66%, p=0.01), lower rates of ≥grade 3 CRS (1.9% vs. 9.1%, p=0.16), and longer PFS (median not reached vs. 10 mos, p=0.001), respectively. The PFS improvement was seen for both cilta-cel (p=0.01) and ide-cel (p=0.04). No differences in neurotoxicity were noted. We also performed analyses based on response at apheresis, regardless of intent (8% ≥VGPR, 23% PR, 27% stable disease (SD), and 42% PD). PFS at 20 mos was 88%, 47%, 55%, and 31% for ≥VGPR, PR, SD, and PD at apheresis, respectively (p=0.015). Median PFS of pts with at least SD (≥SD) at apheresis was not reached vs. 9.4 mos in those with PD (p= 0.003), with 20-month OS of 87% in the ≥SD group and 68% in the PD group (p=0.015). Subgroup analysis confirmed this PFS difference for both cilta-cel and ide-cel, while the OS impact was only seen for cilta-cel. On multivariate analysis, having ≥SD at apheresis was an independent predictor for PFS. No statistically significant differences in CRS and ICANS were observed based on response at apheresis. Pts with ≥SD at apheresis had higher absolute lymphocyte counts at days 7 and 14 post-CAR-T infusion than those with PD, indicating disease status at apheresis may be associated with CAR-T product quality. **Conclusions:** Our data suggest that disease control (≥SD) at time of T-cell collection is associated with more durable responses, supporting use of CAR-T cells as a consolidation strategy in RRMM. We cannot conclude these associations are causal. Further analyses of apheresed T cell characteristics are planned. Research Sponsor: None.

Second primary malignancy (SPM) in patients (pts) with multiple myeloma (MM) receiving chimeric antigen receptor T-cell (CAR T) therapy or other systemic anticancer therapy (SACT): A comparative study using a real-world database.

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Background: Cases of SPM have been reported following CAR T therapy, but comparative studies are scarce. We compared the risk of SPM following CAR T therapy vs other SACT in pts with MM. **Methods:** Pts aged ≥18 years with MM who initiated CAR T therapy or other SACT, except stem cell transplant, in second-line or beyond were identified from Komodo Health claims data (3/26/2021–1/31/2024). Incident SPM was identified by ≥1 diagnostic code through death, disenrollment, or data cutoff (4/30/2024), whichever was earliest. Cumulative incidence of SPM following CAR T therapy or other SACT was estimated through 24 months, weighted by baseline factors including prior MM treatments; p-values were calculated for differences in the area under the curves through 24 months. **Results:** Pts who received CAR T therapy (n=436) or other SACT (n=18,603) were followed for a median of 11.8 months (IQR 5.7–22.8). Compared to pts who received other SACT, pts who received CAR T therapy had nominally higher risk (cumulative incidence [95% CI]) of any SPM (p = 0.05; 24.1% [18.4%, 29.8%] vs. 18.1% [13.5%, 22.8%] at 24 months), driven by significantly higher heme SPM risk (p=0.01; 8.7% [6.1%, 11.4%] vs. 5.6% [3.0%, 8.8%] at 6 months, 12.1% [8.7%, 15.3%] vs. 7.2% [4.3%, 10.4%] at 12 months, and 17.9% [12.8%, 23.5%] vs. 8.7% [5.4%, 11.7%] at 24 months; respectively), including higher risks of myelodysplastic syndrome and leukemias. The risk of solid SPM was nominally lower following CAR T vs other SACT (p=0.28; 9.1% [6.2–12.3] vs 13.9% [9.6–18.4] at 24 months). In the sensitivity analysis requiring ≥2 diagnostic codes to identify an SPM, the absolute risk was reduced and the difference in heme SPM risk was attenuated (p=0.39; Table). Notably, pts were more likely to receive bone marrow examination following CAR T therapy vs other SACT (47% vs 10% at 0–3 months, respectively). **Conclusions:** Pts with MM appeared to have a higher risk of heme SPM through 24 months following CAR T therapy compared with other SACT. However, the difference was attenuated in a sensitivity analysis that required ≥2 diagnostic codes, assumed to represent a confirmed diagnosis. Potential detection bias may exist, suggested by a higher rate of bone marrow examination following CAR T therapy. Longer term studies are needed to further evaluate this association. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Cumulative incidence (%) and 95% CI of SPM at 24 months.

SPM	Analysis	CAR T therapy	Other SACT	p-value
Any	Main	24.1 (18.4–29.8)	18.1 (13.5–22.8)	0.05
	Sensitivity	11.5 (8.1–15.1)	9.5 (6.3–13.2)	0.10
Heme	Main	17.9 (12.8–23.5)	8.7 (5.4–11.7)	0.01
	Sensitivity	5.5 (3.4–7.6)	4.7 (2.3–7.6)	0.39
Solid	Main	9.1 (6.2–12.3)	13.9 (9.6–18.4)	0.28
	Sensitivity	6.4 (3.8–9.7)	5.1 (3.0–8.4)	0.14

Sensitivity analysis requires 2+ diagnostic codes to identify an SPM.

Utilization and cost implications for collection and storage of excess autologous hematopoietic stem cells in patients with multiple myeloma.

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Background: Treatment for transplant-eligible patients with multiple myeloma (MM) is typically induction therapy followed by autologous hematopoietic cell transplantation (autoHCT). Guidelines recommend leukapheresis to collect sufficient hematopoietic progenitor cells (HPCs) for initial and potential second autoHCT. But with novel immune effector therapies, the need for salvage autoHCT has decreased. HPC mobilization and collection are resource-intensive, both in time and costs. We aimed to assess the utilization and costs of cryopreserved HPCs stored for potential second autoHCTs at our center to evaluate the impact for adopting a single-transplant collection strategy for all MM patients. **Methods:** We conducted a retrospective study using clinical and laboratory databases at a small transplant center in upper Midwest. A total of 97 patients (age ≥18 years) with confirmed diagnosis of MM who underwent HPC mobilization and collection between 2013 and 2023 were included. We extracted demographical patient information as well as clinical data including disease characteristics, previous lines of therapies, number of mobilization and apheresis sessions, and number of CD34 cells/kg collected, used, and stored. As part of our quality improvement, we proposed a target collection goal of ≥3.5x10^6 CD34 cells/kg versus current 5-10 x10^6/kg and used this to assess excess HPC apheresis collections. Based on our current institution-specific charges, estimate cost of 1 session of HPC collection was 7625, processing and cryopreservation per product 7792, and storage of excess cells after 1st transplant 3943 per year. **Results:** Of the 97 patients who underwent HPC collection for two autoHCTs (mean age at collection 64.5 ±8.7), only 4 (4.1%) underwent a salvage auto-HCT. Based on the proposed reduced collection target, 29 (29.9%) patients had ≥1 excess collection sessions. Among the patients who underwent excess collections, median cost of these collections was 7625 per patient and median cost for processing and cryopreservation of those products was 23,308 per patient. Total cost for the excess collection sessions plus cryopreservation of the cells collected was 871,768. Median number of years of excess HPC cells stored beyond the 1st transplant but not used was 4 (0.2-11.8), with an estimated median cost of 23,576 per patient. Total storage cost for unnecessary excess HPCs for all patients was 2,471,775. **Conclusions:** This study demonstrates even for our small center excess HPCs collected during the first autoHCT are rarely used for 2nd or salvage transplant, incurring substantial costs for the institution and patient. Similar to prior HPC utilization studies, our results support changing collection practices for MM patients to improve resource allocation and reduce unnecessary expenditures. Research Sponsor: None.

Impact of venous thromboembolism on survival in multiple myeloma patients receiving bispecific antibody therapy: Insights from real-world data.

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Background: Patients with multiple myeloma (MM) have a significantly higher risk of venous thromboembolism (VTE), up to 20 times greater than the general population. This risk is influenced by the disease, anti-myeloma treatments, and patient-related factors. However, there is limited information regarding the rates of VTE and survival outcomes with FDA-approved bispecific antibodies (BsAbs) such as teclistamab, elranatamab, and talquetamab. This study aims to assess these endpoints using real-world data (RWD). **Methods:** A retrospective, multicenter RWD analysis was conducted using the TriNetX database on Jan 17, 2025. Two cohorts were analyzed: 1) MM patients who have been treated with one of the FDA-approved BsAbs (teclistamab, elranatamab, or talquetamab) and who developed VTE (deep vein thrombosis or pulmonary embolism) within 18 months from initiation of BsAb treatment, 2) MM patients treated with the same BsAbs who did not develop VTE in the same time frame. Kaplan-Meier analysis, log-rank test, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI) were used to assess the primary outcomes, which were overall survival and risk of VTE development. Propensity score matching was used to control the impact of specific known confounders. **Results:** We identified 1530 MM patients treated with the aforementioned BsAbs and had data available regarding VTE development within 18 months of treatment initiation. The patients' mean age at the index event (treatment initiation and VTE) was 69±9.9 years, and 52.2% were males. The rate of VTE was 8.5% (n=130). The MM patients treated with BsAbs and developed VTE had a statistically significant higher risk of death compared to the patients without VTE (RR 1.475, 95% CI 1.117-1.946). The MM patients with VTE had statistically significantly shorter overall survival and higher risk of death (526 days vs. not reached median survival, 49.83% vs. 65.61% survival probability at 18 months, log-rank test p=0.003; HR 1.667, 95% CI 1.193-2.329). After propensity score matching for covariates [accounting for age, sex, ECOG, BMI, COVID-19, pneumonia types, certain infectious diseases, hypertensive diseases, surgery, and medications (dexamethasone, epoetin alfa, darbepoetin alfa)] although RR lost statistical significance (RR 1.333, 95% CI 0.888-2.001), the MM patients with VTE still had statistically significantly shorter overall survival and higher risk of death (50.07% vs. 72.27% survival probability at 18 months, log-rank test p=0.007; HR 1.989, 95% CI 1.190-3.325). **Conclusions:** RWD demonstrated that MM patients treated with BsAbs who developed VTE had a higher risk of death and shorter overall survival. Further analysis, possibly evaluating patient-level data on a larger cohort of patients with more sophisticated confounding controls, is needed to further clarify this finding. Research Sponsor: None.

Investigating the association between peak post-infusion absolute lymphocyte count (ALC) and delayed toxicity in myeloma (MM) patients (pts) receiving cilta-cel.

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Background: Movement and neurocognitive treatment emergent adverse events (MNTs), cranial nerve palsies (CNPs) and immune-effector cell enterocolitis (IEC-EC) are late onset toxicities associated with cilta-cel and are associated with significant morbidity and mortality. We aimed to identify predisposing risk factors to allow for formulating risk-reduction strategies. **Methods:** Retrospective study of MM pts who received FDA approved cilta-cel at Mayo Clinic between Feb 2022-Dec 2024. Interrogated factors included demographics, disease and treatment characteristics, and selected lab values at different time points. In odds ratio (OR) analyses, pts were divided by toxicity type (1) No delayed toxicity (2) MNT (3) IEC-EC without MNT (4) isolated CNP. Differences between pts in the MNT, IEC-EC and CNP groups were compared separately in a pairwise manner vs. those with no delayed toxicity. **Results:** Of 235 pts, 26 (11%) had delayed toxicity [MNT = 8 (3%), IEC-EC = 9 (4%), CNP = 14 (6%)]; 3 pts had both MNT/IEC-EC and 2 had both CNP/IEC-EC. Median onset from CAR-T infusion for MNT, IEC-EC and CNP was 19 (range 8-96), 106 (35-169) and 21 (7-43) days respectively. Of 164 evaluable pts, those who had ICANS had increased odds for any delayed toxicity (OR 4.7; 95% CI 1.6-13.8). Pts who had ICANS (OR 7.7; 1.6-36.9), HLH/MAS (OR 6.2; 1.1-6.7) and Ferritin >400mcg/L at time of lymphodepletion (OR 6.3; 1.5-32) had increased odds for MNTs. Pts who received alkylator-based bridging therapy had increased odds (OR 6.1; 1.1-35) for IEC-EC. Analysis of serial post-CAR infusion lab values showed that peak ALC was the most significant variable with differences between groups shown in table. Median time to peak ALC was 12 days (IQR 11-13). ROC analysis determined peak ALC >3 x 10^9/L as a meaningful cut point. Pts with peak ALC >3.0 x 10^9/L had increased odds of developing any delayed toxicity (OR 9.3; 3.5-29.3), MNT and CNP (table). Absolute risk of any delayed toxicity was 33% in pts with peak ALC >3 x 10^9/L vs 5% without. At this threshold, number needed to treat was 3.6. **Conclusions:** Real-world data shows that cilta-cel associated delayed toxicity is seen in ~10% of patients, with specific toxicity rates between 4-8%. Factors associated with these toxicities predominantly occur in the post CAR-T infusion period. Given that ALC expansion in the first 2 weeks correlate with CAR-T expansion, peak ALC is potentially predictive of toxicity and 3 x 10^9/L may be an interventional threshold for primary prophylaxis. Research Sponsor: None.

Peak ALC by toxicity groups.

	No Tox N=138	MNT N=8	CNP N=12	IEC-EC N=6	p value
Peak ALC (10^9/L), median (IQR)	1.8 (1.0-4.1)	6.2 (4.8-14.4)	4.3 (3.2-6.7)	3.6 (1.9-5.2)	<0.001[1]
ALC >3 x 10^9/L, n (%)	43 (31%)	7 (88%)	10 (83%)	4 (67%)	<0.001[2]
Odd Ratios vs no Tox[3], 95% CI		15.5 (2.6-293.7)	11.0 (2.8-73.9)	4.4 (0.8-25.0)	

[1]Wilcoxon/Kruskal-Wallis Tests, [2]Chi square test, [3]Logistic regression analysis.

Risk of second primary hematological malignancy post CAR-T cell therapy in relapsed/refractory multiple myeloma: Propensity-matched analysis using TriNetX database.

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Background: The Food and Drug Administration (FDA) issued a black box warning regarding the risk of T-cell lymphoma post CAR-T cell therapy has drawn global attention yet comprehensive profiling of Second Primary Malignancies is lacking in this group of patients. To address this knowledge gap, we aimed to comprehensively elucidate the current landscape of SPMs post CAR-T therapy in patients with multiple myeloma using real-world, large-scale data from TrinetX. Such efforts will be instrumental in guiding the lifelong safety monitoring of CAR-T products in the future. **Methods:** We conducted a retrospective study that included adult patients with RRMM who received CART cell therapy versus those who did not receive CART cell therapy using the TrinetX database network, a federated EMR network of more than 117 million de-identified patients. The outcomes of interest were assessing Second Primary Hematological Malignancies. Propensity matching analysis was done to assess the risk of SPM post-CART cell therapy. **Results:** A total of 803 RRMM patients received CAR-T cell therapy and 62038 RRMM patients without CART cell therapy were identified. Before matching the median follow-up was 12 months in the CART group versus 33.2 months in the non-CART group. After propensity matching analysis at a median follow-up of 12 months in the CART group and 34.4 months in the non-CART group, it was found that there was no significant increase in the risk of SPM in the CART group. (Table 1) The most common SPM remains to be AML (5%) followed by MDS (3.5%). No cases of Adult T-cell leukemia/lymphoma were detected. **Conclusions:** This real-world study shows no increased risk of second primary malignancies (SPM) following CAR T-cell therapy. Although we may have underestimated the cases if they were not admitted, and also due to limited follow-up which might not capture the late-onset SPMs. The group's next step is to re-evaluate the risk of SPM in this subgroup at five years of follow-up. Research Sponsor: None.

Hematological SPM post CART cell therapy after propensity matching analysis.

Type of SPM	RRMM post CART (n=800)	RRMM without CART (n=796)
Follicular lymphoma	0%	10 (1.25%)
Mantle cell lymphoma	0%	0 %
DLBCL	10 (1.25%)	10 (1.25%)
Hairy cell leukemia	0 %	0%
CLL	10 (1.25%)	10 (1.25%)
Hodgkin lymphoma	0 %	10 (1.25%)
Adult T cell leukemia/lymphoma	0%	0%
Mature T/NK cell lymphoma	0%	10 (1.25%)
AML	40 (5%)	32 (4.0%)
MDS	28 (3.5%)	21 (2.6%)
ALL	13 (1.62%)	20 (2.5%)

MDS: Myelodysplastic syndrome; AML: Acute myelogenous leukemia; ALL: Acute lymphoblastic leukemia; DLBCL: Diffuse Large B Cell Lymphoma; CLL: Chronic Lymphocytic Leukemia; NK: Natural Killer cells; RRMM: Relapse/Refractory Multiple Myeloma; CART: Chimeric Antigen Receptor T cell therapy; SPM: Second primary malignancy.

Investigating metabolic connectivity in patients with multiple myeloma receiving BCMA CAR T cell therapy.

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Background: BCMA-targeted CAR T cell therapy is a highly effective treatment for patients with relapsed/refractory multiple myeloma (MM) with side effects such as CRS, ICANS, and movement and neurocognitive toxicities (MNTs). Regional changes on [^{18}F]fluoro-deoxy-2-D-glucose PET (PET) can be used to derive metabolic connectivity, an emerging technique that models brain function from the uptake on a PET, allowing us to investigate alterations of regional metabolism (SUV) and changes in metabolic brain networks (connectivity) peri-CAR T. **Methods:** Patients were included in this retrospective study if they were treated with commercially available BCMA-directed CAR T cells and had pre-and post-CAR therapy PET imaging. We analyzed the connectivity of the whole brain and parcellated the brain to generate global and regional connectivity matrices and investigated the association of regional metabolic differences and differences in metabolic connectivity with clinical parameters. **Results:** Of the 108 consecutive patients (65 Cilta-cel, 43 Ide-cel), there were 61 men and 47 women (median age 65), with PET a median of 12 days prior to infusion 28 days post infusion. Toxicities included CRS alone (n=66), CRS + ICANS (n=8), CRS+facial palsy (n=3), and CRS + Parkinsonism + facial palsy (n=2). Within the entire cohort, a significantly higher SUV-mean was noted in putamen ($p<0.0004$) post-CAR T compared to pre-CAR T, with other brain regions not showing a difference. These regional differences were significantly and inversely associated with the grade of ICANS (Post-Pre: Left: t=-1.76, p=0.08; Right t=-2.1 p=0.04). When comparing patients with (n = 79) and without (n=29) any post-CAR T cell CRS/ICANS/MNT, the post SUV-mean was significantly higher in the bilateral basal ganglia (BG) of patients who experienced toxicity ($p<0.05$). The SUV-mean was significantly lower in the bilateral inferior frontal opercularis, triangularis, and bilateral Rolandic operculum of those who developed ICANS (Grade 1-2, all with CRS, n=8) vs with CRS alone (all grade 1, n=46) ($p<0.05$). Globally, the metabolic connectivity network had less efficiency (post<pre: $0.69<0.75$), and density (post-<pre: $63<74$). In local measurements, post-CAR T cell PET showed significantly lower local efficiency ($p=10^{-30}$), degree ($p=10^{-15}$), strengths (p=0.001), clustering coefficient ($p=10^{-12}$), and higher edge betweenness centrality (p=0.02) compared to the pre-CAR T timepoint. The decreases in network measurement were more severe in the frontal lobe and basal ganglia ($p=10^{-6}$ and p=0.004, respectively). **Conclusions:** Patients with neurotoxicity after BCMA CAR T had an increased SUV in the putamen, but decreased in the frontal regions and basal ganglia at Day 28. Metabolic networks were globally less efficient and less dense and have changes that signify injury or attempts at compensation. Research Sponsor: U.S. National Institutes of Health; R01CA293922.

