

Safety and efficacy of elranatamab as early intervention in patients with high-risk smoldering myeloma: First results from the phase 2 ERASMM (EMN34) study.

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Background: Early intervention with lenalidomide or daratumumab significantly delays disease progression to active disease in high-risk (HR) smoldering multiple myeloma (SMM) patients (pts). The BCMAxCD3 bispecific antibody elranatamab (Elra) demonstrated strong anti-MM activity with favorable safety profile in relapsed MM. Using T-cell engagers in the early stage of the disease, with a potentially less exhausted immune system, may lead to improved efficacy. Here we report initial efficacy and safety results of Elra monotherapy in HR SMM pts enrolled in the phase 2 ERASMM Study (EMN34; NCT06183489). **Methods:** ERASMM is an international open-label multicenter phase 2 study of Elra as single agent in adult pts with HR SMM, defined as the presence of ≥ 2 Mayo 2018 "20-2-20" criteria. Treatment consisted of a fixed duration (2 years) of single-agent SC Elra with priming doses of 12 mg (C1D1) and 32 mg (C1D4), followed by 76 mg on days 8 and 15 during cycle 1, 1 and 15 during cycles 2-3, and 1 during cycles 4-24 (28-day cycle). The primary objective was the rate of complete response (CR). Safety was a key secondary endpoint. Other secondary objectives included overall response rate (ORR), measurable residual disease (MRD), progression-free survival (PFS), PFS2, time to active MM, and overall survival (OS). **Results:** Fifty pts with previously untreated HR SMM were included from May 2024 to September 2025 in 17 centers collaborating with the European Myeloma Network. Median age was 65 years (range 58-71). All pts had HR SMM, including M-spike >20 g/L in 42 (84%), bone marrow plasma cells $>20\%$ in 36 (72%), or free-light chain ratio >20 in 33 (66%). As of December 4, 2025, the median follow-up was 10 months (range 2.3-18.23). Thirty-four (68%) patients experienced a cytokine release syndrome event, all grade 1-2, except for grade 3 events in 2 pts. No ICANS events were observed. Infections occurred in 25 (50%) pts, including 14% grade 3-4. Other common ($\geq 20\%$) non-hematologic adverse events (AEs) were skin rash (34%), diarrhea (26%), AST/ALT increase (28%), fatigue (20%), and peripheral neuropathy (20%), mostly grade 1-2. Four patients discontinued treatment due to AEs, including AST/ALT increase (n=1), Guillain-Barré syndrome (n=1), and infections (n=2). The ORR was 92%, including a very good partial response or better ($\geq$ VGPR) in 82% of pts, and a complete response or better ($\geq$ CR) in 45%. The 9-month PFS and OS rates were 95% and 100%, respectively. **Conclusions:** In HR SMM pts, single-agent Elra was highly active, with a 92% ORR, 45% of pts achieving $\geq$ CR, and a favorable safety profile. Data on safety and efficacy (response, MRD, PFS) will be updated for the meeting. These data support further investigation of Elra as a therapeutic option for HR SMM. Clinical trial information: NCT06183489. Research Sponsor: Pfizer.

Phase 3 randomized trial to evaluate the impact of anselamimab on all-cause mortality in κ light-chain amyloidosis.

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Background: AL amyloidosis is a plasma cell dyscrasia (PCD) characterized by κ or λ Ig light chain amyloid fibrils that deposit in vital organs. Anselamimab is an investigational mAb designed to complement anti-PCD therapy through accelerated removal of amyloid fibrils. Cardiac Amyloid Reaching for Extended Survival (CARES) studies (NCT04512235 and NCT04504825) investigated the efficacy and safety of anselamimab compared with placebo, in addition to anti-PCD therapy. **Methods:** Alongside anti-PCD therapy with CyBorD (daratumumab was permitted) newly diagnosed patients with European modification of Mayo stage IIIa or IIIb AL amyloidosis were randomized 2:1 to receive anselamimab (1000 mg/m²) or placebo (normal saline) IV every 7 days for 4 weeks followed by every 14 days for the remainder of the blinded study (18 months after the last participant enrolled). The primary endpoint was a hierarchical combination of time to all-cause mortality (ACM) and frequency of adjudicated cardiovascular hospitalizations (CVH) using the Finkelstein-Schoenfeld test and win-ratio in the combined study population. Subgroup analysis by involved κ or λ free light chain (iFLC) was prespecified. **Results:** 271 patients were randomized to receive anselamimab and 135 placebo. Baseline characteristics were similar between treatment arms. The median duration of treatment was 21.4 months and 21.1 in the anselamimab and placebo arms, respectively. Daratumumab was used in 79.3% and 83.7% of the anselamimab and placebo arms, respectively. Results of the primary efficacy analyses are shown in the table. Anselamimab-treated patients with κ iFLC had a 62% reduction in ACM (HR = 0.38; 95% CI, 0.17, 0.86; nominal P = 0.012) and a 71% reduction in risk for CVH (estimated CVH rate ratio = 0.29; 95% CI, 0.10, 0.87; nominal P = 0.028). Patients with λ iFLC had a 10% reduction in risk for CVH; none in ACM. Safety data were comparable between both treatment arms. In anselamimab-treated patients, safety findings were similar between κ subgroup and full population. **Conclusions:** Anselamimab, a κ light chain-directed anti-fibril monoclonal antibody used alongside standard of care chemotherapy, offers a first-in-class, new therapeutic option for patients with newly diagnosed κ AL amyloidosis. Clinical trial information: NCT04512235 and NCT04504825. Research Sponsor: Alexion, AstraZeneca Rare Disease.

Summary of primary efficacy endpoints.