Machine learning–based sequential analysis for optimal selection between IRD and KRD regimen in multiple myeloma patients.

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Background: Multiple myeloma (MM) is hematologic malignancy where personalized treatment strategies are essential to improve outcomes. Proteasome inhibitor-based therapy, including ixazomib (IRD) or carfilzomib with lenalidomide and dexamethasone (KRD), is one of the most commonly used regimens for treatment of MM. Early treatment response (ETR) and progression-free survival (PFS) are critically important, as these factors are among the most significant considerations in clinical decision-making for selecting optimal drug regimens in MM treatment. This study aimed to develop a machine learning (ML) model using real-world data (RWD) to predict ETR and PFS in MM patients treated with these two regimens. **Methods:** This was a retrospective analysis using real-world data (RWD) from 535 MM patients treated with either IRD or KRD regimens. We developed separate ML models for IRD and KRD treatment group to stratify the risk for inadequate treatment response for predicting ETR or PFS outcomes. ETR was assessed based on myeloma protein and the extent of plasma cell proliferation. Patients with complete response (CR), very good partial response (VGPR) were classified as the low-risk (LR) group, indicating optimal treatment response. The other patients were categorized as the high-risk (HR) group, reflecting a suboptimal treatment response. PFS was defined by the standard definition for MM treatment: LR group as at least 2 years of survival without disease progression and otherwise, HR group. ML models were trained using demographic, clinical and genetic data obtained at the initial diagnosis or prescription for IRD or KRD. Additionally, each patient's predicted ETR risk was incorporated as a feature in training the PFS model to enhance its predictive accuracy. **Results:** The area under the receiver-operating characteristic curve (AUROC) of of the PFS models improved significantly from 0.72 and 0.62 without predicted ETR as feature to 0.81 and 0.85 with ETR incorporated. ML models classified patients as 6 subgroups to suggest optimal drug selection for each group to improve ETR and PFS outcomes. Notably, IRD or KRD given to all patients without considering patient subgroups resulted in a PFS hazard ratio of 5.94 (95% CI: 1.59 – 10.31). Implementation of our ML models might inform drug drug selection in 369 patients (69.0%) among a total of 535 patients. **Conclusion:** In this study, ML models were developed to predict ETR and PFS in MM patients, facilitating personalized therapy in clinical practice. PFS models demonstrated improved performance by incorporating predicted ETR risk as an additional feature. The ETR-incorporated models with clinical and genetic data stratified patients into low-and high-risk groups proposing optimal treatment strategies to potentially improve PFS in 185 patients (35%). Our findings implicate the potential of RWD and ML to advance precision medicine and improve outcomes through ML-informed treatment decisions. Research Sponsor: None.

Efficacy and safety of isatuximab subcutaneous (SC) plus carfilzomib and dexamethasone (Isa-Kd) in patients with relapsed/refractory multiple myeloma (RRMM): Results of the phase 2 study IZALCO.

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Background: IV isatuximab (Isa) can provide benefit to patients (pts) in multiple combinations across the therapeutic spectrum for MM. SC administration would offer a more convenient treatment option for pts and caregivers.Results of a Phase 1b study demonstrated safety and efficacy of Isa SC administration via an on-body delivery system (OBDS; an investigational wearable injector), plus pomalidomide and dexamethasone in RRMM pts. In the Phase 2 IZALCO study, we evaluated efficacy (primary objective), safety, pharmacokinetics (PK), and pt preference for Isa SC administration by manual injection or OBDS, in combination with carfilzomib and dexamethasone (Kd), in RRMM pts. **Methods:** Isa SC 1400 mg was given weekly in cycle [C]1 then biweekly. In Part 1 of the study, pts received Isa injected SC manually. In Part 2, pts were randomized to Isa administered SC via OBDS (C1-C3) followed by manual injection (C4-C6), or to manual injection (C1-C3) followed by OBDS administration (C4-C6); from C7, pts could choose either treatment modality.All pts received treatment with carfilzomib (20 mg/m^2 on D1-2 then 56 mg/m^2 biweekly) and dexamethasone (20 mg). Primary study endpoint (EP) was overall response rate (ORR); pt preference for Isa SC administration modality was the key secondary EP. **Results:** Overall, 74 RRMM pts were enrolled: 8 in Part 1 and 66 in the randomized cohort (Part 2). At study entry, pts had a median age of 65 (44-85) yrs and a median of 1 prior therapy line (1-5); 56.8%, 32.4% and 10.8% had ISS stage I, II or III, respectively. The ORR rate was 79.7% (median follow-up 10.1 mo). After treatment with both modalities for Isa SC delivery, 74.5% of pts expressed a preference for the OBDS rather than manual injection (p=0.0004); 8.5% had no preference. Other key efficacy and safety results are shown in table. Treatment with Isa SC plus Kd was well tolerated. A single infusion reaction event (1 of Grade [G]1, 1 of G2) occurred in 2 pts (2.7%, both with manual injection at 1st dose). Six (8.1%) pts had 18 injection site reactions (17 of G1, 1 of G2) in 1297 (1.1%) manual or OBDS injections. Comparable PK exposure was observed between OBDS and manual administration. **Conclusions:** The study met its primary endpoint, demonstrating efficacy and safety of Isa SC administration in combination with Kd, either by manual injection or OBDS. Our study findings are comparable to those reported in the Phase 3 study IKEMA with Isa IV. Pts expressed a clear preference for receiving Isa SC by an OBDS. Clinical trial information: NCT05704049. Research Sponsor: Sanofi.

Isatuximab SC + Kd	All N=74
Efficacy, %	
ORR	79.7
≥VGPR	62.2
≥CR	21.6
Safety, %	
≥G3 TEAE	54.1
Serious TEAE	40.5
G5 TEAE	5.4
Treatment-related ≥G3 TEAE	35.1

G, grade; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

Long-term efficacy and safety of etentamig, a B-cell maturation antigen (BCMA) bispecific antibody in patients with relapsed/refractory multiple myeloma (RRMM).

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Background: Etentamig (etenta) is a differentiated BCMA x CD3 bispecific T-cell engager composed of high avidity bivalent BCMA-binding domains, low-affinity CD3-binding domain designed to reduce cytokine release syndrome (CRS), and silenced Fc tail for extended half-life enabling convenient dosing. We present long term results from 2 ongoing Ph 1 studies evaluating efficacy and safety of etenta in patients (pts) with RRMM. **Methods:** Data were from a Ph 1 multicenter, open-label, dose escalation/expansion (NCT03933735) trial and Arm A of a Ph 1b, open label (NCT05650632) trial of etenta; both enrolled pts ≥18 years with RRMM, ≥3 prior lines of therapy (LoT), and triple-class exposed. Pts received 60 mg Q4W or 40 mg Q3W, both regimens with similar dose intensity, in the Ph 1 trial; pts from Arm A of the Ph 1b trial received a step-up dose (SUD) on day 1 and full dose of 60 mg Q4W on day 4. This pooled analysis assessed long-term efficacy, safety, and tolerability. Tumor response was assessed per IMWG 2016 criteria. **Results:** Of 146 pts with RRMM who received etenta, 87 (60%) were male, median age (range) was 68 (40–87) years, median prior LoT were 4 (3–23), and median duration of follow-up was 13 (1–48) months (mo). ORR was achieved in 96 (66%) pts and ≥VGPR in 79 (54%) pts. Response rates across subgroups are reported in the Table. Median duration of response was not reached (NR) (NR–NR) among responders; Kaplan-Meier (KM) estimate at 12 mo was 71% (58.5%–80.5%). Median PFS (mPFS) was NR (8.7–NR) mo; KM estimate at 12 mo was 55% (44.9%–63.1%). Any grade and G3/4 treatment emergent adverse events (TEAEs) occurred in 145 (99%) pts and 116 (79%) pts. Most common G3/4 TEAEs (≥15%) were neutropenia (38%), anemia (23%), lymphopenia (25%), and thrombocytopenia (16%). Infections G3/G4 were reported in 32 (22%) pts; most common infections G3/G4 (≥5%) were pneumonia (12%) and sepsis (5%). TEAEs leading to etenta discontinuation were reported in 13 (9%) pts. Deaths from TEAEs were reported in 13 (9%) pts; 10 were not attributed to etenta treatment. In Arm A of Ph 1 study where 60mg Q4W was administered with SUD and modified dex as premedication, CRS incidence was 30% (4% G2; No ≥G3 events) with median time to CRS onset of 22.3 (5.5–29.6) hours; and median time to CRS resolution of 20.7 (1.8–131.7) hours. **Conclusions:** Etenta with SUD demonstrated a low CRS incidence, durable response, and tolerability in pts with heavily pretreated RRMM. Efficacy across all subgroups was comparable and maintained, suggesting therapeutic benefits among a broad population and supporting further exploration in the ongoing Ph 3 Cervino study. Research Sponsor: AbbVie.

Subgroup	ORR, n (%)	≥VGPR, n (%)	mPFS, months (range)
Age ≥75years	26 (72)	23 (63.9)	NR (7.5–NR)
Race: Black	15 (63)	13 (54.2)	13.7 (5.0–NR)
High cytogenetic risk	21 (55)	18 (47.4)	7.4 (2.8–NR)
3 prior LoT	29 (64.4)	23 (51.1)	13.5 (5.6–NR)
≥4 prior LoT	67 (67)	56 (56)	NR (8.3–NR)

Efficacy and safety from the phase 1/2 MonumenTAL-1 study of talquetamab, a GPRC5D×CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma: Analyses at an extended median follow-up.

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Background: Talquetamab (Tal) is the first and only approved anti-GPRC5D bispecific antibody (BsAb) for relapsed/refractory multiple myeloma (RRMM). In previous results from the phase 1/2 MonumenTAL-1 study (CCO Jan 2024; median follow-up [mFU] 20–30 mo), Tal elicited deep, durable responses with low discontinuation rates. We report efficacy and ongoing safety from MonumenTAL-1 at an extended mFU of 30–38 mo, the longest mFU for any anti-GPRC5D agent. **Methods:** Patients (pts) were intolerant to or progressed on established therapies (phase 1, NCT03399799) or had ≥3 prior lines of therapy (LOT), including ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb (phase 2, NCT04634552). Pts received recommended phase 2 doses (RP2D) of SC Tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W), with step-up doses. **Results:** As of Sept 2024, mFU was 38.2, 31.2, and 30.3 mo in the QW (n=143), Q2W (n=154), and prior T-cell redirection (TCR; n=78, received either RP2D) cohorts, respectively. Across cohorts, overall response rate (ORR; 67–74%) was unchanged vs previous results. Median duration of response (mDOR) and median progression-free survival (mPFS) continued to demonstrate superior outcomes in the Q2W vs QW cohort (mDOR 17.5 vs 9.5 mo; mPFS 11.2 vs 7.5 mo). In the prior TCR cohort, mDOR was reached with longer mFU (19.2 mo), and mPFS was 7.7 mo. In the QW, Q2W, and prior TCR cohorts, median overall survival (OS) was 34.0 mo, not reached, and 28.3 mo (36-mo OS rates: 49%, 61%, and 45%), respectively (Q2W data not mature). In pts with <4 vs ≥4 prior LOT, ORR was higher (85% vs 72%), but responses were less durable (mDOR 6.8 vs 10.8 mo) in the QW cohort, whereas ORR was similar (71% vs 69%), but responses were more durable (mDOR 20.7 vs 16.8 mo) in the Q2W cohort. As previously reported, most common adverse events (AE) were CRS and GPRC5D-associated (oral and dermatologic) AEs, and most common grade 3/4 AEs were cytopenias. No new discontinuations occurred due to oral or dermatologic GPRC5D-associated AEs and no new discontinuations occurred due to weight loss. In QW, Q2W, and prior TCR cohorts, respectively, any-grade infections occurred in 61%, 71%, and 78% of pts; grade 3/4 infections (23%, 21%, 26%) were mostly limited to early treatment cycles. A new safety signal, ataxia/balance disorders, was recently identified in association with Tal and had low prevalence in MonumenTAL-1. Dose reduction and discontinuation rates due to AEs remained low. No pts died due to Tal-related AEs. **Conclusions:** At an extended mFU, high ORRs elicited by Tal were durable and led to promising 36-mo OS rates (45–61%). The safety profile was consistent with previous results and continued to show lower risk of high-grade infections relative to approved anti-BCMA BsAbs, potentially contributing to the OS benefit seen in pts receiving Tal. Clinical trial information: NCT03399799/NCT04634552. Research Sponsor: None.

Daratumumab + bortezomib, lenalidomide, and dexamethasone (DVRd) vs VRd in transplant-ineligible (TIE)/transplant-deferred (TD) newly diagnosed multiple myeloma (NDMM): Phase 3 CEPHEUS trial cytogenetic subgroup analysis.

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Background: In CEPHEUS, DVRd significantly improved overall MRD negativity (MRD neg + ≥CR) and sustained MRD neg rates and PFS in patients (pts) with TIE/TD NDMM. In this post hoc analysis, we report outcomes in cytogenetic risk subgroups. **Methods:** Pts with TIE/TD NDMM were randomized 1:1 to DVRd or VRd. High-risk (HiR) cytogenetic abnormalities (HRCAs) were assessed by FISH. HiR was ≥1 of: del(17p); t(4;14); t(14;16). Revised HiR (R-HiR) was ≥1 of above or gain (3 copies) or amp(1q) (≥4 copies). Standard risk (SR) was 0 HRCAs; revised SR (R-SR) was 0 revised HRCAs. Additional risk groups included: gain or amp(1q) + other HRCAs; 1 and ≥2 revised HRCAs. We assessed overall MRD neg rate, sustained MRD neg, ≥CR rate, and PFS. We reported all MRD neg rates at 10^{-5} unless noted. **Results:** Of 395 randomized pts (DVRd, n=197; VRd, n=198), 298 had SR (DVRd, n=149; VRd, n=149) and 52 HiR (DVRd, n=25; VRd, n=27). 184 pts had R-SR (DVRd, n=94; VRd, n=90) and 167 R-HiR (DVRd, n=83; VRd, n=84). At median 58.7-month (mo) follow-up, overall MRD neg rate was higher with DVRd vs VRd in SR (64% vs 38%; $P<0.0001$) and R-SR pts (68% vs 38%; $P<0.0001$). Rates by treatment (tx) arm in HiR (48% vs 56%; $P=0.7816$) and R-HiR pts (55% vs 45%; $P=0.2169$) were comparable. DVRd improved ≥1-year (y) sustained MRD neg rate vs VRd in SR (51% vs 26%; $P<0.0001$) and R-SR pts (54% vs 24%; $P<0.0001$). Sustained MRD neg rates by tx arm were comparable in HiR (40% vs 37%; $P=1.0000$) and R-HiR pts (43% vs 30%; $P=0.0782$). PFS was improved with DVRd vs VRd in SR and R-SR pts and was comparable by tx arm in HiR and R-HiR pts (Table), including in MRD neg pts (R-SR: hazard ratio [HR]=0.63 [95% CI, 0.26–1.52]; $P=0.3003$; R-HiR: HR=0.71 [95% CI, 0.32–1.58]; $P=0.3995$). Remaining outcomes, including rates of ≥CR, ≥2-y sustained MRD neg, and overall and ≥1-y sustained MRD neg at 10^{-6}, were improved with DVRd in SR and R-SR pts and comparable by tx arm in HiR and R-HiR pts. **Conclusions:** In CEPHEUS, DVRd consistently improved the key response outcomes of MRD neg and PFS in (R-)SR pts. In HiR pts, MRD and PFS outcomes trended lower in both tx arms vs those in SR pts. Here, DVRd mostly improved PFS outcomes vs VRd; however, pt numbers were small, with the study underpowered for HiR pts. These data support use of DVRd for TIE/TD NDMM regardless of cytogenetic risk status. Clinical trial information: NCT03652064. Research Sponsor: Johnson & Johnson.

	DVRd		VRd		
	n	mPFS, mo	n	mPFS, mo	HR (95% CI); *P*-value
HiR[a]	25	39.8	27	31.7	0.88 (0.42–1.84); 0.7387
R-HiR	83	NE	84	45.6	0.73 (0.46–1.15); 0.1739
SR[a]	149	NE	149	60.6	0.61 (0.41–0.91); 0.0136
R-SR	94	NE	90	60.6	0.54 (0.32–0.91); 0.0189
Gain(1q) + other HRCAs	43	60.3	48	42.2	0.80 (0.45–1.43); 0.4496
Amp(1q) + other HRCAs	31	NE	20	NE	0.97 (0.38–2.47); 0.9525
1 revised HRCA	66	NE	72	47.2	0.63 (0.37–1.09); 0.0938
≥2 revised HRCA	17	22.7	12	29.7	1.01 (0.42–2.44); 0.9868

[a]Unknown cytogenetic risk: DVRd, n=23; VRd, n=22.
mPFS, median PFS; NE, not estimable.

Assessment of normal plasma cell biomarkers after arlocabtagene autoleucel (arlocel) treatment in patients with ≥3L relapsed refractory multiple myeloma (MM).

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Background: B-cell maturation antigen (BCMA) and G protein-coupled receptor class C group 5 member D (GPRC5D) are validated targets in MM. GPRC5D is expressed most strongly on MM cells with minimal expression on normal plasma cells (nPC), while BCMA is highly expressed on MM cells and nPCs. Anti-BCMA chimeric antigen receptor T cell therapy (CAR T) and T cell engagers (TCE), but not anti-GPRC5D TCE, are associated with B cell aplasia and worsened hypogammaglobulinemia. Uninvolved free light chain (uiFLC) and immunoglobulin G (IgG) were used as biomarkers of nPCs following treatment with arlo-cel, a GPRC5D-targeting CAR T therapy with promising efficacy and 19% grade 3/4 infection rate (Bal, et al. ASH 2024 Abstract 922), and treatment with a BCMA CAR T therapy. **Methods:** Clinical endpoints included treatment-emergent adverse events for patients treated with arlo-cel (NCT04674813; n = 84) and idecabtagene vicleucel (ide-cel, NCT03361748; n = 137). Biomarker analysis included complete responders (CR) treated with arlo-cel (n = 42) and ide-cel (n = 38). For uiFLC, Kaplan-Meier curves of time to clearance below the limit of detection (LOD; 1.3 mg/L for κ and 1.7 mg/L for λ) and time to first return above the LOD were used to calculate median time to event and compared using log-rank test. Logistic regression models adjusted for pre-treatment levels were used to test for differences in biomarker levels at specific time points. Hypogammaglobulinemia was defined as IgG levels $<$ 500 mg/dL. Fisher's exact test was used to compare infection rates. All analyses were restricted to the first 6 months after infusion. P-values less than 0.1 were considered statistically significant. **Results:** Arlo-cel cleared uiFLC below the LOD in 67% of CR compared to 100% of ide-cel CR ($p < 0.0001$). When cleared, time to uiFLC clearance was the same (median = 29 days; $p = 0.82$), but time to return above the LOD was significantly faster for arlo-cel (median = 101 days) than for ide-cel (median = 264 days; $p = 0.001$), indicating faster nPC recovery for arlo-cel. Post-infusion uiFLC concentrations were lower in ide-cel CR at 2 ($p = 0.09$), 4 ($p = 0.05$), 5 ($p = 0.02$), and 6 months ($p = 0.09$) compared to arlo-cel. Despite more post-infusion intravenous immunoglobulin usage for ide-cel vs arlo-cel CR (89% vs 26%), IgG levels were lower for ide-cel CR at 2 ($p = 0.09$) and 3 months ($p = 0.01$). Among treated patients, the proportion with hypogammaglobulinemia at 3 months ($p = 0.05$) and the 6-month infection rate ($p = 0.03$) were lower for arlo-cel. **Conclusions:** Arlo-cel patients had higher levels of uiFLC from months 2–6, demonstrating greater anti-tumor specificity and preservation of humoral immunity. As a result, arlo-cel has the potential to achieve lower rates of hypogammaglobulinemia and infections compared to BCMA-targeting therapies, with fewer interventions. Clinical trial information: NCT04674813. Research Sponsor: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

Indirect comparison of linvoseltamab versus elranatamab for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM).

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Background: In the absence of head-to-head trials comparing anti-BCMA×CD3 bispecific antibodies in TCE RRMM, this study used an unanchored matching-adjusted indirect comparison (MAIC) to compare the efficacy of linvoseltamab and elranatamab. **Methods:** Patient (pt)-level data from LINKER-MM1 (117 pts receiving linvoseltamab 200 mg, data cut-off [DCO] 7/2024, median follow-up [mFU] 21.3 months [mos]) and published data from MagnetisMM-3 Cohort A (123 elranatamab pts, DCO 9/2024, mFU 33.9 mos) were analyzed. Ten LINKER-MM1 pts with prior BCMA antibody–drug conjugate exposure were excluded to align with MagnetisMM-3. LINKER-MM1 pts were weighted to match MagnetisMM-3 pts on prespecified prognostic factors deemed most important by an international expert panel: cytogenetic risk, age, refractory status, R-ISS stage, ECOG PS, extramedullary and/or paramedullary disease. Objective response rate (ORR), very good partial response or better (≥VGPR) and complete response or better (≥CR) rates, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were compared. DOR and PFS in LINKER-MM1 were recalculated to match MagnetisMM-3 censoring rules. Additional MAICs matched all available prespecified prognostic factors, included all 117 LINKER-MM1 pts, or matched to a MagnetisMM-3 subgroup with ECOG PS 0/1. **Results:** After matching, linvoseltamab effective sample size (ESS) was 71.3 (range of patient weights: 0.04–2.90). Linvoseltamab demonstrated statistically significantly higher ORR and ≥CR rate, a numerically higher ≥VGPR rate, and longer DOR, PFS, and OS vs elranatamab (Table). The additional MAICs yielded directionally consistent findings. **Conclusions:** Linvoseltamab demonstrated significantly higher ORR and ≥CR rate, numerically better ≥ VGPR rate, DOR, PFS, and OS compared with elranatamab, though the follow-up was shorter. These results highlight the potential of linvoseltamab as a highly effective treatment option for TCE RRMM. Research Sponsor: Regeneron Pharmaceuticals, Inc.

	Elranatamab	Linvoseltamab	Linvoseltamab	Linvoseltamab vs elranatamab	Linvoseltamab vs elranatamab
	N=123	Unadjusted N=107	Adjusted ESS= 71.3	Unadjusted	Adjusted
	%	%	%	*OR (CI)*	*OR (CI)*
ORR	61	71	71	1.57 (1.04–2.37)*	1.60 (1.00–2.57)*
≥VGPR	56	64	65	1.36 (0.93–2.00)	1.45 (0.94–2.24)
≥CR	37	52	50	1.84 (1.26–2.68)*	1.71 (1.12–2.61)*
	Median, mos (CI); 12-mo landmark %	*Median, mos (CI); 12-mo landmark %*	*Median, mos (CI); 12-mo landmark %*	*HR (CI)*	*HR (CI)*
DOR	NR (29.4–NE); 73.9	NR (NE–NE); 82.8	NR (NE–NE); 84.4	0.93 (0.53–1.66)	0.82 (0.43–1.55)
PFS	17.2 (9.8–NE); 56.4	NR (15.7–NE); 65.5	NR (16.2–NE); 64.7	0.86 (0.59–1.27)	0.86 (0.55–1.34)
OS	24.6 (13.4–NE); 62.3	31.4 (27.8–NE); 75.5	NR (27.8–NE); 74.6	0.70 (0.47–1.04)	0.67 (0.42–1.05)

OR >1 or HR <1 favor linvoseltamab.
*Statistically significant at $p<0.05$.
CI: 95% confidence interval, HR: hazard ratio, NE: not estimable, NR: not reached, OR: odds ratio.

Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible (TNE) newly diagnosed multiple myeloma (NDMM): Updated results from the CC-220-MM-001 trial.

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Background: Lenalidomide (LEN), bortezomib (BORT), and dexamethasone (DEX) are recommended for NDMM. Iberdomide (IBER), an oral CELMoD agent, has stronger tumoricidal and immune-stimulatory effects than LEN and shows synergy with DEX and BORT in preclinical models. IberVd has shown meaningful efficacy and safety in patients (pts) with TNE NDMM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030). Here we report updated results with longer follow-up from the IberVd dose-expansion cohort. **Methods:** Eligible pts had untreated NDMM and were TNE or deferred. Oral IBER was given on days (D) 1–14 of each 21-d cycle (C) in C1–8 and on D1–21 of each 28-d cycle in C ≥ 9, with subcutaneous BORT (starting at 1.3 mg/m^2) on D1, 4, 8, and 11 in C1–8, plus oral DEX on D1, 2, 4, 5, 8, 9, 11, and 12 in C1–8 and weekly in C ≥ 9 (20 or 10 mg if > 75 y of age in C1–8; 40 or 20 mg if > 75 y in C ≥ 9). Endpoints included efficacy, safety, pharmacokinetics, and minimal residual disease (MRD) assessment by next-generation flow cytometry. **Results:** As of May 29, 2024, 18 pts had received IberVd (1 pt 1.0 mg; 17 pts 1.6 mg). Median age was 77.5 (57–84) y, 12 (66.7%) pts were male, 17 (94.4%) White, 1 (5.6%) Hispanic/Latino, and 11 (61.1%) had high-risk cytogenetics. Median follow-up was 25 (0.7–29.5) mo. Median treatment duration was 24.9 (0.7–29.5) mo, median number of cycles received was 25 (1–34), and 11 (61.1%) pts remain on treatment; 3 pts discontinued due to withdrawal, 2 to adverse events (AEs), 1 to progressive disease, and 1 to physician decision. One death was reported during follow-up. In the safety population (n = 17), 14 (82.4%) pts had grade (Gr) 3/4 treatment-emergent AEs (TEAEs); primarily infections (47.1%), including pneumonia (17.6%) and COVID-19 (11.8%). The most common hematologic Gr 3/4 TEAE was neutropenia (29.4%); 2 (11.8%) pts had Gr 3–4 peripheral neuropathy. Other Gr 3/4 non-hematologic TEAEs like fatigue and diarrhea were rare. IBER dose interruptions and reductions due to TEAEs occurred in 14 (82.2%) and 10 (58.8%) pts, respectively. Dose reductions were mainly due to peripheral neuropathy (23.5%), neutropenia (11.8%), and thrombocytopenia (11.8%). TEAEs were manageable with dose modifications/interruptions and G-CSF use. In the evaluable pts (n = 16), the overall response rate was 100% with 8 stringent complete responses, 4 complete responses (CRs), 3 very good partial responses, and 1 partial response. Median time to response was 0.7 (0.7–3.9) mo, median duration of response was not reached, and 4 pts deepened response post 1 y treatment. MRD negativity at 10^{-5} was reported in 8 (50.0%) pts, and all had ≥ CR. **Conclusions:** With longer follow-up (13–25 mo), IberVd confirmed durable deep responses, with ≥ CR % rising from 56.3% to 75.0%, and an encouraging safety profile with no new signals in pts with TNE NDMM. These data support IberVd evaluation in the frontline setting. Clinical trial information: NCT02773030. Research Sponsor: Bristol Myers Squibb.

DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs pomalidomide plus bortezomib and dexamethasone (PVd) in relapsed/refractory multiple myeloma (RRMM): A subgroup analysis in patients with high-risk cytogenetic features.

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Background: In DREAMM-8 (NCT04484623), BPd demonstrated a significant improvement in the risk of progression or death vs PVd in patients (pts) with RRMM who received ≥1 prior line of therapy, including lenalidomide. Pts with high-risk cytogenetic abnormalities (HRCAs) have a poor prognosis and need more efficacious treatments. Here we present a subgroup analysis in pts with HRCAs. **Methods:** Pts were randomized 1:1 to BPd (28-day cycles) or PVd (21-day cycles). Pts were treated until progressive disease, unacceptable toxicity, or death. Efficacy assessments occurred every 4 weeks. Pts with HRCAs were defined as having ≥1 of the following: t(4;14), t(14;16), amp1q, and del(17p13). Descriptive statistics were used to summarize the results, along with 95% exact CIs. Hazard ratios (HRs) for progression-free survival (PFS) were estimated using the Cox model, with 95% CIs based on the Brookmeyer-Crowley method. **Results:** The intention-to-treat population included 302 pts: 155 in the BPd arm and 147 in the PVd arm. In the BPd arm, 68 of 155 (44%) pts had HRCAs; of them, 23 (15%) had t(4;14), 7 (5%) had t(14;16), 32 (21%) had del(17p13), and 40 (26%) had amp1q. In the PVd arm, 60 of 147 (41%) had HRCAs; of them, 20 (14%) had t(4;14), 11 (7%) had t(14;16), 26 (18%) had del(17p13), and 33 (22%) had amp1q. Median PFS in pts with ≥1 HRCA was 21.1 mo (95% CI, 13.5 mo-NR) with BPd vs 9.2 mo (95% CI, 6.5-14.8 mo) with PVd (HR, 0.58; 95% CI, 0.36-0.95); 18-mo PFS rates were 53% and 33%, respectively. PFS benefit favored BPd across HRCA subgroups (HR [95% CI]: t(14;14), 0.74 [0.31-1.76]; del(17p13), 0.45 [0.22-0.92]; and amp1q, 0.49 [0.24-1.03]). In pts with ≥1 HRCA, overall response rate (ORR) was higher with BPd (n=52; 76%; 95% CI, 64.6%-85.9%) than PVd (n=39; 65%; 95% CI, 51.6%-76.9%), and more pts achieved ≥ complete response with BPd (Table). Benefit was maintained across HRCA subgroups. **Conclusions:** In pts with RRMM with HRC features, BPd demonstrated clinically meaningful PFS benefit, higher ORR, and a higher rate of deep responses vs PVd. These data support the potential use of BPd as a standard-of-care regimen in this key pt population with a high unmet need. Clinical trial information: NCT04484623. Research Sponsor: This study was sponsored by GSK. Editorial support was provided by Nucleus Global, an Inizio Company, and funded by GSK. Drug-linker technology licensed from Seagen Inc; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

Patients achieving ≥CR in HRC groups n/N (%); 95% CI	BPd	PVd
t(4;14)	9/23 (39); 19.7-61.5	5/20 (25); 8.7-49.1
t(14;16)	3/7 (43); 9.9-81.6	2/11 (18); 2.3-51.8
del(17p13)	11/32 (34); 18.6-53.2	0/26; 0-13.2
amp1q	17/40 (43); 27.0-59.1	3/33 (9); 1.9-24.3
≥1 HRCA	29/68 (43); 30.7-55.2	9/60 (15); 7.1-26.6

Immune profiling to identify a functionally high-risk smoldering multiple myeloma patient population.

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Background: Smoldering multiple myeloma (SMM), a precursor to active multiple myeloma (MM), is characterized by a high plasma cell burden but no evidence of the end-organ damage that defines MM. The Mayo 2/20/20 model, and others, relies on tumor-burden estimates to assign risk scores. We hypothesized that algorithm-assisted and explainable artificial intelligence (xAI) tools could ingest peripheral blood (PB) T cell profiles to identify immune signatures predictive of progression to active MM. **Methods:** We analyzed a cohort of Mayo risk-matched SMM patients with and without early progression to active MM. This included 9 patients with early progression from SMM to MM (median PFS 2.1 years) and a 9 patient "mayo risk matched" cohort without clinical progression (median follow-up 8.6 years). Using high-dimensional spectral cytometry with a 37-color T cell focused panel, we captured 1.4 million PB T cells from 18 SMM patients banked at the time of SMM diagnosis. Algorithm-assisted analysis was performed using dimensionality reduction analysis with UMAP and cell clustering using PhenoGraph. xAI analysis was performed by training a random forest (RF) classifier to predict clinical outcomes using single-cell data followed by feature importance analysis using Shapley Additive Explanations (SHAP) scores. **Results:** Analysis identified 21 unique T cell characteristic clusters across all patients. Among these, SMM patients with early progression had enrichment for $CD8^{+}CD45RA^{+}CD62L^{-}CCR7^{-}$ T effector cells re-expressing CD45RA when compared to non-progressing SMM patients (4.3-fold increase, $p = 0.018$). This cluster had the highest mean expression level of CD57 and TOX among all algorithm-defined clusters, demonstrating similar phenotypic characteristics to terminally exhausted effector T cells. The RF model to predict progression had an overall accuracy of 75% (stratified five-fold cross validated, repeated ten times). A UMAP analysis of c misclassified cells did not reveal any obvious patterns. SHAP analysis identified high expression of Granzyme B, CD272, Granzyme K, and CD45RA as the four most influential features for predicting progression. **Conclusions:** Our results show that patient-specific immune phenotypes could offer a method of prognosticating SMM outcomes separate from traditional tumor burden quantification. Both the clustering-based and feature importance analyses demonstrated that a more differentiated T cell phenotype is associated with early progression in SMM. Recent reports have found more differentiated T cell biology in MM patients compared to SMM patients. Our results support the hypothesis that SMM patients displaying an "MM-like" T cell phenotype are at increased risk of early progression to active MM. These results support work to identify a clinically usable patient-specific immune signature to identify SMM patients at increased risk of progression to overt MM. Research Sponsor: ASCO / CCF Young Investigator Award.

Carfilzomib, lenalidomide, and dexamethasone (KRd) as maintenance therapy after autologous stem-cell transplantation (ASCT) in patients with newly diagnosed multiple myeloma (NDMM).

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Background: In patients with NDMM, therapy after ASCT aims to deepen remission and prolong survival. Although lenalidomide (R) monotherapy after ASCT is well established, the impact of combination therapy on survival remains to be established. Interim results of the ATLAS study suggested that extended KRd after ASCT treatment prolongs progression-free survival (PFS) compared with R alone in patients with NDMM (Dytfeld et al, Lancet Oncol. 2023; 24:139–150). Here we provide the results from the primary analysis of the ATLAS study. **Methods:** This international, open-label phase 3 study randomly assigned adults with NDMM who completed induction and had stable disease or better after ASCT 1:1 to KRd or R alone as maintenance therapy. Randomization was stratified by post-transplant response, presence or absence of ≥1 high-risk cytogenetic abnormality, and by country. For the KRd group, patients with standard-risk cytogenetics and measurable residual disease (MRD) negativity at 10^{-5} after cycle 6 were switched to R maintenance after cycle 8; remaining patients continued KRd up to 36 cycles and then switched to R. The preplanned primary endpoint was PFS. Secondary endpoints included overall survival (OS), MRD negativity, response rate, and safety. **Results:** At data cutoff (21 Oct 2024), median follow up was 5.7 years. The median number of treatment cycles initiated was 35 and 31 for KRd and R, respectively. After cycle 8, 40 of 81 patients on KRd switched to R. The 4-year PFS rate with KRd was superior to R (67.5% vs 36.8%; HR 0.46 [95% CI: 0.30, 0.70]; p=0.0002). The PFS benefit was consistent across subgroups, including high-risk cytogenetics (HR 0.52 [95% CI: 0.24, 1.1]) and MRD-positive status at randomization (HR 0.52 [95% CI: 0.29, 0.93)]. Median PFS was 72.8 months and 37.3 months in the KRd and R groups, respectively. The 4-year OS rate also was increased with KRd vs R (84.3% vs 79.2%; HR 0.49 [95% CI: 0.26, 0.90]; p=0.02). The depth of response improved across all response categories; the rate of MRD $<10^{-5}$ and at least a complete response as best response was 74% and 51% (OR 2.7 [95% CI: 1.5, 5.1]; (p=0.002), and 12-month sustained MRD-negativity was 48% and 24% (OR 2.9 [95% CI 1.5, 5.5]; p=0.001) for KRd and R, respectively. No new safety signals were observed (Table). **Conclusions:** The ATLAS phase 3 study demonstrated superior PFS as well as longer OS with MRD-directed, risk-stratified KRd treatment compared with R alone in patients with NDMM after ASCT. Extended KRd maintenance treatment may represent a new standard of care. Clinical trial information: NCT02659293. Research Sponsor: Amgen Inc.; Celgene [Bristol Myers Squibb].

Treatment emergent adverse events.