Endpoint	Overall			κ Isotype			λ Isotype		
	Anselamimab (N=271)	Placebo (N=135)	P-value	Anselamimab (N=481)	Placebo (N=24)	P-value	Anselamimab (N=219)	Placebo (N=109)	P-value
ACM and CVH win ratio (95% CI)	1.1 (0.8, 1.5)		0.332	2.06 (0.98, 4.31)		0.100	0.9 (0.6, 1.3)		0.848
ACM									
n (%)	90 (33.2)	52 (38.5)		15 (31.3)	14 (58.3)		73 (33.3)	37 (33.9)	
HR (95% CI)	0.8 (0.6, 1.1)		0.290	0.38 (0.2, 0.9)		0.012	1.0 (0.7, 1.5)		0.647
CVH									
Frequency/year (95% CI)	0.6 (0.4, 0.8)	0.9 (0.6, 1.4)	0.145	0.41 (0.2, 0.8)	1.4 (0.6, 3.4)	0.028	0.7 (0.4, 1.0)	0.8 (0.4, 1.3)	0.664
Incidence risk ratio (95% CI)	0.7 (0.4, 1.2)			0.29 (0.1, 0.9)			0.9 (0.5, 1.7)		

First results from the phase 1/2 LINKER-AL2 trial of linvoseltamab (LINVO) in patients (pts) with relapsed or refractory (RR) systemic light chain (AL) amyloidosis.

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Background: Systemic AL amyloidosis is caused by deposition of misfolded amyloid fibrils produced by clonal plasma cells in vital organs. With no currently approved therapies, there is a need for new targeted agents eliciting rapid normalization of involved free light chain (iFLC), which is linked to improved organ function recovery and overall survival. Here are the first results of LINVO (human BCMA×CD3 bispecific antibody) in RR systemic AL amyloidosis from the Phase 1 portion of the Phase 1/2 LINKER-AL2 trial (NCT06292780). **Methods:** Eligible adults with RR systemic AL amyloidosis and ≥ 1 prior therapy received intravenous step-up doses of LINVO 5 mg and 25 mg (Cycle [C] 0 Days 1 and 8, respectively) followed by 28-day cycles of full subcutaneous (SC) doses of 80 mg or 240 mg administered once weekly in C1–C2 and then once every 4 weeks in C3–C12. The Phase 1 primary endpoint was incidence of dose-limiting toxicities (DLTs) within 28 days after the first full dose. Key secondary endpoints were rates of hematologic complete response (hCR; by FLC ratio and absence of AL), very good partial response or better ($\geq$ hVGPR), objective response (hOR), time to hCR, and safety. **Results:** As of data cut-off (DCO) August 25, 2025, 20 pts (median age, 64 years; prior daratumumab therapy, 60.0%) received LINVO 80 mg (n=7) or 240 mg (n=13), with a median follow-up of 9.6 (range 1.1–25.0) weeks. No DLTs or ICANS occurred. All pts had ≥ 1 treatment-emergent adverse event (TEAE; Grade (Gr) ≥ 3 , 55.0%). One pt with prior cardiac disorder discontinued (Gr 5 ventricular fibrillation, unrelated to LINVO). Most common TEAEs were CRS (50.0%; Gr 1, 35.0%; Gr 2, 15.0%) and infusion-related reactions (45.0%; Gr 1, 25.0%; Gr 2, 20.0%), most during step-up dosing. LINVO elicited rapid responses (Table): hOR rates were 100% (80 mg: $\geq$ hCR, 57.1%) and 92.3% (240 mg: $\geq$ hCR, 38.5%), which are expected to deepen with longer follow-up. Most pts reached iFLC < 20 mg/L (80 mg: 100%; 240 mg: 84.6%). **Conclusions:** LINVO demonstrated generally manageable safety and rapid, meaningful clinical activity, with most pts achieving hOR and iFLC < 20 mg/L. These results support continued evaluation of LINVO in RR systemic AL amyloidosis. Longer follow-up data, including organ responses, are being evaluated. Clinical trial information: NCT06292780. Research Sponsor: Regeneron Pharmaceuticals Inc.

Investigator-assessed hematologic responses (ISA criteria).

Response, n (%) [*]	LINVO 80 mg (n=7)	LINVO 240 mg (n=13) [†]
Median follow-up, weeks (range)	12.1 (6.9–25.0)	6.7 (1.1–15.3)
hOR	7 (100)	12 (92.3)
hCR	4 (57.1)	5 (38.5)
$\geq$ hVGPR	7 (100)	12 (92.3)
Low dFLC [‡]	0	1 (7.7)
dFLC < 10 mg/L	7 (100)	11 (84.6)
iFLC < 20 mg/L	7 (100)	11 (84.6)
Median time to hCR, weeks (range)	3.2 (2.1–18.3)	3.1 (1.0–7.1)

^{*}Unless stated otherwise.

[†]Not evaluable, n=1.

[‡]If baseline dFLC ≥ 20 mg/L and < 50 mg/L, response other than hCR reached with dFLC < 10 mg/L. dFLC, difference between iFLC and uninvolved FLC; ISA, International Society of Amyloidosis.

DREAMM-9 final analysis: Belantamab mafodotin (belamaf), bortezomib, lenalidomide, and dexamethasone (BVRd) for transplant-ineligible (TI) newly diagnosed multiple myeloma (NDMM).