Patients, n (%)	KRd (n=91)	R (n=87)
Any grade	89 (98)	83 (95)
Grade ≥3	72 (79)	64 (74)
Grade 5	2 (2.2)[a]	2 (2.3)[b]
Any serious adverse event	29 (32)	20 (23)

[a]Lung infection (n=2).
[b]Lung/Covid infection (n=1); heart failure (n=1).

Belantamab mafodotin + pomalidomide + dexamethasone (BPd) vs daratumumab + bortezomib + dexamethasone (DVd) in relapsed/refractory multiple myeloma: An indirect comparison using patient-level data.

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Background: Belantamab mafodotin (belamaf) is being studied in combination with bortezomib + dexamethasone (BVd) or pomalidomide + dexamethasone (BPd) in the phase 3 DREAMM-7 (D7; NCT04246047) and DREAMM-8 (D8; NCT04484623) trials, respectively; both enrolled patients (pts) with relapsed/refractory multiple myeloma (RRMM) who had received ≥1 prior line of therapy. D7 compared BVd vs daratumumab + bortezomib + dexamethasone (DVd); D8 compared BPd vs bortezomib + pomalidomide + dexamethasone (PVd). In both trials, belamaf combinations showed significant progression-free survival (PFS) benefits vs comparators. In D7, median PFS (95% CI) was 36.6 mo (28.4-not reached [NR]) with BVd vs 13.4 mo (11.1-17.5) with DVd (HR, 0.41; 95% CI, 0.31-0.53; $P<.001$). In D8, median PFS (95% CI) was NR with BPd vs 12.7 mo (9.1-18.5) with PVd (HR, 0.52; 95% CI, 0.37-0.73; $P<.001$). This study compared the efficacy of BPd (D8 active arm) vs DVd (D7 comparator). **Methods:** The overlapping D7 and D8 RRMM population was analyzed. To align cohorts, D8 BPd pts refractory to any anti-CD38 were excluded, as were D7 DVd pts without prior lenalidomide exposure or pomalidomide-refractory disease. The primary endpoint was PFS. Secondary endpoints included overall survival (OS), minimal residual disease (MRD)–negativity rate, duration of response (DOR), overall response rate (ORR), and time to treatment discontinuation (TTD) with all treatments. This indirect comparison used inverse probability of treatment weighting to match baseline characteristics between DVd and BPd arms, estimating the average treatment effect in the treated population (IPTW-ATT). In the matched population, time-to-event analyses used the Kaplan-Meier method and Cox proportional hazards models. **Results:** Of 155 pts in the D8 BPd arm and 251 in the D7 DVd arm, 120 and 111, respectively, met inclusion criteria for this analysis. Baseline characteristics were generally balanced after IPTW-ATT. After adjustment, BPd significantly improved PFS vs DVd (median [95% CI], NR [21.1-NR] vs 11.1 mo [6.4-19.1]; HR, 0.41; 95% CI, 0.25-0.65; $P=.0002$). Median (95% CI) DOR was NR (24.9-NR) with BPd vs 10.5 mo (5.0-17.7) with DVd; adjusted MRD-negativity (CR+) rates (95% CI) were 30.2% (21-39.4) vs 5.3% (0.9-9.8), respectively (OR, 7.67; 95% CI, 3.10-22.72; $P<.0001$). ORR and TTD favored BPd vs DVd (ORR not significant). **Conclusions:** This post hoc indirect comparison analysis showed that BPd significantly improved PFS vs DVd (similar HR to BVd vs DVd in D7). Median PFS for the adjusted DVd population was similar to that reported with PVd in D8. These findings suggest that BPd may be a more effective treatment option vs DVd, warranting further studies of belamaf combinations in this population. Research Sponsor: GSK.

GPRC5D and BCMA bi-specific CAR-T: Ex vivo study to simulate early to late-line multiple myeloma (MM) with elevated soluble BCMA.

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Background: GPRC5D and BCMA are near-universally expressed on MM cells, with independent target expression and double-negative cells relatively rare. This profile supports the rationale for developing a bi-specific CAR-T therapy to enhance patient coverage, improve efficacy, and reduce the risk of relapse due to antigen loss. Dual-targeting GPRC5D and BCMA represents a novel advancement in the developed antibody therapies. The clinical outcomes of combination of GPRC5DxCD3 and BCMAxCD3 were highly promising. Tri-specific antibodies (GPRC5DxBCMAxCD3) have exhibited superior preliminary efficacy compared to bsAbs or their combinations, However, these approaches require weekly administrations and may pose potential risk. A recent publication (Freeman et al., Blood, 2024) reported that elevated pre-lymphodepletion soluble BCMA (sBCMA) levels were significantly associated with high-risk characteristics as well as high incidence and severity of CRS & ICANS, and metabolic tumor volume (MTV) were correlated with poor clinical outcomes. To address these challenges, we have developed bi-specific CAR-Ts incorporating novel armors to effectively eliminate heavy MM burdens and enhance efficacy, even in the presence of sBCMA. **Methods:** Aiming to broadly eradicate MM subsets and reduce heavy tumor burden or extramedullary disease (EMD), we have developed a bi-specific CAR-T with two novel humanized VHH binders specifically targeting either BCMA or GPRC5D. Our design incorporates novel secreted and/or membrane-bound armors. Pre-clinical studies were conducted to evaluate the features and drugability of these armored and non-armored bispecific-CAR-Ts. **Results:** Targeting dual-Ag, the bi-specific CAR-T showed increased T cell activation, superior functionality, and enhanced expansion under re-stress. Notably, the bi-CAR-T retained its functionality against single-Ag expressing cells and displayed robust potency against MM cells with very low BCMA expression, even in the presence of high concentrations of sBCMA. Compared to industry benchmarks, Oricell's bi-CAR-T showed superior efficacy in a xenograft mouse model with heterogeneous MM cells. Armored bi-CAR-Ts were potent in eliminating heavy tumor burdens and enhancing T cell infiltration and expansion. **Conclusions:** The pre-clinical data demonstrated that the bi-specific CAR-T not only outperformed in targeting MM cells mimicking early or middle lines but also reduced the incidence of antigen-negative escape. By enhancing sensitivity and leveraging unique epitopes, the bi-CAR-T maintained robust efficacy in late-line MM models. Future clinical studies will be conducted to validate the safety and efficacy in treating high-risk MM patients. Research Sponsor: None.

Ciltacabtagene autoleucel (cilta-cel) vs standard of care (SOC) in patients (pts) with relapsed/refractory multiple myeloma (MM): CARTITUDE-4 survival subgroup analyses.

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Background: In CARTITUDE-4, a single cilta-cel infusion significantly improved progression-free survival (PFS; hazard ratio [HR] weighted, 0.29 [95% CI, 0.22–0.39]) and overall survival (OS; HR, 0.55 [0.39–0.79]; *P*=0.0009) vs SOC in pts with relapsed and lenalidomide-refractory MM after 1–3 prior lines of treatment (pLOT) at 33.6 mo median follow-up (Mateos et al, IMS 2024). PFS and OS from subgroups in the intent-to-treat (ITT) population are reported. **Methods:** Pts randomized to cilta-cel underwent apheresis, received pomalidomide, bortezomib, and dexamethasone (PVd), or daratumumab, pomalidomide, and dexamethasone (DPd) bridging treatment, lymphodepletion, and then cilta-cel infusion. Pts randomized to SOC received physician's choice of PVd or DPd until progression. HR for PFS was analyzed using unweighted Cox proportional hazards model for the ITT set. **Results:** As of May 1, 2024, median follow-up was 33.6 mo. PFS and OS benefit of cilta-cel over SOC in the ITT analysis was consistent across pts with standard-risk cytogenetics and high-risk cytogenetics, defined as del(17p), t(4;14), t(14;16), or gain/amp(1q) (Table). Comparing cilta-cel (n=21) vs SOC (n=18) in pts with extramedullary disease (EMD), median PFS was 13 mo vs 4 mo (HR, 0.71 [95% CI, 0.34–1.49]), respectively, and median OS was not reached (NR) vs 16 mo (HR, 0.61 [95% CI, 0.26–1.47]). In pts with 1, 2, or 3 pLOT (cilta-cel, n=68, 83, 57; SOC, n=68, 87, 56), median PFS was NR with cilta-cel across all pLOT vs 17 mo (HR, 0.41 [95% CI, 0.25–0.67]), 12 mo (HR, 0.30 [95% CI, 0.19–0.49]), and 8 mo (HR, 0.20 [95% CI, 0.11–0.34]) with SOC, respectively; median OS was NR with cilta-cel across all pLOT vs NR (HR, 0.56 [95% CI, 0.28–1.11]), NR (HR, 0.63 [95% CI, 0.36–1.09]), and 34 mo (HR, 0.49 [95% CI, 0.26–0.91]) with SOC. **Conclusions:** ITT analysis showed that cilta-cel improved PFS and OS vs SOC in all subgroups, including pts with EMD and 1 pLOT and beyond. Compared with SOC, cilta-cel improved PFS and OS in pts with high-risk cytogenetics, suggesting it may overcome the poor prognosis associated with these high-risk features. These data continue to support a positive benefit-risk ratio for cilta-cel in pts with lenalidomide-refractory MM as early as after first relapse. Clinical trial information: NCT04181827. Research Sponsor: Johnson & Johnson; Legend Biotech USA Inc.

	Cilta-cel, n	SOC, n	Median PFS cilta-cel, mo	Median PFS SOC, mo	HR (95% CI)	Median OS cilta-cel, mo	Median OS SOC, mo	HR (95% CI)
Standard-risk cytogenetics	69	70	NR	21	0.43 (0.26–0.72)	NR	NR	0.62 (0.33–1.19)
High-risk cytogenetics[a]	123	132	37	10	0.38 (0.27–0.52)	NR	38	0.54 (0.35–0.85)
del(17p)	49	43	30	9	0.40 (0.24–0.68)	NR	NR	0.52 (0.26–1.04)
t(4;14)	30	30	37	7	0.34 (0.17–0.68)	NR	27	0.46 (0.20–1.08)
gain/amp(1q)	89	107	37	10	0.39 (0.27–0.57)	NR	38	0.58 (0.35–0.96)
≥2 cytogenetic abnormalities[a]	43	49	30	7	0.43 (0.25–0.73)	NR	23	0.57 (0.30–1.07)

[a]Cytogenetic abnormalities: del(17p), t(4:14), t(14;16), or gain/amp(1q).

Carfilzomib or bortezomib with lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): Long-term follow-up of the ECOG-ACRIN ENDURANCE phase 3 trial.

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Background: The combination of a proteasome inhibitor (PI) with lenalidomide (R) and dex (d) has been a common initial therapy for newly diagnosed myeloma (NDMM). We designed a randomized phase 3 trial to examine if carfilzomib (K), a next generation PI, improved progression free survival (PFS) compared with bortezomib (V) when either is combined with Rd for initial treatment of NDMM. Initial analysis at a median follow up of 15.3 months (mos) showed comparable PFS for both triplets. We present the long-term results of the trial with ~70 months median follow up. **Methods:** Patients (Pts) with NDMM, were randomized 1:1 to receive VRd or KRd for 36 weeks followed by a 2nd randomization (1:1) to indefinite versus 2 yrs of R maintenance. Pts without del17p, t(14;16), t(14;20), plasma cell leukemia or high-risk GEP70 profile, were enrolled. VRd arm included V 1.3 mg/m^2 on days(d) 1, 4, 8, and 11 (d1, 8 for cycles 9-12), R 25 mg d1-14, and d 20 mg d1, 2, 4, 5, 8, 9, 11, 12 of a 3-week (wk) cycle for 12 cycles, while pts in the KRd arm received K 36 mg/m^2 d1, 2, 8, 9, 15, 16 with R 25 mg daily on d1-21 and d 40 mg wkly, in 4 wk cycles for 9 cycles. Maintenance used 15 mg R d1-21 q4 wks. **Results:** The study accrued 1087 pts (VRd=542, KRd=545). Median age was 65y; baseline characteristics including intent to transplant were similar across the arms. Median induction duration (mos; IQR) was 7.2 (3.4-8.9) and 8.4 (5.1-9.1) for VRd and KRd, respectively; 59.8% in VRd and 45.3% in KRd did not proceed to Step 2. Median PFS (mos) was VRd=41.9 and KRd=44.6; HR = 0.89 (0.76-1.04). Toxicity data, PFS sensitivity analyses and OS probabilities are as in the table. **Conclusions:** In this randomized trial, with median follow up of nearly 6 years, KRd and VRd had comparable PFS and OS in an intent to treat analysis. While similar numbers proceeded to SCT in the 2 arms, more did so during induction in the VRd arm while more patients in the KRd arm went to SCT later. VRd remains a standard triplet induction regimen in standard and intermediate risk NDMM, and a suitable backbone for 4 drug combinations. Clinical trial information: NCT01863550. Research Sponsor: None.

N (%)		VRd (n=527)	KRd (n=526)
SCT anytime		186 (34.3)	183 (33.6)
SCT without Step 2 registration		146	112
Median Time to SCT (mos; range)		7.7 (3.5-83.9)	10.6 (3.7-70.6)
Grade 3-4 Treatment-Related Toxicity		315 (59.8)	344 (65.4)
Grade 5 Treatment-Related Toxicity		2 (0.4)	9 (1.7)
Grade 5 All Events		11 (2.1)	20 (3.8)
Survival outcomes			
	HR	Median (95% CI)	Median (95% CI)
PFS Primary: PD or death within 3 months of last evaluation as events	0.89 (0.76-1.04)	41.9 (35.7, 50.3)	44.6 (38.2, 51.9)
PFS Sensitivity: All deaths as events,	0.87 (0.75-1.02)	39.5 (34.9, 46.0)	42.8 (37.4, 49.7)
PFS Sensitivity: Censor at alternate Rx	0.83 (0.69-0.99)	35.0 (31.3, 42.6)	38.7 (34.7, 49.0)
PFS Sensitivity: Event at alternate Rx	0.84 (0.73-0.97)	18.0 (14.2, 23.0)	24.4 (20.9, 27.9)
Overall survival	0.92 (0.75-1.12)	119 (100, NE)	118 (103-NE)

Clinical characteristics, cytogenetic associations, and outcomes in multiple myeloma with chromosome 1q abnormalities.

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Background: Multiple myeloma (MM) is characterized by recurrent cytogenetic abnormalities, including translocations involving the immunoglobulin heavy chain locus on chromosome 14 and trisomies, which are considered primary and clonal. Throughout disease progression, MM cells may acquire additional abnormalities, which include chromosome 1 abnormalities (gain or amplification of 1q or deletion of 1p) and chromosome 17 abnormalities (del 17p or monosomy 17p). All these factors are considered high-risk markers that predict below-average outcomes. While outcomes related to 1q have been documented, their relationship with other abnormalities and clinical characteristics is less clearly defined. **Methods:** We created a cohort of newly diagnosed MM (NDMM) patients from April 1996 to December 2023 for whom FISH testing was performed using a panel that included 1q findings. Data on clinical and laboratory characteristics, other FISH abnormalities, and survival outcomes were collected from existing databases and the electronic medical record (EMR). **Results:** The cohort included 875 patients, with a median age of 65. Of these patients, 60% were male and 91% identified as white. A 1q abnormality was observed in 443 patients (51%); 87% exhibited a gain of 1q, while 13% showed amplification of 1q. Among those tested, other abnormalities included del13 (58%), t(11;14) (25%), t(4;14) (17%), t(14;16) (6%), del 17p (13%), and trisomies (51%). The distribution of abnormalities concerning the presence of 1q is presented in the table. Patients with 1q abnormalities were more likely to present with additional high-risk cytogenetic abnormalities. The median overall survival (OS) for those with a 1q abnormality was 73 months, compared to 105 months for those without it. Among these, patients with 1q amplification tended to have worse outcomes than those with a 1q gain, though this observation did not reach statistical significance. **Conclusions:** Abnormalities of chromosome 1, including 1q gain and amplification, can be seen in nearly 50% of patients with NDMM who are tested. 1q abnormalities are associated with other high-risk cytogenetic abnormalities. Measures of disease burden are higher among those with a 1q abnormality. Interestingly, we observed a higher proportion of patients with lambda light chain and those with IgA among those with a 1q abnormality. The presence of a 1q abnormality was associated with inferior survival, with a trend towards worse outcomes among those with 1q amplification compared to 1q gain. Research Sponsor: None.

Clinical characteristics and cytogenetic associations of multiple myeloma patients with and without 1q abnormalities.

	1q abnormality present	1q abnormality absent	P
del13	78%	39%	<0.01
t(4;14)	25%	8%	<0.01
t(11;14)	22%	27%	NS
t(14;16)	15%	3%	<0.01
Trisomies	48%	53%	NS
17p del	24%	12%	<0.01
Lambda light chain	45%	26%	<0.01
IgA	32%	16%	<0.01
Hemoglobin	10.3 g/dL	11.2 g/dL	<0.01

Real-world comparison of anti-BCMA vs anti-GPRC5D BiTE therapy in relapsed/refractory multiple myeloma without prior CAR-T cell exposure.

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Background: In recent years, three bispecific T-cell engager (BiTE) agents have been approved for Refractory/Relapsed Multiple Myeloma (rrMM). These have shown remarkable efficacy, particularly in patients who have failed multiple lines of prior therapy. However, there is a paucity of data to guide choice between available agents. **Methods:** We performed a multicenter, retrospective, propensity score matched (PSM), safety and efficacy comparison between anti-BCMA (Cohort 1: Teclistamab and Elranatamab) and anti-GPRC5D (Cohort 2: Talquetamab) therapy in rrMM, using TriNetX database. Patients with prior CAR-T therapy were excluded. Outcomes assessed included survival, remission rates, subsequent CAR-T therapy, subsequent alternate BiTE therapy, risk of infections, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), hypogammaglobulinemia and IVIG use with a follow up of 2 years following treatment. **Results:** A total of 888 and 296 patients were identified in cohort 1 (C1) and cohort 2 (C2), respectively. The two cohorts were matched for 25 characteristics yielding 266 patients in the PSM analysis. No differences in survival probability (HR 0.95; 95% CI 0.65-1.39, p=0.83) or remission rates (C1 vs C2: 37.2 vs 35.0 %, p=0.588) were observed. Subsequent CAR-T therapy was used in 3.8% in C1 and 15% of patients in C2. Any grade CRS (C1 vs C2: 34.6 vs 48.1%, p=0.002) was more common in the Talquetamab cohort, with majority being grade<3 CRS (C1 vs C2: 16.2 vs 27.8%, p=0.001). There was no difference observed for any grade ICANS (C1 vs C2: 14.7 vs 9.8%, p=0.08). No significant differences were found between rates of overall infection (C1 vs C2: 45.5 vs 43.6 %, p=0.63), bacterial (C1 vs C2: 23.3 vs 21.1%, p=0.53), viral (C1 vs C2: 28.6 vs 28.2 %, p=0.92), or fungal (C1 vs C2: 5.8 vs 8.9 %, p=0.29) infections rates. The incidence of hypogammaglobulinemia (C1 vs C2: 74.4 vs 77.8%, p=0.36) and treatment with IVIG (C1 vs C2: 52.3 vs 44.4 %, p=0.06) were similar across both groups. **Conclusions:** Our analysis of real-world patients with relapsed/refractory multiple myeloma (rrMM) showed similar efficacy and tolerability between anti-BCMA and GPRC5D BiTE therapies. However, the Talquetamab group had a higher rate of CRS, consistent with the high incidence observed in the phase 2 MonumenTAL-1 trial. The extent of comorbidities, safety profile of individual agents and plan for subsequent CAR-T cell therapy can guide the choice between available BiTE therapies. Research Sponsor: None.

BiTE therapy: Demographics and outcomes.

Outcome	Cohort 1	Cohort 2	p-value
Total # of pts	266	266	
Mean Age (years)	67.2	67.4	0.82
Male/Female (%)	52.6 / 43.6	50.4 / 43.2	0.60/0.93
Mean duration of treatment (Days)	246 (Teclist) 163 (Elra)	182	
2-yr Survival	55 (54.5%)	53 (50.6%)	0.76
Complete Remission	99 (37.2%)	93 (35.0 %)	0.59
CRS	92 (34.6%)	128 (48.1%)	0.002

7543 Poster Session

Correlation of a senescence-associated gene signature with prognosis in multiple myeloma.

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Background: Multiple myeloma (MM), an incurable malignancy of plasma cells, is predominantly a disease of aging. Cellular senescence, a fundamental biological process associated with aging, has been implicated in developing age-related malignancies, including MM. This study investigated the prognostic significance of senescence-associated genes within a large cohort of MM patients. **Methods:** Gene expression and clinical data from 1,416 MM patients were obtained from four GEO datasets (GSE24080, GSE4204, GSE57317, and GSE9782) and integrated into a unified database. Rigorous preprocessing of raw data ensured cross-platform comparability. We employed the SenMayo gene signature, a curated set of senescence-associated genes, computed as a weighted mean expression of the genes. Cox proportional hazards regression, Kaplan-Meier survival analysis, and multivariate models were used to evaluate the prognostic value of the SenMayo signature. Univaraite visualizations were plotted using the Kaplan-Meier plotter (www.kmplot.com). Clinical parameters, including gender, isotype, and molecular subtypes, were incorporated into multivariate analyses, and False Discovery Rate (FDR) correction was applied to correct for multiple hypothesis testing. **Results:** The SenMayo gene signature strongly correlated with overall survival (OS) in MM patients (HR = 0.6, 95% CI = 0.47–0.76, p = 1.7e-05). Patients in the low-expression group had an upper quartile survival duration of 36.1 months, compared to 57 months for those in the high-expression group. Independent validation across three datasets confirmed its prognostic value (GSE4204: HR = 0.58, 95% CI = 0.39–0.88, p = 0.0089; GSE24080: HR = 0.61, 95% CI = 0.45–0.83, p = 0.0012; GSE57317: HR = 0.25, 95% CI = 0.08–0.77, p = 0.0095). Multivariate analyses underscored the SenMayo signature as a prognostic factor, even after adjusting for established clinical parameters such as gender and isotype. **Conclusions:** These findings underscore the pivotal role of cellular senescence in the progression of MM. The senescence gene signature warrants further investigation to support its integration into clinical practice for improved risk stratification and informed therapeutic decision-making. Research Sponsor: None.

Baseline ocular conditions and risk of ocular events in patients (pts) with relapsed/refractory multiple myeloma (RRMM) from the DREAMM-7 and DREAMM-8 trials of belantamab mafodotin (belamaf).

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Background: Belamaf combinations were evaluated for RRMM in the phase 3 DREAMM-7 (belamaf + bortezomib + dexamethasone [BVd]; NCT04246047) and DREAMM-8 (belamaf + pomalidomide + dexamethasone [BPd]; NCT04484623) trials, and significant progression-free survival benefits were reported over standard of care, with significant overall survival benefit reported for BVd. Ocular events (e.g., ocular adverse events [oAEs], blurred vision, dry eye) occurred with belamaf and most resolved with dose holds and modifications. We examined the baseline eye health of pts with RRMM receiving BVd or BPd, and whether baseline ocular conditions affected rates of treatment-emergent (TE) oAEs. **Methods:** Pts with ≥1 prior therapy were eligible for DREAMM-7/8; pts with ocular conditions were eligible except for corneal epithelial disease (mild punctate keratopathy was allowed). Mandatory ophthalmic examinations (best corrected visual acuity [BCVA], slit lamp, and funduscopic exams) were performed in both arms of the trials at baseline and routinely during treatment. oAEs were graded by Common Terminology Criteria for Adverse Events. Regardless of presence/absence of baseline ocular conditions, the same protocol-defined strategies were used for ocular event management during the studies. **Results:** In 392 pts treated with belamaf (n=242 DREAMM-7 and n=150 DREAMM-8), baseline ocular conditions were reported in 62% of pts (n=135 and 106); baseline conditions included cataract 50% (n=101 and 96), keratopathy 14% (n=33 and 23), dry eye 14% (n=31 and 24), visual acuity of 20/50 or worse 6% (n=18 and 7), glaucoma 6% (n=11 and 13), blepharitis 2% (n=4 and 3), age-related macular degeneration 1% (n=3 and 2), and diabetic retinopathy <1% (n=0 and 2). Any TE oAE was reported in 74% (n=100/135) and 87% (n=92/106) of pts with baseline ocular conditions in DREAMM-7 and DREAMM-8, respectively, compared with 79% (n=85/107) and 91% (n=40/44) of pts without baseline ocular conditions (Table). **Conclusions:** The safety profiles of belamaf combinations for oAEs were similar between patients with vs without baseline ocular conditions, suggesting that these baseline ocular conditions did not increase the risk of TE oAEs. The effect of each baseline ocular condition on TE oAEs, as well as TE corneal exam findings and visual acuity changes, will be presented. Clinical trial information: NCT04246047, NCT04484623. Research Sponsor: GSK (207499/207503); drug linker technology licensed from Seagen; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

TE ocular events in patients receiving a belamaf combination in DREAMM-7/8.

	DREAMM-7		DREAMM-8	
	With any baseline ocular condition, n=135	No baseline ocular condition, n=107	With any baseline ocular condition, n=106	No baseline ocular condition, n=44
Any oAE, n (%)	100 (74)	85 (79)	92 (87)	40 (91)

DREAMM-7 study of belantamab mafodotin plus bortezomib and dexamethasone (BVd) vs daratumumab plus bortezomib and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM): A subgroup analysis in patients (pts) with high-risk cytogenetic (HRC) features.

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Background: In DREAMM-7 (NCT04246047), BVd exhibited a significant improvement in the risk of progression or death vs DVd in pts with RRMM who had ≥1 prior line of treatment. In a post hoc analysis (Mateos et al; ASCO 2024) of pts with ≥1 HRC abnormality (HRCA), including t(4;14), t(14;16), and 17p13del, more pts had deep responses (defined as complete response [CR] or better) with BVd (45%; 95% CI, 32.6%-57.4%) than with DVd (13%; 95% CI, 6.1%-23.3%). Up to 70% of pts at early relapse have amp1q, which confers an increased risk of disease progression. Here we present an updated post hoc efficacy analysis in pts with HRCA, including amp1q. **Methods:** Pts were randomized 1:1 to BVd or DVd as previously reported. For this analysis, pts with HRC were defined as those having ≥1 HRCA, including t(4;14), t(14;16), t(14;20), 17p13del, and amp1q (defined as ≥4 copies of chromosome 1q21). Descriptive statistics were used to summarize results, with 95% exact CI. Hazard ratios (HRs) for progression-free survival (PFS) were estimated using the Cox model, with 95% CI based on the Brookmeyer-Crowley method. **Results:** The ITT population included 494 pts: BVd, n=243; DVd, n=251. In the BVd arm, 122/243 pts (50%) had HRC, of which 41 (17%) had t(4;14), 8 (3%) had t(14;16), 1 (0.4%) had t(14;20), 30 (12%) had 17p13del, and 94 (39%) had amp1q. In the DVd arm, 115/251 (46%) had HRC, of which 42 (17%) had t(4;14), 6 (2%) had t(14;16), 1 (0.4%) had t(14;20), 35 (14%) had 17p13del, and 79 (31%) had amp1q. Median PFS in pts with ≥1 HRCA was 33.2 mo (95% CI, 20.1 mo-not reached) with BVd vs 11.1 mo (95% CI, 9.0-15.1 mo) with DVd (HR, 0.40; 95% CI, 0.27-0.59), and 18-mo PFS rates were 61% and 38%, respectively. PFS benefit favored BVd across subgroups (HR [95% CI]): t(4;14), 0.36 [0.19-0.67]; 17p13del, 0.25 [0.11-0.61]; amp1q, 0.48 [0.31-0.73]; t (14;16) and t(14;20) were not analyzed due to low numbers. In pts with ≥1 HRCA, overall response rate was 81% (n=99; 95% CI, 73.1%-87.7%) with BVd and 69% (n=79; 95% CI, 59.4%-77.0%) with DVd; more pts achieved ≥CR with BVd than with DVd (Table). The benefit was maintained across subgroups. **Conclusions:** In pts with RRMM and ≥1 HRCA, PFS benefit favored BVd vs DVd, and BVd demonstrated a higher rate of deep response. Current outcomes in pts with HRC features are suboptimal, and these data support BVd as a potential standard-of-care regimen in these pts with high unmet need. Clinical trial information: NCT04246047. Research Sponsor: This study was sponsored by GSK. Editorial support was provided by Nucleus Global, an Inizio Company, and funded by GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

Patients achieving ≥CR in HRC Groups n/N (%); 95% CI	BVd	DVd
t (4;14)	20/41 (49); 32.9-64.9	6/42 (14); 5.4-28.5
t (14;16)	1/8 (13); 0.3-52.7	0/6; 0-45.9
17p13del	11/30 (37); 19.9-56.1	4/35 (11); 3.2-26.7
amp1q	31/94 (33); 23.6-43.4	16/79 (20); 12.0-30.8
≥1 HRCA	48/122 (39); 30.6-48.6	20/115 (17); 11.0-25.6

7547 Poster Session

Leveraging AI for validating the association between minimal residual disease (MRD) and survival outcomes in multiple myeloma.

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Background: Minimal residual disease (MRD) has been recently accepted by the Food and Drug Administration (FDA) as an endpoint for accelerated approval in Multiple Myeloma. However, emerging data from recent trials were not included in previous analyses. While literature-based meta-analyses on the correlation between MRD and approved clinical outcomes typically require extensive manual review, leveraging AI with expert-in-the-loop validation can efficiently generate reliable evidence from comprehensive clinical studies with up-to-date outcomes. **Methods:** An AI-assisted framework was developed to identify relevant studies and extract critical information via two independent objectives. The first objective examined trial-level associations, modeling treatment effects on MRD and clinical endpoints across patient populations using weighted least squares, with association strength measured by coefficients of determination (R^2) and 95% confidence intervals (CIs). The second objective analyzed individual-level associations using synthetic individual patient data (SynthIPD) generated from the published Kaplan-Meier plots and summary statistics of patient subgroups. **Results:** AI-assisted screening identified eligible studies (>50 patients per treatment arm) reporting progression-free survival (PFS), overall survival (OS), and MRD-negative complete response rates (MRD-CR rate) using multi-parameter next-generation flow cytometry or sequencing methods (sensitivity threshold $\geq 10^{-5}$), expanding previous analyses from 15 to 20 two-arm studies. Trial-level analysis demonstrated an R^2 of 0.69 (95% CI 0.50–0.89) for PFS log hazard ratio versus MRD-CR rate log odds ratio. Analysis of synthetic individual data from Kaplan-Meier curves using a novel digitization method yielded a global odds ratio of 7.28 (95% CI 5.60–8.95) for individual-level correlation between MRD-CR rates and PFS outcomes. **Conclusions:** This study validates MRD-CR rate as an endpoint for accelerated approval in MM through rapid AI-assisted literature review and synthetic individual patient data. The findings demonstrate moderate correlation between MRD-CR rate and median PFS at both trial and individual levels, consistent with previous literature but incorporating additional eligible studies. The novel SynthIPD approach presents an efficient alternative to traditional data-sharing methods while maintaining analytical robustness. These results align with current Oncologic Drugs Advisory Committee (ODAC) surrogacy analysis methods and support the utility of MRD assessment in MM clinical trials. Research Sponsor: None.

Efficacy and safety outcomes in patients (pts) with renal impairment in the phase 3 DREAMM-7 and DREAMM-8 trials.

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Background: Renal impairment is a frequent complication in relapsed/refractory multiple myeloma (RRMM). Results from DREAMM-7 (NCT04246047) showed significant PFS and OS benefit favoring belantamab mafodotin (belamaf), bortezomib, and dexamethasone (BVd) vs daratumumab-Vd (DVd). DREAMM-8 (NCT04484623) showed significant PFS benefit with belamaf, pomalidomide, and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd). In an ongoing phase 1 study (NCT04398745), renal impairment did not impact belamaf pharmacokinetics. We report outcomes in pts with mild/moderate renal impairment from DREAMM-7 and DREAMM-8. **Methods:** Renal function of eligible pts with RRMM was defined based on estimated glomerular filtration rate (eGFR) derived by local labs at screening: normal (≥90 mL/min/1.73 m^2), mild (≥60 to <90 mL/min/1.73 m^2), or moderate (≥30 to <60 mL/min/1.73 m^2) impairment. Pts with eGFR <30 mL/min/1.73 m^2 were ineligible for these trials. **Results:** Results included pts with mild/moderate renal impairment in DREAMM-7 (BVd, n=175; DVd, n=183) as of October 2, 2023, and DREAMM-8 (BPd, n=117; PVd, n=109) as of January 29, 2024. Median PFS was NR with BVd vs 12.6 mo with DVd (HR, 0.39; 95% CI, 0.29-0.53) in DREAMM-7 and 24.0 mo with BPd vs 9.7 mo with PVd (HR, 0.52; 95% CI, 0.35-0.76) in DREAMM-8. Belamaf-containing regimens in both trials had numerically higher 18-mo PFS rates, overall response rates (ORRs), and complete response or better (≥CR) rates (Table). OS benefit favored BVd vs DVd (HR, 0.58; 95% CI, 0.39-0.86) and BPd vs PVd (HR, 0.71; 95% CI, 0.46-1.09). Median OS was NR in either arm of both trials. In pts with mild/moderate renal impairment in DREAMM-7, 95% with BVd and 79% with DVd had a grade 3/4 AE. AEs leading to discontinuation of any study drug occurred in 33% and 18%, respectively. Fatal serious AEs occurred in 10% with BVd and 8% with DVd. In DREAMM-8, 90% with BPd and 73% with PVd had a grade 3/4 AE. AEs leading to discontinuation of any study drug occurred in 13% with BPd and 15% with PVd. Fatal serious AEs were observed in 13% and 12%, respectively. **Conclusions:** In pts with mild/moderate renal impairment, belamaf-containing regimens (BVd and BPd) showed improved efficacy vs standard triplets, indicating they are an efficacious alternative SOC in a broad range of pts with RRMM. Safety results in this pt population were consistent with the ITT populations. Research Sponsor: This study was sponsored by GSK. Editorial support was provided by Nucleus Global, an Inizio company, and funded by GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

ITT population with mild/moderate renal impairment	BVd n=175	DVd n=183	BPd n=117	PVd n=109
18-mo PFS rate (95% CI)	0.69 (0.61-0.75)	0.41 (0.33-0.48)	0.61 (0.51-0.70)	0.40 (0.29-0.50)
ORR (95% CI), %	86 (79.6-90.5)	74 (67.4-80.5)	76 (67.3-83.5)	72 (62.1-79.8)
≥CR (95%CI), %	34 (26.8-41.2)	15 (10.4-21.3)	38 (29.6-47.9)	13 (7.2-20.6)

Safety population with mild/moderate renal impairment	BVd n=175	DVd n=183	BPd n=112	PVd n=107
Grade 3/4 AE, %	95	79	90	73
AEs leading to discontinuation of any study drug, %	33	18	13	15
Serious fatal AEs, %	10	8	13	12

7549 Poster Session

Efficacy and safety of less frequent dosing with elranatamab (ELRA) in patients with relapsed or refractory multiple myeloma (RRMM): A US subgroup analysis from MagnetisMM-3.

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Background: The ongoing phase 2 MagnetisMM-3 (NCT04649359) study demonstrated the efficacy and safety of ELRA in patients (pts) with RRMM and no prior BCMA-directed therapy (Cohort A). With a median follow-up of 33.9 mo, ORR was 61.0%, mPFS was 17.2 mo, and mOS was 24.6 mo. Here we report results for the subgroup of pts enrolled in MagnetisMM-3 in the US. **Methods:** Eligible pts had RRMM with disease refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 antibody. Pts were given subcutaneous ELRA as step-up priming doses followed by 76 mg QW for 6 cycles. Pts given QW dosing for ≥6 cycles who achieved partial response or better lasting ≥2 mo were transitioned to Q2W dosing and to Q4W after ≥6 cycles of Q2W dosing. The subgroup of pts within Cohort A enrolled in the US (n=47) was analyzed. As of the data cutoff date (September 10, 2024), the median follow-up was 33.8 mo (95% CI, 32.9-35.7; estimated by reverse Kaplan–Meier), approximately 32 mo after the last pt first dose. **Results:** Pts in the US subgroup received a median of 5 prior lines of therapy (range, 2-22); 93.6% were triple-class refractory, and 46.8% were penta-drug refractory. Eight (17.0%) pts were Black or African American. ORR (95% CI) by Blinded Independent Central Review was 66.0% (50.7-79.1); 42.6% of pts achieved complete response (CR + stringent CR). Median (range) time to response was 1.08 mo (0.95-7.36), and median time to CR or better was 4.76 mo (1.22-12.75). Median duration of response (95% CI) was not reached (NR) (24.0 mo-not estimable [NE]); the probability of maintaining response at 30 mo (95% CI) was 65.7% (43.3-81.0). Median (95% CI) PFS was 27.3 mo (4.3–NE). Median (95% CI) OS was NR (14.9–NE); the probability of survival at 30 mo (95% CI) was 55.8% (40.1-68.9). Any grade [G] and G3/4 treatment-emergent adverse events were reported in 100% and 78.7% pts, respectively. Infections (any G, G3/4, G5) were reported in 70.2%, 40.4%, and 0.0%, respectively; 51.1% received Ig replacement. Anti-viral, anti-pneumocystis jirovecii pneumonia, anti-bacterial, and anti-fungal prophylaxis were received by 80.9%, 21.3%, 14.9%, and 8.5% of pts, respectively. The rate of cytokine release syndrome (CRS) was 61.7% (G1, 34.0%; G2, 27.7%; G≥3, 0.0%). Immune effector cell-associated neurotoxicity syndrome was reported in 8.5% of pts (G1, 4.3%; G2, 4.3%; G≥3, 0.0%). 22 pts switched from QW to Q2W, and 8 pts further switched from Q2W to Q4W dosing. **Conclusions:** The pts with RRMM enrolled in MagnetisMM-3 Cohort A, including the US subgroup, were heavily pretreated. Consistent with overall Cohort A data, ELRA was associated with deep, durable responses in the US subgroup, with a mPFS of 27.3 mo. CRS was G1 and G2 only. Infections were consistent with what was observed in the overall study population; infection prophylaxis including Ig replacement are recommended. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

Belantamab treatment of multiple myeloma: Results from part 1 of the first-in-human phase 1/2 DREAMM-20 trial.