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Background: DREAMM-9 (NCT04091126) was a phase 1 dose and schedule evaluation study of BVRd in adults with TI NDMM. **Methods:** Patients (pts) received BVRd in 1 of 8 belamaf dosing cohorts at an induction/maintenance schedule of Q3/4W (SHORT: 1.9, 1.4, 1.0 mg/kg), Q6/8W (STRETCH: 1.9, 1.4 mg/kg), Q9/12W (step-down [S/D]: 1.9 for 1 dose then 1.4 mg/kg; 1.4 for 1 dose then 1.0 mg/kg), or Q12W (1.0 mg/kg). The primary endpoint was safety. Responses, minimal residual disease negativity (MRD[-]) in complete response or better (CR+), and pt-reported outcomes (PROs) were assessed. Median dose intensities (mDIs) were calculated as mg/kg/21 days in induction and mg/kg/28 days in maintenance. **Results:** As of June 2, 2025, 118 pts were enrolled (intention-to-treat population). Median duration of follow-up was 15.9–47.1 months. Induction mDI generally decreased as planned dosing intervals increased and was lowest in S/D Q9/12W or Q12W cohorts. Maintenance mDI was similar across cohorts due to dose modifications. Overall response rates were $\geq 83\%$ across cohorts. Cohorts with higher induction mDI had the deepest responses (CR+/MRD[-] 75/55% for pooled SHORT+STRETCH and 59/43% for pooled Q9/12W+Q12W). Grade (Gr) ≥ 2 ophthalmic exam findings (OEFs; best-corrected visual acuity changes/slit lamp findings [Keratopathy and Visual Acuity scale]) were 90% for pooled SHORT+STRETCH/69% for pooled Q9/12W+Q12W, while Gr 3/4 OEF rates were higher with higher induction mDI (79%/35%). Most cohorts (5/8) had no belamaf discontinuations due to Gr ≥ 3 OEFs, which occurred only in SHORT cohorts (n = 1 each). First Gr ≥ 2 OEFs resolved prior to end of treatment in 83–100% across cohorts. The long-interval group (Q9/12W and Q12W dosing schedules) remained largely below the vision-related function (VRF) deterioration threshold (12.5 points per Ocular Surface Disease Index) across most timepoints, suggesting a favorable VRF profile vs the SHORT interval group. **Conclusions:** BVRd had high response rates across all cohorts ($\geq 83\%$), highlighting the promising efficacy of the regimen. Regimens with higher belamaf induction mDI had the deepest responses, while those with lower induction mDI had milder OEFs. Belamaf dosing with a higher induction DI is optimal to achieve deeper responses, and a lower maintenance DI (i.e., using longer schedules) improves tolerability, PROs, and maintains responses. Clinical trial information: NCT04091126. Research Sponsor: GSK.

Impact of sustained MRD negativity for up to 5 years on long-term outcome of transplant-eligible newly diagnosed multiple myeloma patients enrolled in the randomized phase 2 FORTE trial.

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Background: Novel combinations induce high rates of minimal residual disease (MRD) negativity (neg) in multiple myeloma (MM) patients (pts). However, the optimal duration of MRD negative status to predict long term outcomes remains a matter of debate. We analyzed the impact of different sustained (sust) MRD neg cut-offs on progression free survival (PFS) and overall survival (OS) in transplant eligible Newly Diagnosed MM pts treated in the randomized phase 2 FORTE trial (NCT02203643). **Methods:** We included all pts enrolled in the trial who were randomized to maintenance. MRD was assessed in the bone marrow in pts with $\geq$ very good partial response by multiparameter flow cytometry (sensitivity of 10^{-5}) at premaintenance and every 6 months thereafter. SustMRD neg was defined as consecutive MRD-negative evaluations for at least 1, 2, 3, 4 or 5 years without intercurrent MRD-positive results. The primary aim of the analysis was the impact of different SustMRD neg durations on PFS. A subgroup analysis according to a modified Consensus Genomic Staging (mCGS as described in Avet-Loiseau et al JCO 2025 without the use of molecular data), and the presence of an MGUS-like profile at diagnosis (Burgos et al JCO 2023) was performed. **Results:** 356 pts were randomized to maintenance according to study protocol. After a median follow-up of 85 months from maintenance randomization, 77% of pts have > 1 MRD negative evaluation. The rate of at least 1, 2, 3, 4, 5-years sustMRD neg was 53%, 42%, 36%, 28% and 20% respectively. Compared to MRD positive patients (n=83), MRD neg lasting < 1 year (HR 0.72; 95% CI 0.47-1.09), 1 year (HR 0.40; 95% CI 0.22-0.72), 2 years (HR 0.36; 95% CI 0.19-0.66), 3 years (HR 0.17; 95% CI 0.07-0.40), 4 years (HR 0.15; 95% CI 0.06-0.35) and 5 years (HR 0.06; 95% CI 0.03-0.15) significantly and progressively improved pts' PFS. In pts with ≥ 3 -years sustMRD neg vs < 3 -year sustMRD, 7-years PFS rates were 84.7% vs 35.4% (HR 0.16, 95% CI 0.10-0.27) and 7-years OS rates were 97% vs 69% (HR 0.08, 95% CI 0.02-0.27). Stratifying patients according to mCGS and 3-years sustMRD neg, 7-years PFS rates were 84% for mCGS standard risk with ≥ 3 -y sustMRD, 83% for mCGS high risk and ≥ 3 -y sustMRD, 43% for mCGS standard risk with < 3 -y sustMRD, 23% for mCGS high risk with < 3 -y sustMRD. Among patients with < 3 -years sustMRD neg, the presence of an MGUS-like profile predicted a significantly better PFS and OS compared to non MGUS-like pts (7-years PFS 67% vs 33%, HR 0.37 95% CI 0.17-0.85; 7-years OS 93% vs 66%, HR 0.15 95% CI 0.02-1.08). **Conclusions:** SustMRD neg for more than 3 years significantly improved PFS and OS of NDMM pts, with pts with at least 5-year SustMRD neg having a 7-year PFS of 91%. Reaching > 3 -y sustMRD neg is mandatory in high-risk pts to achieve long term remissions, while MGUS-like pts may have good outcomes despite the absence of 3-y sustMRD neg. Clinical trial information: NCT02203643. Research Sponsor: Amgen; Celgene/Bristol Myers Squibb.

New IMS/IMWG risk criteria by next-generation sequencing (NGS): Analysis of daratumumab benefit in both high- and standard-risk patients (pts) in the PERSEUS study.

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Background: IMS/IMWG recently proposed novel Consensus Genomic Staging (CGS) high-risk criteria for newly diagnosed multiple myeloma (NDMM), including genetic alterations not identifiable by fluorescence in situ hybridization (FISH) but by NGS (eg, *TP53* mutations). PERSEUS/EMN017 (NCT03710603) evaluated the addition of daratumumab to VRd induction/consolidation and to R maintenance (DVRd arm) vs VRd+R (VRd arm) in transplant-eligible (TE) pts. PERSEUS previously reported that DVRd significantly improved progression-free survival (PFS) regardless of cytogenetic risk as defined by previous criteria. **Methods:** 709 pts with NDMM were randomized 1:1 to DVRd vs VRd. Unique molecular assay (UMA)-NGS target panel was used on DNA extracted from CD138+ bone marrow (BM) cells. Of 664 pts from whom BM was collected, 434 patient DNA samples were available for NGS testing. Per the new IMS/IMWG CGS criteria, high risk was defined post-hoc by the presence of del17p/*TP53* mutations; t(4;14) or t(14;16) or t(14;20) with additional amp1q or del1p; amp1q and del1p; biallelic del1p; and high $\beta 2$ microglobulin with normal renal function. Classic FISH high risk was defined per-protocol by the presence of del17p, t(14;16), and/or t(4;14). Minimal residual disease negativity (MRD neg) was assessed by NGS (Adaptive) in pts with complete response or better. **Results:** Of 434 pts evaluated, 152 (35%) were high risk by CGS. The most common genetic lesions were del17p/*TP53* (n=59, 14%), IgH translocation with amp1q/del1p (12%), and del1p with amp1q (9%); 2% had biallelic focal del1p. Using CGS criteria, 17% of pts were reclassified from standard risk to high risk; additionally, 4% of pts previously classified as high risk were reclassified as standard risk. DVRd was associated with increased MRD neg rates at 10^{-6} compared to VRd in both CGS standard-risk (67% vs 39%, $P=0.0001$) and high-risk pts (56% vs 26%, $P=0.0003$). Sustained MRD neg (10^{-6}) rates for ≥ 12 months (+/-1 mo) were higher with DVRd vs VRd for both CGS standard-risk (57% vs 24%; $P<0.0001$) and high-risk pts (41% vs 19%; $P<0.0001$), and pts who achieved sustained MRD negativity (10^{-6}) had superior PFS outcomes versus those who did not, regardless of CGS risk status ($P<0.0001$). DVRd led to improved PFS in both CGS standard-risk (HR 0.38, 95% CI 0.20–0.73; $P=0.001$) and high-risk pts (HR 0.54, 95% CI 0.31–0.95; $P=0.039$), adjusting for ISS, lactate dehydrogenase, and age (>65 years). **Conclusions:** DVRd improved MRD negativity and PFS over VRd in both the new IMS/IMWG CGS high-risk and standard-risk subgroups. UMA-NGS panel successfully stratified risk according to CGS criteria, identifying nearly twice as many high-risk pts in the PERSEUS study. These data further support DVRd induction/consolidation and DR maintenance as standard of care for TE-NDMM, regardless of cytogenetic risk. Clinical trial information: NCT03710603. Research Sponsor: Johnson & Johnson.

Mezigdomide, carfilzomib, and dexamethasone (MeziKd) vs carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): Results from the phase 3 SUCCESSOR-2 trial.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

MajesTEC-9: A phase 3 randomized study of teclistamab monotherapy vs investigator's choice of pomalidomide, bortezomib, and dexamethasone or carfilzomib and dexamethasone (PVD/Kd) in patients (pts) with relapsed refractory multiple myeloma (RRMM).

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Background: Triplet and quadruplet regimens have greatly improved outcomes in newly diagnosed multiple myeloma, yet a high unmet need remains for more effective, broadly accessible treatments for anti-CD38- and lenalidomide- (Len) exposed/refractory RRMM. Teclistamab (Tec) is the most widely used BCMA×CD3 BsAb in heavily pretreated RRMM, with improved outcomes in earlier lines of therapy (LOTs). In MajesTEC-3, the synergistic Tec-daratumumab combination significantly improved progression-free and overall survival (PFS/OS) as early as first relapse. MajesTEC-9 (NCT05572515) is the first phase 3 study of Tec monotherapy in pts with 1–3 prior LOTs. **Methods:** Pts with RRMM and 1–3 prior LOTs including anti-CD38 and Len were randomized 1:1 to receive 28-day cycles (C) of Tec (C1–2: 2 step-up doses then 1.5 mg/kg QW; C3–6: 3 mg/kg Q2W or Q4W depending on response; C7+: 3 mg/kg Q4W) or investigator's choice of PVD/Kd (21/28-day C). Primary endpoint was PFS by IRC; secondary endpoints included OS, complete response or better ($\geq$ CR), and safety. **Results:** 593 pts were randomized (Tec, n=296; PVD/Kd, n=297). Median (range) age: 70 (34–86) yrs; number of prior LOTs: 2 (1–3); Len refractory: 80%; anti-CD38 refractory: 85%; refractory to last LOT: 92%. With 17.3-mo median follow-up, Tec significantly improved PFS vs PVD/Kd (HR, 0.29; 95% CI, 0.23–0.38; $P<0.0001$); mPFS: NR vs 8.2 mo; 18-mo PFS rate: 69.8% vs 26.9%. OS was significantly improved with Tec vs PVD/Kd (HR, 0.60; 95% CI, 0.43–0.83; $P=0.0020$). Of 174 PVD/Kd pts who received subsequent treatment, 68.4% received BsAb or CAR-T. PFS favored Tec across all prespecified subgroups, including anti-CD38-refractory pts and Len-refractory pts. $\geq$ CR rate was significantly higher with Tec vs PVD/Kd (65.9% vs 16.8%; OR, 10.42; 95% CI, 6.89–15.76; $P<0.0001$). At data cutoff, 65.3% of pts remained on Tec vs 24.0% on PVD/Kd (safety set: Tec, n=291; PVD/Kd, n=283). TEAEs were similar for Tec and PVD/Kd (99.7% vs 97.9%). Grade (Gr) 3/4 TEAEs (84.9% vs 76.3%) and Gr 5 TEAEs (6.5% vs 3.5%) were higher with Tec vs PVD/Kd, noting the median treatment duration was nearly doubled with Tec (13.1 vs 7.0 mo). Treatment discontinuation due to TEAEs was lower with Tec vs PVD/Kd (10.7% vs 13.1%). Gr 3/4 infections were higher with Tec vs PVD/Kd (41.6% vs 29.0%). Any-onset Gr $\geq$ 3 infections decreased over time. CRS occurred in 66.0% of pts with Tec (Gr 1/2: 48.8%/16.5%) and ICANS in 4.1% (Gr 1/2: 2.4%/1.4%). **Conclusions:** Tec monotherapy significantly improved PFS/OS vs standard of care (SoC) in this high unmet need population. CRS and infections were managed with established protocols. Results of phase 3 studies support Tec-based regimens as a SoC as early as second line, across all treatment settings and regardless of prior anti-CD38/Len exposure. Clinical trial information: NCT05572515. Research Sponsor: Johnson & Johnson.