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Background: Belantamab mafodotin (belamaf) is a B-cell maturation antigen (BCMA)–targeted monoclonal antibody (mAb) conjugated with a monomethyl auristatin-F (MMAF) payload. In DREAMM-7 and DREAMM-8 phase 3 trials in relapsed/refractory multiple myeloma (RRMM), belamaf combinations significantly improved progression-free survival vs standard care, and DREAMM-7 showed significant overall survival benefit. Belantamab (GSK2857914) is the naked BCMA mAb without MMAF; therefore MMAF-related toxicities are not expected. DREAMM-20 is a phase 1/2 trial to evaluate safety, tolerability, and clinical activity of belantamab in patients (pts) with MM. We present the planned analysis of part 1 of belantamab dose escalation. **Methods:** Part 1 of DREAMM-20 (NCT05714839) is a phase 1, open-label, multicenter, dose-escalation study in pts with RRMM with ≥3 prior lines of therapy. Dose escalation was conducted using a modified toxicity probability interval method. The primary endpoint was incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Secondary endpoints included overall response rate (ORR). **Results:** Across 3 cohorts, 18 pts enrolled and received belantamab 300, 900 or 2000 mg IV Q2W (n=6 each). Data cutoff (DCO) was Aug 23, 2024. Median age was 76 y (range, 42-86 y), 17 of 18 pts were triple-class exposed, and 2 of 18 pts had prior BCMA-targeted therapy. The overall median duration of exposure was 63.5 days. No DLTs or treatment-related AEs (TRAEs) leading to permanent discontinuation were reported. The most common TRAEs were infusion-related reactions and hematologic AEs (Table). Two pts had grade ≥2 corneal events per the Keratopathy and Visual Acuity (KVA) scale that were considered unrelated to belantamab. The ORR was 28% (5/18 pts; very good partial response, n=2 [900 mg]; partial response, n=3 [1 in 300 mg and 2 in 2000 mg]) with responses across all cohorts. Median duration of exposure in the 5 responders was 253 days; none of the responders had progressed as of DCO. No pts had minimal response and 28% (5/18 pts) had stable disease. Follow-up is ongoing. **Conclusions:** Belantamab showed an encouraging safety profile with no DLTs, AEs leading to discontinuation, or belantamab-related grade ≥2 corneal events. Durable responses were observed across dose levels in this triple-class–exposed population. Results support the hypothesis that belantamab provides clinical antimyeloma activity with an acceptable safety profile. Clinical trial information: NCT05714839. Research Sponsor: This study was sponsored by GSK (study 218670). Editorial support was provided by Nucleus Global, an Inizio Company, and funded by GSK. Monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

n (%)	Belantamab 300, 900, or 2000 mg (N=18)
Any-grade AEs	17 (94)
TRAEs	12 (67)
Most common TRAEs (≥2 patients)	
Infusion-related reactions	4 (22)
Neutrophil count decreased	4 (22)
Anemia	2 (11)
Vision blurred	2 (11)
Platelet count decreased	2 (11)
Grade ≥3 AEs	12 (67)
Most common grade ≥3 AEs (≥2 patients)	
Neutrophil count decreased	4 (22)
Anemia	3 (17)
Serious AEs	6 (33)
Treatment related	1 (6)
Fatal AEs	0

Positron emission tomography with computed tomography (PET/CT) and minimal residual disease (MRD) for efficacy assessment in transplant-ineligible newly diagnosed myeloma (Ti NDMM) patients (pts): IMROZ analysis.

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Background: MRD is a measure of response in the bone marrow (BM) but is limited by patchy infiltration of BM plasma cells and lack of plasmacytoma assessment. Imaging-based MRD assessment, which is non-invasive, such as PET/CT, may overcome these limitations, and distinguish metabolically active MM from non-active. Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with bortezomib, lenalidomide and dexamethasone (VRd) in Ti NDMM pts based on the Phase 3 IMROZ study. Here, we present an analysis of IMROZ (NCT03319667), investigating PET/CT negativity (−) with MRD− in front line efficacy assessment. **Methods:** In IMROZ, pts were randomized 3:2 to receive Isa-VRd or VRd as initiation, then Isa-Rd or Rd as maintenance. BM MRD was assessed by next generation sequencing at 10^{-5} sensitivity at baseline (BL), then in case of complete response (CR) or very good partial response at end of initiation, and every 6 months for 2 years, then once a year until disease progression (PD). PET/CT scans were assessed by central review and performed at BL, then yearly until PD; if positive for soft tissue plasmacytoma, repeated at time of CR and/or end of induction, then following time points for MRD assessment. PET/CT positivity (+) was defined as FDG 5PS Score ≥4, and PET/CT− as FDG 5PS ≤3. **Results:** Across the global and China populations, 244 Isa-VRd and 162 VRd pts had PET/CT at BL, of which 153 (62.7%) and 101 (62.3%) were PET/CT+, respectively. Of these, 121 (41.6%) and 83 (43.0%) had a post-BL PET/CT assessment. 155 pts presented with plasmacytoma at BL (95 Isa-VRd, 60 VRd), with comparable BL characteristics to the global population. Among PET+ pts at BL, the double negativity rate (PET/CT FDG 5PS score ≤3 + MRD−) was significantly higher in Isa-VRd pts than VRd (odds ratio [OR] 1.54; 95% CI 1.04-2.29; p=0.0155), and similarly for double negativity + ≥CR (OR 1.60; 95% CI 1.07-2.38; p=0.0108). As shown in Table, more Isa-VRd than VRd pts with plasmacytoma reached PET/CT 5PS ≤3 and MRD−, and PET/CT 5PS ≤3 with MRD− + ≥CR. Progression-free survival (PFS) in pts PET/CT+ at BL was in favor of the Isa-VRd arm (median PFS [mPFS] not reached [NR; 95% CI 59.4-NR]) vs VRd (mPFS 49.1 [95% CI 39.1 -NR]) (hazard ratio [HR] 0.58; 95% CI 0.39-0.88; p=0.6303), and HR was comparable to the intent to treat population. PFS in pts with plasmacytoma at BL was similar to the global population (HR 0.685; 95% CI 0.40-1.18; p=0.5332). **Conclusions:** This analysis of IMROZ shows the prognostic value of BL PET/CT findings. More Isa-VRd pts reached double negativity than VRd, including pts with plasmacytomas. This translated to a better PFS in pts treated with Isa-VRd. Clinical trial information: NCT03319667. Research Sponsor: Sanofi.

	Isa-VRd (n=77)	VRd (n=52)
PET/CT 5PS score ≤3 and MRD−, %	45.5	34.6
OR (95% CI), p	1.57 (0.76-3.26), 0.1107	
PET/CT 5PS score ≤3 and MRD− + ≥CR, %	44.2	32.7
OR (95% CI), p	1.63 (0.78-3.39), 0.0966	

Impact of autoimmune disease on toxicity and outcomes after idecabtagene vicleucel in patients with multiple myeloma.

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Background: Idecabtagene vicleucel (ide-cel), an autologous BCMA-directed chimeric antigen receptor (CAR) T-cell therapy, has the potential to cure patients with relapsed/refractory multiple myeloma (RRMM). However, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are common treatment-related adverse events. Historically, patients with autoimmune disease (AD) have been excluded from CAR-T trials due to uncertain outcomes. This study evaluates differences in ICANS, relapse, and survival in RRMM patients with and without AD treated with ide-cel. **Methods:** A retrospective study of RRMM patients with AD treated with ide-cel at Moffitt Cancer Center in Tampa, FL between 2021-2024 was conducted. Clinically significant AD requiring medical management prior to apheresis included AIHA, autoimmune thyroiditis, ITP, RA, AIDP, CIDP, UC, SLE and PMR. T-tests and Kaplan-Meier estimates analyzed associations between AD, toxicities, and survival. **Results:** Of 179 patients with RRMM who received ide-cel, 13 (7%) had clinical AD with a median age of 72 years (range: 58 - 81 years, 54% female [n=7]). The incidence of ICANS was 23.1%, versus 23.6% for patients without AD (n = 166). The incidence (p = 1) and duration (p = 0.822) of ICANS was not significantly different in those with or without AD. Two patients (with AIHA and ITP) were tapered off of prednisone prior to ide-cel. Per medical records, the remaining patients were not on immunosuppressive medications for AD at treatment. All AD patients experienced CRS versus 85% of patients without AD (p = 0.225). For AD patients who experienced ICANS, median LDH (202 U/L vs 189 U/L, p = 0.061) and ferritin (528 ng/mL vs 284 ng/mL, p = 0.866) 5 days prior to infusion (day -5) was not significantly higher versus AD patients with no ICANS. However, median CRP at day -5 was significantly higher (1.2 mg/L vs 0.365 mg/L, p = 0.05). In AD patients who experienced ICANS, median LDH (872 U/L vs 268U/L, p = 0.01) and ferritin (10200 ng/ml vs 3000 ng/ml, p = 0.05) were significantly higher at the day of maximum grade ICANS versus patients without AD. However, there was no difference in median CRP (7.46 mg/L vs 7.72 mg/L, p = 0.9). Among patients who experienced ICANS, AD patients did not have significantly lower progression free survival (PFS) versus patients without AD at 30 days, 12 months, and 18 months (p = 0.07). There was no difference in overall survival between patients with or without AD. **Conclusions:** This retrospective study shows that pre-existing AD does not increase the risk of ICANS in patients with RRMM who were treated with ide-cel. Although LDH and ferritin levels were similar, levels of CRP were significantly higher in AD patients who experienced ICANS versus those that did not. Given notable differences in levels of inflammation and relapse rates among patients with AD, these patients may benefit from close monitoring. Research Sponsor: None.

Carfilzomib, iberdomide, and dexamethasone (KID) in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): Updated results from phase 1/2 study.

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Background: SOC regimens for patients (pts) with transplant-eligible NDMM include VRd, D-VRd, and KRd. Iberdomide, a cereblon modulator, enhances immune stimulatory activity *in vitro* compared to thalidomide analogs. A phase 1 study reported the MTD of iberdomide 1.6 mg plus carfilzomib (CFZ) and dexamethasone (DEX), KID regimen, in NDMM pts (Biran 2023). Herein we report longer term safety and efficacy data from a phase 2 dose expansion study of KID in NDMM pts (NCT05199311). **Methods:** Adults with NDMM eligible for ASCT were enrolled in this multicenter, investigator-initiated phase 1/2 study. In the phase 2 portion, pts received CFZ (IV; 20 mg/m^2 on C1D1; then 56 mg/m^2 C1 D8, 15; then 56 mg/m^2 C2-4 D1, 8, 15), iberdomide (1.6 mg; D1-21), and DEX (40 mg if ≤75 years; 20 mg if >75 years; D1, 8, 15) in 28-day cycles for 2-3 cycles followed by ASCT. The primary objective is to evaluate the rate of CR + sCR. **Results:** As of 1/10/25, 38 pts signed consent, including 20 in follow-up, 7 off study (5 screen failures/1 consented/1 withdrew due to rash), and 4 on treatment (tx). Of 31 pts who received tx, median age was 66 years (range 41-78), 52% male, 77% White, 16% Black, 3% Asian, 58%/16%/6% ISS stage 1/2/3, respectively. Thirteen pts (42%) had high-risk cytogenetics: t(4;14) (n=3), t(4;16) (n=1), del(17p)/monosomy 17/*TP53* (n=2), 1q21 (n=9), and *MYC* (n=1). Two pts had double- and 1 was triple-hit MM. Thirty-one pts completed a median of 3 cycles (range 1-4) of KID. At end of induction, ORR was 96% (23/24, CR 4%, VGPR 42%, PR 50%). Twenty-three pts proceeded to ASCT; 8 did not (4 on tx/1 collecting cells/1 withdrawal/1 death). Median number of stem cells mobilized was 11.3 x 10^6 cells/kg (range 4.74-29.8). At 3 months post-ASCT, ORR was 100% (19/19, sCR 5%, CR 21%, VGPR 53%, PR 21%), CR + sCR is 26%, and of those, 100% are MRD-negative. Median tx duration was 84 days (IQR, 63-91). At median follow-up of 12.4 months, median PFS and OS were NR (95% CI, NA-NA). Most common hematologic TEAEs were anemia (19%), neutropenia (39%), and thrombocytopenia (23%). Most common non-hematologic TEAEs were pruritus (23%) and rash (23%). Grade 3 TEAEs occurred in 26% of pts; most common were neutropenia (26%), thrombocytopenia (6%), and rash (6%). Six pts developed grade 1-2 SAEs unrelated to tx. One patient experienced grade 3 SAE of fever and colonic hemorrhage that required hospitalization and supportive care. No tx-related deaths occurred; 1 patient died on study due to a possible thrombotic event in the setting of medication non-compliance. **Conclusions:** Induction therapy with KID appears safe and effective leading to deep responses and adequate stem cell collection despite short tx duration and 42% harboring high-risk cytogenetics. Long-term follow-up is needed to determine durability of response. Correlative studies are underway to evaluate immune phenotype and microbiome changes pre/post-tx. Clinical trial information: NCT05199311. Research Sponsor: Amgen; Bristol Myers Squibb.

Updated results from phase 2b study of selinexor in combination with carfilzomib, daratumumab, or pomalidomide in patients with multiple myeloma (MM) relapsing on current therapy.

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Background: Selinexor is a potent selective inhibitor of nuclear export and exhibits synergistic effects when combined with other myeloma therapies. Preliminary results on the combination of selinexor with carfilzomib (CFZ), daratumumab (DARA), or pomalidomide (POM)-based regimens in patients relapsing on therapy were reported (Biran 2023); overall response rate (ORR) Arm 1 (33%), Arm 2 (29%), and Arm 3 (44%). Herein we present the updated results with longer follow-up of selinexor plus CFZ, POM or DARA in MM patients relapsing on current treatment (NCT04661137). **Methods:** Patients were enrolled to each arm if their disease was refractory to the specific drug. Patients on Arm 1 were treated with selinexor 80 mg on D1, 8, 15; CFZ 20 mg/m^2 IV on D1, 8, 15; and dexamethasone (DEX) on D1, 8, 15, 22. Arm 2 patients received selinexor 60 mg on D1, 8, 15; POM 4 mg on D1-21; and DEX on D1, 8, 15, 22. Arm 3 patients were treated with selinexor 100 mg on D1, 8, 15, 22; DARA 16 mg/kg IV or 1,800 mg SQ on D1, 8, 15, 22 for C1-2; then D1 and 15 for C3-6; then D1 for ≥C7; and DEX on D1, 8, 15, 22. The primary objective was to investigate the ORR of selinexor plus CFZ, POM, or DARA-based regimens. **Results:** As of Jan 10, 2025, 28 patients were enrolled. Twenty-four were evaluable for response; 7 withdrew consent in which 5 were due to disease progression. Median age was 68 years (range 52-82), 50% male, 54% White, 96% had prior autologous transplant and 21% had extramedullary disease. Nineteen (79%) patients had high-risk cytogenetics, including 1q21 duplication (n=11), t(4;14) (n=8) and *TP53* mutation (n=6). The ORR was 38% (95% CI, 19-59%) (PR, 8 [33%]) and clinical benefit rate (CBR) was 83% (95% CI, 63-95%) (PR, 8 [33%]; MR, 1 [4%]; SD, 11 [46%]). With a median follow-up of 11.0 months, the median PFS was 5.7 months (95% CI, 4.7-NR), and median OS was NR months (95% CI, 15-NR). Median DOR was 3.6 months (IQR, 2.5-5.1) with a median treatment duration of 4.0 months (range 0.3-10.8 mos). Most commonly reported Grade 1-2 TEAEs were electrolyte abnormalities (50%) and fatigue (38%). Most commonly reported grade ≥3 TEAEs were neutropenia (25%) and pneumonia (8%).Three patients experienced treatment-related grade 3 SAEs and recovered. One developed chest pain that required hospitalization. One had parainfluenza A-1 pneumonia requiring a treatment delay. One experienced sepsis and pneumonia which led to hospitalization and interruption of treatment. **Conclusions:** Selinexor as an add-on to CFZ, POM, or DARA-based regimens, in patients actively progressing on these regimens, is well tolerated and safe. This trial demonstrates that selinexor can restore sensitivity to regimens to which MM patients are actively refractory. Future studies can evaluate these combinations in the setting of chimeric antigen receptor T-cell bridging or in the post-bi-specific T-cell engager setting. Clinical trial information: NCT04661137. Research Sponsor: Karyopharm Therapeutics.

Clinical activity of novel targeting of S100A9 with tasquinimod for relapsed and refractory multiple myeloma (RRMM).