Etentamig in patients (pts) with relapsed/refractory multiple myeloma (RRMM) with prior exposure to B-cell maturation antigen (BCMA)–targeted therapy.

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Background: Data on response to BCMA-targeted therapies among BCMA-exposed pts with RRMM are limited. Outcomes after sequential/subsequent anti-BCMA bispecific T-cell engagers (Bs-TCE) are vital to evaluate. Etentamig is a next-generation differentiated BCMA x CD3 Bs-TCE composed of a bivalent BCMA-binding domain with a high-avidity, low-affinity CD3-binding domain potentially reducing cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life and convenient monthly (Q4W) dosing. Phase 1 results of etentamig in RRMM showed robust efficacy and potential best-in-class safety. **Methods:** Arm B of the open-label, Phase 1b MOVISO study (NCT05650632) evaluated etentamig in pts with RRMM with ≥2 prior lines of therapy (PLT), including triple-class and prior BCMA exposure (antibody-drug conjugate [ADC] >30 days or CAR-T >6 months [mo] after last exposure). Primary safety endpoints were CRS and immune effector cell-associated neurotoxicity syndrome (ICANS); efficacy endpoints included objective response rate (ORR; IMWG 2016), duration of response (DoR), and progression-free survival (PFS). Pts received etentamig (60 mg IV; no step-up dosing [SUD]) on Cycle 1 Day 1 and Q4W thereafter. **Results:** At cutoff (June 11, 2025), 41 prior BCMA-exposed pts (CAR-T, n=24; ADC, n=17) had been treated; 24 (57%) were male, 38 (93%) were White, median (mdn) (range) age was 68 (43–89) years, 37 (88%) had ECOG PS ≤1, and 34 (81%) were triple-class refractory. Mdn (range) PLT was 6 (3–15). For 21 (51%) pts, the last PLT was BCMA directed; 23 (56%) had previously responded to anti-BCMA therapy (17/24 [71%] for CAR-T and 6/17 [35%] for ADC). Mdn (range) time from last prior CAR-T or ADC to first dose of etentamig was 15 (1–30) and 4 (1–45) mo, respectively. Mdn (range) follow-up was 5.5 (0.2–17.1) mo. Despite no SUD, CRS and ICANS were reported in 24 (57%) and 3 (7%) pts, respectively; all G1/2 events, except 1 G3 ICANS. G3/4 neutropenia and infections were reported in 15 (36%) and 17 (41%) pts, respectively. Efficacy outcomes are detailed in the Table (NE, not estimable). For pts whose last PLT was BCMA directed, MRD negativity (clonoSEQ, 10⁻⁵) was seen in 2/3 (67%) evaluable pts, along with robust peak activation and proliferation of CD8+ T cells. **Conclusions:** Pts treated with etentamig achieved durable responses; rates were higher in pts who received CAR-T as last line. No new safety signals were observed; only low-grade CRS was seen despite no SUD. Clinical trial information: NCT05650632. Research Sponsor: AbbVie Inc.

	All prior BCMA (N=41)	Prior BCMA CAR-T (N=24)
ORR, n/n (%) [95% CI]		
Overall	17/36 (47) [30–65]	11/22 (50) [28–72]
BCMA-directed last PLT	11/19 (58) [34–80]	7/11 (64) [31–89]
Mdn DoR, mo [95% CI], No. of pts		
Overall	13 [7–NE], N=17	13 [7–NE], N=11
BCMA-directed last PLT	13 [7–NE], N=11	13 [7–NE], N=7
Mdn PFS, mo [95% CI], No. of pts		
Overall	3.4 [3–11], N=41	8.3 [2–NE], N=24
BCMA-directed last PLT	9.4 [2–NE], N=21	9.4 [2–NE], N=12

Updated results from inMMMyCAR, the ongoing first-in-human phase 1 study of KLN-1010 in patients (pts) with relapsed and refractory multiple myeloma (RRMM).

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Background: KLN-1010 is a modified lentiviral vector generating a novel, fully human anti-BCMA CAR-T cell *in vivo* when administered intravenously without preparative chemotherapy to pts with RRMM. Here, we report updated findings from inMMMyCAR, the first sponsored, multicenter study of an *in vivo* CAR-T therapy for pts with RRMM. **Methods:** Eligibility required RRMM with measurable disease, adequate end-organ and bone marrow (BM) function, and ≥ 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. **Results:** To date, 6 pts were infused across two dose levels (6×10^6 and 2×10^7 IU/kg). Pts ranged in age from 61–72 and had received 3–5 prior lines of therapy. 5 pts had high-risk cytogenetics. BM plasma cell involvement ranged from $<5\%$ to 80% . 1 pt had extramedullary disease (EMD). Median time from consent to infusion was 13.5 days. All pts experienced treatment-emergent adverse events. Infusion-related reactions (IRR) occurring in 3 pts (2 at 2×10^7 IU/kg, 1 at 6×10^6 IU/kg) were manageable and resolved within 6–48 hrs. Cytokine release syndrome (CRS) was observed in 4 pts, with median onset on day 11 and median duration of 3.5 days; all events were Gr 2 and were managed with tocilizumab and corticosteroids. No immune effector cell-associated neurotoxicity syndrome (ICANS) or delayed neurotoxicity were observed. Peak absolute lymphocyte counts occurred between days 13–22, with median counts of $6.9 \times 10^9/L$ (range 2.3 – $43.1 \times 10^9/L$) and no associated clinical sequelae. CAR-T cells were detectable in peripheral blood through 4 months follow-up and were predominantly memory-phenotype by month 3 (M3). All 6 pts achieved minimal residual disease (MRD) negativity (5 at 10^{-6} and 1 at 10^{-5} sensitivity) at M1 in the BM. MRD negativity was maintained through M6 (10^{-6} sensitivity) in the pt with the longest follow-up. All pts achieved a response by IMWG criteria, and responses deepened over time. The pt with EMD showed complete resolution by M1. **Conclusions:** Results from inMMMyCAR continue to demonstrate compelling early clinical activity. All pts achieved early MRD-negative responses and deepening of IMWG response over time. The pt with the longest follow-up remains MRD-negative with a stringent CR at M6. Activity was also observed in EMD, with radiologic resolution within 1 month. KLN-1010 was generally well-tolerated, with manageable toxicities related to IRR and CRS, supporting potential feasibility for outpatient administration. No ICANS or delayed neurotoxicity were observed. The study remains ongoing; updated results will be presented. Clinical trial information: NCT07075185. Research Sponsor: Kelonia Therapeutics, Inc.