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Background: S100A9, a protein produced by myeloid-derived suppressor cells in the bone marrow microenvironment, promotes multiple myeloma (MM) progression and confers therapeutic resistance. Tasquinimod (tasq), an oral S100A9 inhibitor, has pre-clinical anti-myeloma effects alone and combined with proteasome inhibitor (PI) and immunomodulator (Imid) therapy (Cancer Res Commun 2023;3(3):420) and improved progression-free survival in prostate cancer patients (pts) (JCO 2016;34(22):2636-43). We previously reported preliminary results of a phase 1 trial of tasq alone and in combination with ixazomib (ixa), lenalidomide (len), and dexamethasone (dex) (IRd) in pts with RRMM (JCO 2023;41(16)suppl:8042; NCT04405167). For single-agent tasq, the recommended phase 2 dose (RP2D) was 1 mg daily (qd) after a 1 week (wk) run-in at 0.5 mg qd. We now report updated results of tasq in combination with IRd. **Methods:** In dose escalation, pts were refractory, intolerant, or contra-indicated to len, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody. In dose expansion, pts were refractory to the most recent Imid/PI combination or triple-class refractory. Tasq was given in 28-day cycles at 1 mg daily with either a 2 wk run-in (dose level 1: 0.25 mg qd x1 wk then 0.5 mg qd x1 wk) or a 1 wk run-in (dose level 2: 0.5 mg qd x1 wk). In dose escalation, pts received full doses of ixa (4 mg days 1/8/15), len (25 mg days 1-21, adjusted for renal dysfunction), and dex (40 mg qwk), but in dose expansion, doses of ixa, len, and dex were reduced per investigator discretion. **Results:** 16 pts received tasq with IRd at dose levels 1 (3 pts) and 2 (13 pts: 3 in escalation, 10 in expansion). Median age was 67 y (range 52-81); 75% were male; 19% were African American and 81% Caucasian. Pts had received median 7 prior lines of therapy (range 3-19), and all were triple-class refractory, with 81% (13 pts) refractory to their most recent Imid/PI combination. In dose escalation, no dose limiting toxicities were observed, and dose level 2 was the RP2D of tasq with IRd. The most common treatment-emergent adverse events were fatigue (10 pts: grade [gr] 3 in 1 pt), pain (9 pts: 0 gr $\geq$3), respiratory infection (9 pts: 4 gr 3, 2 gr 5), nausea/vomiting (8 pts: 0 gr $\geq$3), dyspepsia/gastritis (5 pts: 1 gr 3), and thrombocytopenia (5 pts: 1 gr 3, 3 gr 4). Among all 16 pts, there was 1 partial response (PR) and 7 minimal responses (MR). Among the 13 pts who were previously refractory to their most recent Imid/PI combination and would therefore not be expected to respond to the IRd backbone, there was 1 PR (lasting 20 months) and 5 MRs (lasting 1, 1, 2, 2, and 7 months). **Conclusions:** Tasquinimod, an S100A9 inhibitor, is well tolerated in combination with IRd and has anti-myeloma activity, as evidenced by responses in patients previously refractory to Imid/PI combination therapy. Further study is warranted of tasquinimod in combination with standard myeloma therapies. Clinical trial information: NCT04405167. Research Sponsor: Leukemia and Lymphoma Society; 6609; Active Biotech, AB.

7557 Poster Session

ASCOmind: Is instant ASCO abstract analysis possible with AI agents?

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Background: The ASCO Annual Meeting receives thousands of abstracts annually on ongoing therapies. Extracting actionable insights from this large volume of data through manual review is time-consuming. To reduce manual workload and accelerate evidence synthesis, we implemented an AI-Agent system to assess the feasibility of deploying AI agents for efficient, large-scale data analysis and insight generation. **Methods:** GPT4o-based ASCOmind was designed with a robust framework of six autonomous and collaborative AI agents: Pre-processor, Categorizer, MetadataExtractor, Analyzer, Visualizer, and ProtocolMaker to systematically generate and visualize insights from ASCO abstracts. We demonstrate and evaluate ASCOmind by applying it to 2024 multiple myeloma (MM) studies. Using human reviewers as the gold standard, we assessed the quality and efficiency of the system focusing on outcome data accuracy, visualized charts, and workflow recipes documentations. **Results:** ASCOmind processed abstracts in the plasma cell dyscrasia section, categorizing 60 MM abstracts into 26 clinical trials and 34 as real-world studies. Manual abstraction of 51 predefined data elements required >60 mins/abstract, whereas ASCOmind completed the same task in <5min/article. The ASCOmind not only significantly reduced the processing time but also instantly analyzed and visualized the extracted data within 10 min. For instance, 27 included high-risk populations with cytogenetic abnormalities (n=20), extramedullary disease (n=7), or elderly patients (n=4). Across 51 interventional studies, 33 targeted relapsed/refractory MM (RRMM) and 18 focused on newly diagnosed MM (NDMM). ASCOmind generated a treatment distribution table for RRMM and NDMM (Table 1), with one misclassification corrected by humans-Mezigdomide reclassified from ADC to the correct category. Additionally, granular efficacy/safety outcome values and summarized study findings were also successfully extracted and visualized. **Conclusions:** Our preliminary analysis of ASCOmind demonstrated high accuracy and efficiency in automating abstract analysis, enabling rapid analysis of trends and outcomes. This feasibility study highlights the scalability of AI systems across all cancer types, supporting decision-making. Research Sponsor: None.

Treatment distribution in RRMM and NDMM studies.

Total (N=51)	Therapy Category	Examples	No. of Studies	%
RRMM (N=33)	BCMA-CAR-T Therapies	Cilta-cel, Ide-cel, ARI0002h	8	24.3%
	BCMA-Bispecific Ab Therapies	Teclistamab, Talquetamab, Elranatamab, Linvoseltamab, ABBV-383	16	48.5%
	ADC	Belantamab mafodotin, Elotuzumab,	5	15.2%
	Cereblon E3 Ligase Modulator	Mezigdomide, Iberdomide,	2	6.0%
	Others	OriCAR017, Venetoclax	2	6.0%
NDMM (N=18)	Triplet/Quadruplet SOC	VRd, Isa-VRd	8	44.5%
	Transplantation	ASCT, Tandem Transplantation	6	33.3%
	ADC	Belantamab mafodotin,	2	11.1%
	BCMA-Directed Therapies	Cilta-cel + Lenalidomide, Teclistamab	2	11.1%

Gene-expression-profiling plus integrated multidisciplinary approach to detect new-generation risk-adapted prognostic index in smoldering myeloma and multiple myeloma (GIMPI).

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Background: In our Institution, a prospective study to test the combination of gene-expression-profiling (SKY92 gene signature) and new generation imaging (PET/CT + Whole body MRI) was applied to all consecutive patients affected by smoldering (SMM), newly diagnosed (NDMM) and relapsed/refractory (RRMM) MM and evaluated its potential to predict or correlate with established HR markers of this disease and potentially defining new basis for a personalized treatment. **Methods:** Patients' bone marrow aspirate, plasma, imaging and clinical data were collected in our Institute under approved protocol and according to the Declaration of Helsinki guidelines. **Results:** In this study a cohort of 139 patients referring to our Institute was enrolled (SMM n=47, NDMM n=54 and RRMM n=38): here we present only the molecular part of the study, combination with imaging analysis is currently ongoing. Proportion of patients with SKY92 HR increased from SMM (8.4%) to NDMM (36.7%) and RRMM (53.3%, p=0.0162). Virtual FISH in NDMM patients showed 100% accuracy (95% CI) (100.0-100.0) for both t(4;14) and gain(1q) and of 90.0 (71.4-100.0) for del(17p), and this could be really useful for the daily clinical practice. The concentration of sBCMA was measured in our patients' cohort and in healthy subjects (n=12, control) with a statistically significant increase of sBCMA in the blood of NDMM and RRMM with respect to SMM (p=0.0009, p=0.0222) and control ($p<0.0001$, p=0.0010). Consistently with the literature, no statistically significant differences were observed among NDMM and RRMM. Thus, we hypothesize that SKY92 HR could capture patients with high levels of sBCMA. We compared the concentration of this disease biomarker among SR and HR including SMM, NDMM and RRMM patients and we observed increased levels of sBCMA in HR patients with respect to SR (p=0.0049). A risk-based intragroup comparison showed a similar trend in SMM and RRMM and, importantly, this result was confirmed in NDMM patients (p=0.0445). However, in this category of MM patients ISS could partially recapitulate differences in sBCMA among risk classes with the only statistically significant difference between Class I and III (p=0.0381). Therefore, we combined ISS with SKY92 and we observed that n=11 patients considered as LR by ISS (Class I), were relocated to the IR from this analysis with an overall improvement in the distribution of sBCMA levels according to risk categories (SR vs HR p=0.0011, IR vs HR p=0.0036). **Conclusion:** The results of this first pilot Italian study, that in the next future will be framed in a national network contest, strengthen the prognostic relevance of SKY92 based on its potential to (i) predict HR cytogenetic markers of disease; (ii) capture MM patients with high levels of sBCMA supporting the introduction of this GEP-based tool in the clinical diagnostic practice. Research Sponsor: None.

The impact of glucagon-like peptide-1 agonists on MGUS progression in patients with type 2 diabetes.

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Background: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition with limited interventions to reduce progression to multiple myeloma (MM). Glucagon-like peptide-1 (GLP-1) agonists, widely used for glycemic control and weight loss in type 2 diabetes mellitus (T2DM), have demonstrated cardiovascular, renal, and anti-cancer benefits, including reduced risks of obesity-associated cancers. This study assesses the association between GLP-1 agonists and MGUS progression in T2DM patients. **Methods:** We queried TriNetX – a Research Network - of 141 healthcare organizations from 30 countries between 2011 and 2024.MGUS patients with T2DM were divided into two cohorts: those on GLP-1 agonists and those not on GLP-1. Two sub-analyses were conducted: one in MGUS T2DM patients with a normal body mass index (BMI), and another in patients with BMI ≥25. Patients aged 18–80 years with monoclonal protein <3 g/dL, and GLP-1 use or other diabetic medications ≥2 years prior to MGUS diagnosis were included. Patients with prior diagnosis of MM, progression to MM within 1 year, kappa/lambda light chain >100 mg/dL, osteolytic lesions, creatinine >2 mg/dL, hemoglobin <10 g/dL, calcium >10.2 mg/dL, or prior treatment with bortezomib, lenalidomide, or daratumumab, were excluded. A 1:1 propensity score matching was performed to match the covariates (age, sex, race [white or African American], M protein, kappa/lambda ratio, and BMI). MM rates were compared at 2, 3, 5, 7, and 10 years. **Results:** The study included 5,901 MGUS patients with T2DM in the main analysis (22.45% on GLP-1 [n=1,325]; 77.55% not on GLP-1 [n=4,576]). The sub-analysis involved 818 normal-BMI patients (22.37% on GLP-1 [n=183]; 77.63% not on GLP-1 [n=635]). Matched cohorts (main analysis: n=1,319 each, sub-analysis n=181each) revealed significantly lower MM rates in GLP-1 users at 2- (1.21% vs 2.50, p=0.014), 3- (1.36% vs 2.50%, p=0.33), 5- (1.36% vs 2.57%, p=0.025), 7- (1.36% vs 2.57%, p=0.025) and 10-years (1.51% vs 2.65%, p=0.041). Similar findings were observed in the sub-analysis among patients with MGUS and T2DM with BMI ≥ 25 at 2- (1.08% vs 3.05%, p=0.001), 3- (1.18% vs 3.15%, p=0.002), 5- (1.08% vs 3.05%, p=0.001), 7- (1.18% vs 2.85%, p= 0.07, and 10-years (1.37% vs 3.05%, p=0.01). However, in the sub-analysis, normal-BMI GLP-1 users showed no difference in MM rates compared to non-users at 10-years (5.52% vs 5.52%, p=1.00). **Conclusions:** The use of GLP-1 agonists was significantly associated with reduced rates of MM among patients with T2DM and MGUS over a 10-year period, particularly in those with a body mass index ≥ 25. The lack of significant effects in normal-BMI patients suggests weight loss or related metabolic changes may mediate these protective effects. These results underscore GLP-1 agonists as a promising therapeutic strategy for managing MGUS in T2DM patients, especially those with elevated BMI. Research Sponsor: None.

Role of the combination of 3 T whole-body MRI and 18F-FDG PET/CT in the management of multiple myeloma and smoldering myeloma: The new era of imaging.

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Background: FDG-PET/TC and MRI are both imaging diagnostic tools adopted in diagnosis and/or response assessment in multiple myeloma (MM) which can be useful in smoldering, newly diagnosed as well in relapsed myeloma. **Methods:** From January 2021 to January 2025, we enrolled into a prospective trial 139 consecutive patients (54 Male; mean age, 67 years ± 10 [SD]) divided into 3 groups; 34 had a newly diagnosed MM according to the IMWG (group 1); 20 were in follow-up after autologous stem cell transplantation with clinical or laboratory data suspicious for relapse or progression (group 2) and 38 were affected by relapsed/refractory MM during treatment (group 3). In addition we enrolled 47 patients newly diagnosed high risk SMM, according to IMWG (19 Male, mean age 59 years+-10 [SD]). **Results:** On a per-patient basis, 126/139 (90%) had concordant PET/CT and WB-MRI scans, while 13/139 (10%) had discordant scans in terms of positivity/negativity. Among concordant studies, 47/139 (34%) were negative with both imaging methods while 93/139 (67%) were positive at both (including FLs and/or BMI). Among discordant studies, 8/9 had a positive WB-MRI scan and a negative PET-CT scan (6 cases with BMI or micronodular involvement alone), whereas 1/9 had a positive PET-CT and a negative WB-MRI. PET/CT detected FLs pattern in 83/139 patients, WB-MRI alone identified FLs pattern in 6 patients. PET-CT led to a change of treatment approach in 72/139 patients (52%), WB-MRI in 84/139 patients (60%), the combination of the two methods led to a change of management in 86/139 (62%), highlighted in the case of suspected post-transplant relapse. Furthermore, WB-MRI led to a change of management for incidental findings in additional 9 patients (8 suspected malignancies and 1 spinal cord compression). Interim analysis in HR-SMM showed discordance between the results of the two imaging modalities in 32/139 (23%). WB-MRI detected BMI pattern without any overt focal lesion in 11 patients (only 1 correlated with PET/CT) and FLs pattern in 7 patients (4 confirmed also in PET/CT), while PET/CT detected an additional FLs pattern in 1 patient, without bone lytic lesion evidence at the CT images. Both methods led to 6 changes of management, whereas MRI alone led to a change of treatment approach in 14 patients (10%), 13 diagnoses and 1 accessory finding of suspected cholangiocarcinoma. **Conclusions:** Our preliminary data underlines the fundamental role of functional imaging in the evaluation of FLs and BMI in MM with a superior detection rate of WB-MRI related to the ability to identify diffuse and micronodular pattern. A potential complementary role of the two methods in clinical management could be suggested in suspicion of relapsed or progressing MM. Furthermore our prospective trial supports the utmost role of WB-MRI (performed according to MY-RADS) in the assessment of high risk Smoldering Myeloma. Research Sponsor: None.

Real-world analysis of thromboembolism in SAVED/IMPEDE risk-stratified newly diagnosed multiple myeloma (NDMM).

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Background: The rate of thromboembolic (TE) events in NDMM patients (pts) treated with IMiD-containing regimens ranges from 11-19%, with venous events (VTE) being more common than arterial events (ATE). The SAVED and IMPEDE scores have been developed to risk-stratify thrombotic risk in NDMM. However, data on risk of VTE based on SAVED and IMPEDE VTE scores is largely unavailable for adequate contextual understanding of the problem. **Methods:** We queried the electronic medical record at Vanderbilt University Medical Center for pts with NDMM treated between January 2017 and May 2022, with a follow up for $\geq$ 2 years or until death. Information on incidence of TE, SAVED and IMPEDE scores at diagnosis, and the type of thromboprophylaxis (ppx) [any dose anticoagulation (AC) vs any dose aspirin (ASA) vs no ppx] present at induction therapy was analyzed. Pts were categorized as having elevated VTE risk if they had either SAVED $\geq$ 2 or IMPEDE $\geq$ 4 (patients with ATE were excluded). VTE rates were compared by χ^2 tests, and time to event was compared by Wilcoxon rank-sum test. **Results:** Among 178 pts with NDMM, the median (range) age was 65 (39-88) years. Upfront transplant was done in 76 (42.7%) of pts and IMiD containing therapy was used in 113 (63.5%) pts. The median (range) SAVED score was 1 (-2 to 7), and the median IMPEDE score was 2 (-3 to 12). Overall, 39 pts (21.9%) were diagnosed with TE [35 (19.7%) VTE, 4 (2.2%) with ATE]. Median (range) time to VTE was 7.7 months (mo) (0-42.3). Overall, 132 (74.1%) pts were on ASA, 26 (14.6%) were on AC, and 20 (11.2%) on no ppx. Among VTE pts, 25 (71.4%) were on ASA, 5 (14.3%) were on AC, and 5 (14.3%) on no ppx. Among VTE pts vs those without an event, a total of 20 (57.1%) vs 67 (48.2%) (p = 0.3) pts were categorized as having elevated risk, respectively. Among all pts with elevated VTE risk (n=84) vs not (n=90): VTE incidence was 23.8% (n=20) vs 16.7% (n=15) (p=0.24), and median (range) time to VTE was 5.5 (0-24.1) mos vs 9.1 (0-42.3) mos (p=0.12). Among those with elevated VTE risk, 18 (21.4%) received AC, 53 (63.1%) received ASA, and 13 (15.5%) were on no ppx. Among pts with elevated risk on AC versus ASA, VTE incidence was 11% (n=2) vs 26.9% (n=14) (p=0.3). Lastly, VTE rate was 19.1% (deep vein thrombosis (DVT) 12.2%, pulmonary embolism (PE) 6.9%), 19.2% (15.4% DVT, 3.8% PE), and 30% (10% DVT, 20% PE) among all pts on ASA, AC, and no ppx, respectively. **Conclusions:** Despite most patients harboring low predicted VTE risk at diagnosis by SAVED/IMPEDE, VTE rate was unacceptably high, and primarily occurred beyond 6 mos in our real-world NDMM cohort. Furthermore, VTE risk was not adequately mitigated in this ASA-ppx-enriched cohort. Though limited by small sample size, VTE events were numerically higher and had faster onset among patients with elevated SAVED/IMPEDE risk compared to those with low risk, while AC ppx in elevated-risk pts showed a trend towards reduced VTE incidence compared to ASA. Research Sponsor: None.

Teclistamab in relapsed/refractory systemic AL amyloidosis.

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Background: Systemic light chain amyloidosis (AL) is clonal plasma cell disorder characterized by the deposition of fibrils derived from immunoglobulin light chains. Treatment paradigms have been based on therapies for multiple myeloma. Teclistamab is a bispecific antibody approved for use in relapsed refractory multiple myeloma. We report on its impact in patients with AL. **Methods:** We analyzed data on hematologic and organ responses and treatment-related side effects in patients receiving Teclistamab for relapsed refractory AL. Mayo systems were used to characterize the disease stages. Adverse events were graded with the NCI CTCAE v5.0; CRS was graded according to ASTCT criteria. **Results:** Eight patients were identified (Table 1). All had relapsed refractory disease. Six had AL-λ and 2 AL-κ type. Five had cardiac involvement, 3 with stage III and 2 with stage II. Median prior lines of therapy was 4 (3-10). All were previously treated with Daratumumab and 5/8 had previously undergone autologous stem cell transplant. Median bone marrow plasmacytosis was 8.5% and median involved free light chain (iFLC) was 64.3mg/L (23.1 - 331). CD138-selected marrow findings included t(11;14), gain 1q and del 17p, each in 2 patients. Patients received escalating doses of Teclistamab. Two patients had grade 3 toxicities; one, a woman in her 80's, experienced a hepatic aminotransferase spike greater than 1000 the day after receiving the first 0.6mg/kg dose and subsequently after only that dose achieved an unmaintained CR that has continued for over 7 months; the other, a woman in her 70's, had grade 3 thrombocytopenia that has slowly resolved after Teclistamab was stopped. Two patients experienced grade 1 CRS. The hematologic response rate was 100% with 7 CR and 1 VGPR. The cardiac response rate was 29% (2/7; 1 CR, 1 PR) and the renal response rate was 20% (1/5). No patients have relapsed or died. **Conclusions:** In patients with relapsed refractory AL Teclistamab showed impressive hematologic activity and manageable side effects. A strong case exists for investigating Teclistamab prospectively in this population. Research Sponsor: None.

Baseline characteristics and response.

Patient	iFLC	Cytogenetics	BM Plasma cells	Cardiac stage	Renal stage	Organs involved	Prior lines of therapies	Best Hematological response	Organ response
1 (78M)	313 (λ)	gain 1q, trisomy 9, 15, 19, 21	3-5%	1	1	Tongue Soft Tissue	3	CR	Not Evaluable
2 (81F)	23.1 (λ)	t(11:14)	12.4%	3a	2	Heart Kidney	4	CR	No Response
3 (72F)	59.6 (λ)	Low risk	10%	2	1	GI Heart	7	CR	Cardiac Response
4 (78M	114 (κ)	Normal	3-5%	3a	2	Heart Kidney	10	CR	No Response
5 (68)	35.1 (λ)	Normal	30-40%	3a	2	Heart Kidney	3	VGPR	No Response
6 (65F)	69 (κ)	t(11:14), del(17p)	3-5%	3b	2	Peripheral Nervous System Heart Kidney	4	CR	No Response
7 (69M)	228 (λ)	Normal	7%	3a	1	Heart	4	CR	No Response
8 (69f)	42.4 (λ)	gain 1q, trisomy 9, del17p	10%	2	2	Heart Kidney	4	CR	Renal Response

TPS7563 Poster Session

QUINTESSENTIAL: A multicenter phase 2 study evaluating the efficacy and safety of arlocabtagene autoleucel (arlo-cel) in triple- and quad-class exposed patients with relapsed or refractory multiple myeloma (RRMM).

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Background: There are limited treatment options for patients (pts) with RRMM who are triple-class exposed (TCEx: immunomodulatory drugs [IMiD], anti-CD38 antibodies [aCD38], and proteasome inhibitors [PI]) and quad-class exposed (QCEx: IMiD, aCD38, PI, and B-cell maturation antigen [BCMA]-targeted therapy). To address this unmet need, new treatment options are needed for late-line populations, which will continue to grow with more QCEx pts due to the approval of BCMA-targeted therapies in earlier lines. G protein-coupled receptor class C group 5 member D (GPRC5D) is an orphan receptor expressed on plasma cells, with limited expression elsewhere, making it a promising therapeutic target for MM. Data from a phase 1 first-in-human study (NCT04674813) suggested that arlo-cel, a GPRC5D-directed autologous chimeric antigen receptor (CAR) T-cell therapy, is safe and efficacious in pts with TCEx RRMM, including pts who received prior BCMA-targeted therapy. At the recommended phase 2 dose (RP2D) of 150×10^6 CAR T cells, overall response rate (ORR) was 91% (21/23), median progression-free survival (PFS) was 18.3 months, and median overall survival (OS) was not reached in those with ≥3 prior lines of therapy (LOT) (Bal S et al. ASH 2024. Abstract 922). Here, we present the study design of QUINTESSENTIAL, an open-label, multicenter, phase 2 study (NCT06297226) evaluating arlo-cel in pts with TCEx and QCEx RRMM. **Methods:** For analyses, enrollment is planned at ~138 pts with ~125 pts receiving therapy. Key inclusion criteria include age ≥18 years, confirmed diagnosis of MM as per IMWG criteria, ≥3 classes of MM treatment (including IMiD, PI, and anti-CD38), and ≥3 prior LOT. Pts must also have documented disease progression (PD) during or after the most recent regimen as per IMWG, measurable disease, and an ECOG performance status of 0 or 1. Pts who previously received a GPRC5D-targeted therapy are excluded. After screening, pts will undergo leukapheresis followed by bridging therapy. Pts will then receive lymphodepleting chemotherapy followed by a single infusion of arlo-cel at the RP2D of 150×10^6 CAR T cells (range: $120–180 \times 10^6$). The primary endpoint is ORR by IMWG response criteria per an independent review committee in pts who are QCEx and received ≥4 prior LOT. Key secondary endpoints are ORR and complete response rate in all pts. Other secondary and exploratory endpoints include time to response, duration of response, PFS, OS, minimal residual disease-negative status, and safety. Pts will be followed for ≤5 years after the last pt receives arlo-cel, with a subsequent long-term follow-up study continuing for ≤15 years. This study will recruit at 47 centers across the USA, Canada, and Japan. The first pt first visit was achieved on March 21, 2024. Clinical trial information: NCT06297226. Research Sponsor: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

TPS7564 Poster Session

QUINTESSENTIAL-2: A phase 3 study comparing efficacy and safety of arlocabtagene autoleucel (arlo-cel) versus standard regimens in adult patients with relapsed or refractory multiple myeloma (RRMM) refractory to lenalidomide.

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Background: Despite advances in MM treatment, nearly all patients (pts) will relapse, highlighting the need for new drug classes to improve outcomes in RRMM. Further, MM refractory to lenalidomide, an immunomodulatory drug (IMiD) used in frontline and maintenance therapies, poses an additional challenge as the disease is less likely to respond to subsequent treatment. G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising therapeutic target for MM as the receptor is highly expressed on malignant plasma cells; it has little to no expression on non-plasma immune cells and limited expression elsewhere. Arlo-cel is a GPRC5D-directed autologous CAR T-cell therapy that has demonstrated safety and efficacy in patients with RRMM in a first-in-human ph1 study. Following a single infusion of arlo-cel at the recommended ph2 dose (RP2D) of 150×10^6 CAR T cells, overall response rate (ORR) was 96% (23/24) and 91% (21/23) in those with 1-3 and ≥3 prior lines of therapy (pLOT), respectively (Bal S, et al. ASH 2024. Abstracts 2069 and 922). Here we present the design of the QUINTESSENTIAL-2 study. **Methods:** QUINTESSENTIAL-2 (NCT06615479) is a randomized, open-label, multicenter, ph3 confirmatory study comparing the efficacy and safety of arlo-cel versus standard of care (SOC) in adults with RRMM. Pts aged ≥18 y must have received 1-3 pLOT (may include a proteasome inhibitor, IMiD, and anti-CD38 monoclonal antibody) and be refractory to lenalidomide (progression on or within 60 days of completing therapy). Additional inclusion criteria include confirmed MM diagnosis per International Myeloma Working Group criteria, measurable disease during screening, and Eastern Cooperative Oncology Group performance status 0 or 1. Eligible pts will be randomized 1:1 to one of 2 treatment arms. Arm A: single infusion of arlo-cel (RP2D of 150×10^6 CAR T cells), including leukapheresis within 3 days of randomization, bridging therapy of DPd (daratumumab, pomalidomide, dexamethasone) or Kd (carfilzomib, dexamethasone) per Investigator within 3 days of leukapheresis, and lymphodepleting chemotherapy prior to arlo-cel infusion. Arm B: SOC of DPd or Kd per Investigator, dosed per labeling. Primary endpoints are progression-free survival and minimal residual disease (MRD) negativity in complete response. Secondary endpoints include overall survival, ORR, MRD negative status, complete response rate, time to response, duration of response, pharmacokinetics, patient-reported quality of life outcomes, and safety. Pts will be followed for ≤5 years after the last patient is randomized, with a subsequent long-term follow-up study (≤15 years post infusion) for pts receiving arlo-cel. The trial is expected to enroll 440 pts across 111 sites globally, with first patient enrollment planned for Feb 2025. Clinical trial information: NCT06615479. Research Sponsor: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

TPS7565 Poster Session

Prophylactic interventions for oral toxicities with the GPRC5D×CD3 bispecific antibody talquetamab in relapsed/refractory multiple myeloma: An update on the open-label, phase 2, randomized TALISMAN study.

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Background: Talquetamab (Tal) is the first GPRC5D×CD3 bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM). Early onset oral toxicities, including dysgeusia, have been reported with Tal and can impact patient (pt) quality of life. Current CTCAE grading limits detailed assessment of dysgeusia. We provide an update on the TALISMAN study (NCT06500884), which investigates prophylactic interventions for GPRC5D-related oral toxicities using objective and subjective assessment tools that may establish a standard to measure taste changes and mitigation strategies in future studies with MM pts. **Methods:** This phase 2, multicenter, open-label, randomized study is enrolling pts aged ≥18 years with RRMM and prior exposure to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody; prior anti-GPRC5D therapy is not permitted. Pts must have an ECOG PS of 0/1 (ECOG PS of 2/3 permitted once physical limitations are stable) and cannot have a "severe" score for dysgeusia per the Waterless Empirical Taste Test (WETT) scale. Pts are randomized to 1 of 4 cohorts: 1 control cohort (Tal only) and 3 experimental cohorts (Tal plus an experimental prophylaxis). The experimental prophylaxes are dexamethasone mouthwash (0.5 mg/5 mL twice daily [BID]), oral pregabalin (50 mg BID), or clonazepam orally dissolving tablets (0.25 mg BID). Pts take their prophylaxis 7 days before the first step-up dose (cycle 1 day 1) of Tal (3 step-up doses followed by 0.8 mg/kg every other week). A dose reduction to every 4 weeks is permitted if a ≥VGPR or ≥PR is achieved at cycle 5 or 7, respectively. Study assessments and procedures include taste assessment using WETT strips; smell assessment using the University of Pennsylvania Smell Identification Test and threshold testing; pt-reported outcomes (PROs, including PRO-CTCAE); optional tongue and/or salivary gland biopsies (at selected sites); microbiome analysis via tongue swab (control cohort only); and salivary flow and salivary-specific protein content assessments. The 4 co-primary endpoints are the rate of occurrence of dysgeusia, rate of occurrence of severe dysgeusia, time to first onset of severe dysgeusia, and rate of resolution/improvement of dysgeusia at 3 and 6 months, as defined by the WETT score. Key secondary endpoints include changes from baseline in WETT score, body weight, and smell identification and smell detection threshold test scores over time; characterization of the safety and efficacy of Tal; change from baseline in PRO (including impacts of oral toxicities) assessments; and frequency of dose modifications. Enrollment opened in August 2024 for these 4 cohorts and target enrollment is 70–130 pts across 6 countries, with the potential to open additional cohorts. Clinical trial information: NCT06500884. Research Sponsor: None.

TPS7566 Poster Session

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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Background: Elranatamab (ELRA), a BCMA–CD3 bispecific antibody, induced deep and durable responses with a manageable safety profile as a single agent in patients (pts) with RRMM enrolled in the phase 2 registrational MagnetisMM-3 study (Lesokhin et al, *Nat Med* 2023). Iberdomide (IBER) is a novel CELMoD agent that enhances 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 (NCT06215118) 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 guided by BOIN for dose-escalation and Part 2, randomized for dose optimization. In Part 1, after 2 step-up priming doses of subcutaneous (SC) ELRA followed by 1 full dose, pts will receive SC ELRA at dose level (DL) 1 or DL2 in 28-day cycles. IBER will be given daily for 21 days of each cycle. In DL1, pts will receive ELRA weekly followed by every 2 weeks (Q2W) and finally Q4W. In DL2, pts will receive ELRA Q2W followed by Q4W, with a higher IBER dose. If DL1 or DL2 is not tolerated, IBER dosing will be lowered (DL-1 and DL-2). Once 2 combination dose levels are selected from Part 1 as the recommended doses for expansion 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 or 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). Primary endpoints are dose-limiting toxicities during the first cycle of treatment (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. This study is ongoing; Part 1 and Part 2 will enroll up to approximately 36 and 60 pts, respectively. Clinical trial information: NCT06215118. Research Sponsor: Pfizer.

TPS7567 Poster Session

Design of the phase 3 DREAMM-10 study: Belantamab mafodotin plus lenalidomide and dexamethasone (BRd) vs daratumumab plus lenalidomide and dexamethasone (DRd) in transplant-ineligible, newly diagnosed multiple myeloma (TI-NDMM).

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Background: Treatment options have advanced for patients (pts) with TI-NDMM, but outcomes remain worse compared to pts with transplant-eligible NDMM, indicating a need for novel therapies to improve the prognosis of TI-NDMM. Belantamab mafodotin is an antibody-drug conjugate targeting B-cell maturation antigen. Phase 3 studies have shown significant survival benefits with belantamab mafodotin in combination regimens vs standard of care combinations for relapsed/refractory MM [1–3], and preliminary data have shown promising clinical activity with belantamab mafodotin combination regimens, including BRd, for TI-NDMM [4,5]. The design of the DREAMM-10 study, investigating BRd vs DRd in pts with TI-NDMM, is presented here. **Methods:** DREAMM-10 (NCT06679101) is a randomized, phase 3, open-label, multicenter study. Pts aged ≥18 years with TI-NDMM, measurable disease, and Eastern Cooperative Oncology Group performance status 0–2 are eligible. Specific reasons for transplant ineligibility will be collected. Pts who were previously treated for MM or smoldering MM are excluded. Approximately 520 eligible pts will be randomized 1:1 to BRd or DRd, stratified by age (<75, ≥75 years), International Staging System (I, II, III), and region (North America, rest of world). Belantamab mafodotin will be administered intravenously at 1.9 mg/kg every 8 weeks for 24 weeks, then 1.9 mg/kg every 12 weeks thereafter. Daratumumab will be administered subcutaneously using the approved dose and schedule. In both treatment arms, lenalidomide will be administered orally at 25 mg on Days 1–21, and dexamethasone will be administered orally at 40 mg on Days 1, 8, 15, and 22 of every 28-day cycle. Pts will be treated until disease progression, death, unacceptable toxicity, consent withdrawal, or end of study. The dual primary endpoints are progression-free survival (PFS) and minimal residual disease negativity rate. Key secondary endpoints are overall survival and PFS2 (time from randomization to progression on first subsequent anti-myeloma therapy or death). The statistical plan includes multiplicity adjustment for primary endpoints and hierarchical testing for key secondary endpoints. Other efficacy endpoints, safety (adverse events [AEs]/serious AEs), and health-related quality of life will also be assessed. The study opened for enrollment on December 30, 2024. 1. Hungria V, et al. *N Engl J Med* 2024. 2. Dimopoulos MA, et al. *N Engl J Med* 2024. 3. https://us.gsk.com/media/11819/belamaf-dreamm-7-os-full-data-press-release_final_us-version-08dec24.pdf. 4. Terpos E, et al. *Haematologica* 2024. 5. Usmani SZ, et al. *Blood* 2024;144(Suppl 1):497. Clinical trial information: NCT06679101. Research Sponsor: GSK (214828); drug linker technology licensed from Seagen; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

TPS7568 **Poster Session**

MagnetisMM-32: A phase 3 randomized study of elranatamab vs EPd, PVd, or Kd in patients with relapsed or refractory multiple myeloma (RRMM) and prior anti-CD38–directed therapy.

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Background: Elranatamab (ELRA), a BCMA-CD3 bispecific antibody, has shown efficacy and manageable safety as a monotherapy in patients with RRMM. This study will evaluate ELRA monotherapy vs elotuzumab-pomalidomide-dexamethasone (EPd), pomalidomide-bortezomib-dexamethasone (PVd), or carfilzomib-dexamethasone (Kd) in patients with RRMM to determine whether ELRA can provide superior clinical benefit in early relapse (2L+). **Methods:** MagnetisMM-32 (NCT06152575), a phase 3, open-label, multicenter, randomized study, will enroll ≈492 patients. Patients will receive ELRA (Arm A) or investigator's choice of EPd, PVd or Kd (Arm B), until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, or study termination. Patients treated with ELRA will receive 2 step-up priming doses followed by weekly doses and subsequently less frequent doses in 28-day cycles. Patients will be randomized 1:1 (stratified by prior line of therapy [1 vs 2 vs 3/4] and International Staging System disease stage [1/2 vs 3]). Key inclusion criteria include age of ≥18 years, prior multiple myeloma diagnosis with measurable disease (per IMWG criteria), evidence of progressive disease or failure to achieve a response to last line of multiple myeloma therapy, 1 to 4 prior lines of therapy including an anti–CD38 antibody–containing regimen (for ≥2 consecutive cycles) and a lenalidomide-containing regimen (for ≥2 consecutive cycles), adequate bone marrow function, and an ECOG performance status of ≤2. Key exclusion criteria include stem cell transplant ≤12 weeks prior to enrollment or active graft vs host disease; active, uncontrolled infection; any other active malignancy <3 yrs prior to enrollment; ongoing grade ≥3 peripheral sensory or motor neuropathy; history of any grade ≥3 peripheral motor polyneuropathy, prior BCMA-directed or CD3-redirecting therapy; never achieved ≥PR with any treatment during disease course; and unable to receive any of the Arm B regimens (EPd, PVd, or Kd). The primary and key secondary endpoints are progression-free survival (PFS) by blinded independent central review (BICR) per IMWG criteria and overall survival (OS), respectively. Other secondary endpoints include PFS and PFS2 (PFS on next line of therapy) by investigator per IMWG, objective response rate, duration of response, very good partial response rate, complete response rate, duration of complete response, and time to response (all by BICR per IMWG), MRD negativity rate (including sustained for ≥12 months) and duration, safety and pharmacokinetics of ELRA, immunogenicity, and health-related quality of life outcomes. The primary endpoint and OS will be compared statistically between treatment arms by stratified log-rank tests. Study funding: Pfizer. Clinical trial information: NCT06152575. Research Sponsor: Pfizer.