Pt	Dose, $\times 10^7$ IU/kg	Timepoints of MRD-negative results ^a	IMWG response	Duration of follow-up, months
1	2	M1, M3, M6	sCR	6+
2	2	M1, M3	VGPR	5+
3	2	M1, M3	VGPR	4+
4	0.6	M1, M3	VGPR	3+
5	0.6	M1	sCR	1+
6	0.6	M1	PR	1+

^aBy next-gen flow cytometry or sequencing with sensitivity of 10^{-5} or 10^{-6} .

Optec/Optal: A phase 2 study to evaluate outpatient (OP), step-up administration of teclistamab (Tec) or talquetamab (Tal) with prophylactic tocilizumab (prophyToci) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).

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Background: Tec, a B-cell maturation antigen x CD3 bispecific antibody (bsAb), and Tal, a G protein-coupled receptor class C group 5 member D x CD3 bsAb, are approved for the treatment of pts with triple-class exposed (TCE) RRMM. Cytokine release syndrome (CRS) is a common adverse event associated with T-cell therapies. CRS occurred in 72% and 73–79% of pts in the MajesTEC-1 (TEC-1) and MonumentAL-1 (TAL-1) studies, respectively. One cohort of pts in TEC-1 received prophyToci, resulting in a lower rate of CRS (26%) without negatively impacting safety or efficacy. A cohort of pts in TAL-1 received prophyToci, with 18% experiencing CRS; safety and efficacy were comparable to the overall TAL-1 population. **Methods:** This non-randomized, multicenter, prospective study evaluates prophyToci in RRMM pts treated with Tec (Arm A) or Tal (Arm B) using the approved step-up dose (SUD) schedule in the OP setting. ProphyToci 8 mg/kg was administered before SUD 1 of either Tec or Tal. Specific recommendations (home monitoring, IV immunoglobulin [IVIG] for IgG levels <400 mg/dL) and restrictions (caregiver requirements and travel distance) are also provided for pt safety. Primary endpoint is incidence of any grade CRS in cycles 1–2. Secondary endpoints include safety and efficacy measures. Safety parameters encompass incidence of Grade ≥ 2 CRS, any grade recurrent CRS, any grade infections, neurotoxicity (NT), and neutropenia throughout the study. Efficacy endpoints include overall response rate (ORR), best overall response (BOR) and progression-free survival (PFS). **Results:** As of 06 January 2026, 43 pts enrolled in Arm A, and 7, in Arm B. In Arm A, the CRS rate was 5%, all G1. In Arm B, G1 CRS occurred in 14% of pts. Adverse events $G \geq 3$ included neutropenia (G3, n=4; G4, n=6), anemia (G3, n=1), and febrile neutropenia (G3, n=1). Twenty pts (47%) in Arm A experienced infections, with 19% $\geq G3$. Among Arm A patients who experienced infections, 10 (50%) exhibited IgG levels <400 mg/dL, of whom 2 (20%) received IVIG. In Arm B, 4 pts (57%) experienced infections, with 29% (n=2) $\geq G3$. BOR in Arm A included 3 stringent complete responses (sCRs), 6 CRs, 11 very good partial responses (VGPR), 8 PRs, 1 stable disease, 5 progressive disease (PD), and 9 non-evaluable pts. Among the 34 evaluable pts in Arm A, the ORR was 82%. BOR in Arm B included 1 sCR and 6 non-evaluable pts. After a median follow-up of 11.8 months, 74.4% of pts (n=32) in Arm A did not experience progression. **Conclusions:** A single dose of prophyToci before SUD 1 of Tec or Tal reduced the incidence of CRS, with no impact on safety or efficacy, and supports administration of these bsAbs in the OP setting. The protocol was amended to add an arm evaluating the effect of prophylactic oral dexamethasone on CRS in pts treated with Tec (Arm C). Enrollment is ongoing (NCT05972135). Clinical trial information: NCT05972135. Research Sponsor: Johnson & Johnson Innovative Medicine; Sarah Cannon Research Institute.

Survival outcomes comparing sequencing of CAR-T followed by BiTE versus BiTE followed by CAR-T in patients with relapsed multiple myeloma.

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Background: Chimeric antigen receptor T-cell (CAR-T) therapies and bispecific T-cell engager (BiTE) antibodies for relapsed and refractory multiple myeloma (MM) are increasingly used earlier in the disease course but the optimal sequencing remains unclear. It has been hypothesized that CAR T before BiTE would lead to less T-cell exhaustion and better outcomes than BiTE before CAR T. **Methods:** A multicenter retrospective cohort study using the TriNetX Global Collaborative Network from 2021–2025 to evaluate outcomes among MM pts who received both CAR-T (idecel or ciltacel) and a BiTE (teclistamab, talquetamab, or elranatamab). Cohorts by treatment sequence: CAR-T followed by BiTE (CAR-T→BiTE) or BiTE followed by CAR-T (BiTE→CAR-T). Primary outcome: 5-yr mortality from the initiation of first advanced immunotherapy. Secondary outcomes: incidence of CRS, ICANS, infection, sepsis, ICU admission, and 1-yr mortality following each therapy. Propensity score matching included demographic variables, comorbidities, prior myeloma therapies (including prior SCTx) and baseline laboratory values. **Results:** 389 pts were included (244 CAR-T→BiTE; 145 BiTE→CAR-T); in the CAR T 1st group, 72% received ide-cel and 28% had cilta-cel, whereas in the BiTE 1st group 86% went on to receive cilta-cel as the CAR T product. Median overall survival was reached in the BiTE-first cohort (3.59 years) but not in the CAR-T-first cohort. Five-year survival was significantly higher with CAR-T-first sequencing (57.1% vs 25.5%; log-rank $p = 0.045$). In adjusted Cox regression, CAR-T-first sequencing was independently associated with lower 5-year mortality (hazard ratio 0.57, 95% CI 0.34–0.95). In unmatched analyses stratified by the specific BiTE (anti-BCMA vs anti-GPRC5D) used, overall survival did not differ significantly within each treatment sequence (all log-rank $p > 0.05$). In propensity score-matched analyses (112 patients per group), CAR-T-first pts experienced higher ICANS (all grades, 22% vs 10.7%) after first therapy but lower ICU admission (52% vs 70%), and significantly lower CRS (37% vs 56%, all grades) following second therapy. Rates of infection, sepsis, and 1-yr mortality were similar between groups. **Conclusions:** Among patients with MM who received both CAR-T and BiTE therapies, CAR-T-first sequencing was associated with significantly improved long-term survival in spite of a much higher percentage receiving the less effective CAR T product. The additional finding of a lack of survival differences by specific BiTE used also suggests that treatment order, rather than product selection, may be the primary determinant of long-term outcomes. These findings support consideration of earlier CAR-T deployment when feasible and underscore the importance of sequencing strategy in the evolving landscape of MM immunotherapy. Research Sponsor: None.

Belantamab mafodotin with daratumumab, lenalidomide, and dexamethasone in transplant-ineligible, newly diagnosed multiple myeloma patients: Phase 1/2 BelaDRd study.

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Background: The MAIA trial established daratumumab with lenalidomide, dexamethasone (DRd) as standard therapy for transplant-ineligible (TI) NDMM. Belantamab mafodotin (belamaf) showed high efficacy in relapsed/refractory disease. Quadruplet regimens improved clinical outcomes, providing a strong rationale to evaluate belamaf in combination with DRd in TI NDMM. **Methods:** BelaDRd is a phase 1/2, open-label study (EUCT-2024-515634-32) evaluated this combination in TI-NDMM. Part 1 (dose-finding phase) assessed the safety and tolerability of two belamaf doses (1.9/1.4 mg/kg Q8W) with DRd. This part established belamaf 1.9 mg/kg Q8W, extended to Q12W to account as the recommended phase 2 dose (RP2D). Part 2 (dose-expansion phase) evaluates the safety and efficacy of the RP2D in two cohorts Groups A and B, guided by ophthalmologist and hematologist (using Vision-Related Anamnestic, VRA tool), respectively. **Results:** In Part 1, 24 pts (median age: 73 years; male: 54.2%) entered the study; 12.5% had high-risk cytogenetics (HRC). At a median follow-up of 34.3 months, 18 (75%) pts remained on treatment, while 6 (25%) discontinued; 3 (12.5%) death, 1 (4.2%) AE/SAE, 1 (4.2%) withdrew consent, and 1 (4.2%) due to PD. The median dose intensity (MDI) of belamaf was 0.5 mg/kg/Q4W. MRD negativity was achieved in 13 (81.3%) of evaluable patients (n=16). The ORR was 22 (91.7%). Sixteen patients (69.6%) achieved both $\geq$ CR and $\geq$ VGPR. In Part 2 (n=12; median age: 74 years; male: 58.3%), 16.7% of pts had HRC. At a median follow-up of 17.9 months, 11 pts (91.7%) remained on treatment; 1 pt (8.3%) discontinued due to PD. Of 113 planned belamaf doses 13 doses were skipped due to OAEs. The MDI was 0.8 mg/kg/Q4W. MRD negativity was achieved in 5 (71.4%) of evaluable patients (n=7). ORR was 11 (91.7%) in evaluable pts. The median time to $\geq$ PR was 1.1 months for both parts. At 18 months, PFS was 91.7% (95% CI 76.4-97.2) and 87.5% (95% CI 66.1-95.8) in the overall and RP2D populations, respectively; corresponding TTP rates were 97.1% (95% CI 80.9-99.6) and 95.5% (95% CI 71.9-99.4). Grade $\geq$ 3 BCVA decline was observed in 74(10.4%) of ocular assessments in part 1 and 4(3.9%) and 5(5.3%) in part 2 groups A and B, respectively. Grade $\geq$ 2/ $\geq$ 3 keratopathy occurred in 20.2%/0.6% of assessments in Part 1; in Part 2, rates were 6.7%/0% (Group A) and 10.6%/0% (Group B). Median $\geq$ Grade 2 BCVA OAE/keratopathy resolution time was 1.1/1.0 months (Part 1) and 1.9/1.0 months (Part 2). **Conclusions:** BelaDRd demonstrated robust clinical activity, with rapid and deep responses. Low frequency of $\geq$ Grade 3 OAEs was observed and were rapidly resolved. Moreover, a similar frequency of OAEs was noted when dosing was guided by haematologist vs ophthalmologist ocular assessment. The remarkable PFS supports further evaluation of this quadruplet in a phase 3 study versus other novel quadruplet combinations in NDMM. Clinical trial information: EUCT-2024-515634-32. Research Sponsor: None.

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

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Background: The phase 3 CEPHEUS study established that DVRd improved overall minimal residual disease (MRD)-negativity (neg) rates and progression-free survival (PFS) vs VRd in pts with TIE or transplant-deferred (TD) NDMM. The first analysis of the DVRd TIE subpopulation at a median follow-up of 58.7 months (mo) showed a complete response or better ($\geq$ CR) rate of 80.6% and overall MRD neg rate of 60.4%, with ~70% of pts alive and progression free. This final analysis of the CEPHEUS TIE subpopulation describes a longer median follow-up of 76.0 mo. **Methods:** The primary endpoint of overall MRD neg rate (10^{-5} and $\geq$ CR), and secondary endpoints, including investigator-assessed PFS and $\geq$ CR rate, and sustained MRD neg (confirmed MRD neg ≥ 12 months +/- 1 mo apart without MRD positivity in between and $\geq$ CR) were assessed in the TIE population. The study was closed at the final analysis and pts were able to continue their study treatment via post-study access. **Results:** Of 395 pts enrolled, 289 pts with TIE NDMM received either DVRd (n=144) or VRd (n=145). The overall MRD neg rate at 10^{-5} was 61.1% for DVRd and 40.0% for VRd (odds ratio [OR] 2.35; 95% CI 1.47–3.77; $P=0.0004$) and at 10^{-6} was 46.5% for DVRd vs 27.6% for VRd (OR 2.27; 95% CI 1.39–3.71; $P=0.0010$). Sustained MRD neg rate at 10^{-5} was 49.3% for DVRd and 29.0% for VRd (OR 2.40; 95% CI 1.47–3.91; $P=0.0005$) and at 10^{-6} was 37.5% for DVRd and 16.6% for VRd (OR 3.01; 95% CI 1.73–5.24; $P<0.0001$). Overall $\geq$ CR rate was 80.6% for DVRd and 61.4% for VRd (OR 2.64; 95% CI 1.54–4.51; $P=0.0003$). Median investigator-assessed PFS was not estimable (NE; 95% CI 74.81–NE) for DVRd and was 50.20 mo (95% CI 41.95–62.95) for VRd (HR 0.55; 95% CI 0.39–0.78; $P=0.0007$), with 59.3% for DVRd vs 38.3% for VRd alive and progression free at 72 mo. OS favored DVRd over VRd (HR 0.84; 95% CI 0.57–1.24), particularly when censoring for COVID-19, which significantly impacted this study (HR 0.74; 95% CI 0.49–1.12). The treatment effect was consistent across most subgroups (Table). **Conclusions:** After median follow-up of over 6 years, the final analysis of the CEPHEUS trial demonstrated that TIE pts treated with DVRd continue to have deep and durable responses compared with those on VRd, which is crucial for patients for whom transplant is not an option. These data continue to reinforce DVRd as a standard of care in the TIE NDMM population. Clinical trial information: NCT03652064. Research Sponsor: Johnson & Johnson.

BL characteristic	MRD neg (10^{-5}) rate, %				Median PFS, mo			
	DVRd	VRd	OR	95% CI	DVRd	VRd	HR	95% CI
ISS stage I	66.0	41.7	2.72	1.30–7.11	NE	60.5	0.52	0.28–0.97
II	59.3	45.6	1.73	0.82–3.68	NE	49.4	0.50	0.28–0.88
III	57.5	30.0	3.16	1.26–7.94	66.4	43.8	0.66	0.35–1.24
Cytogenetic risk High	50.0	50.0	1.00	0.28–3.57	58.0	31.7	0.82	0.36–1.87
Standard	63.8	39.6	2.68	1.55–4.66	NE	61.6	0.58	0.38–0.89
ECOG PS 0	57.7	45.6	1.63	0.76–3.47	NE	59.9	0.33	0.17–0.64
≥ 1	63.0	36.4	2.99	1.63–5.48	74.8	47.2	0.70	0.46–1.06

Efficacy and safety of iberdomide, daratumumab, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma.

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Background: Iberdomide (Iber) is a CELMoD that binds with greater specificity & affinity to the cereblon protein of the E3 ligase complex than a traditional IMiD. Both transplant-eligible (TE) & ineligible (TIE) patients (pts) with newly diagnosed multiple myeloma (NDMM) are currently treated with quadruplet induction, consisting of an anti-CD38 monoclonal antibody, a proteasome inhibitor, an IMiD & dexamethasone (dex). We conducted a clinical trial (NCT05392946, IDEAL) to examine the efficacy of a novel finite-duration approach, using Iber, daratumumab, bortezomib & dex (Iber-DVd) quadruplet induction followed by Iber monotherapy maintenance. **Methods:** Both TE and TIE pts with NDMM were enrolled in this Phase 1 (3+3 design)/Phase 2 (single stage) trial. The primary goal was to assess the $\geq$ complete response (CR) rate — utilizing the more sensitive serum MASS-FIX assay in lieu of serum immunofixation — during induction. Treatment involved twelve 28-day cycles of induction with Iber, given PO at the recommended phase 2 dose (RP2D), days 1–21, daratumumab 1800mg SQ, weekly for 2 cycles, every other week during Cycles 3–6, & every 4 weeks thereafter, bortezomib 1.3 mg/m² SQ, weekly & dex 40 mg, weekly, followed by Iber monotherapy (24 cycles). Growth factor was not allowed during the dose-limiting toxicity (DLT) assessment period (Cycle 1). **Results:** Among 47 pts enrolled, 9 pts were in Phase 1 portion which assessed the maximum tolerated dose (MTD), with Iber starting at 1 mg/day dose, days 1–21 [Dose Level (DL) 1]. DLT (all grade 4 neutropenia) was noted in 3 pts, 2 at DL 1 & 1 at DL -1. This analysis includes 44 pts who received Iber at the RP2D (0.75 mg/day, days 1–21), including 6 pts from the Dose Confirmation Cohort (Phase 1, DL -1), dosed at MTD, & 38 pts in the Dose Expansion Cohort. The median age at registration was 65 years (range 36–86 years), & 23 pts (52.3%) were deemed high-risk. At data cut-off, pts had received a median of 15 cycles (range 3–36) of therapy. Overall response rate was 100%; $\geq$ CR rate, 36.4% (95% CI: 22.4, 52.2) during induction & 52.3% (95% CI: 36.7, 67.5), overall, including the maintenance phase. The marrow flow-based (10^{-5}) MRD negative rate was 29.5% during induction & 47.7% overall. At a median follow-up (FU) 18.3 mos, 2 pts have died (one during FU due to progressive disease & the other on-treatment due to COVID-19). 12- (& 18-) month progression-free survival & overall survival rates were 91% (88%) & 97% (94%), respectively. Most common toxicities at RP2D were lymphopenia, neutropenia (leading 27% of pts to require pegfilgrastim support), rash, peripheral neuropathy, diarrhea, & infections. Cases of high-grade fatigue were low (<5%). Updated data will be presented at the meeting. **Conclusions:** Iber-DVd is an active and safe regimen for both TE and TIE pts with NDMM, leading to high response rates which improved over time, with nearly one-half of the pts achieving MRD negative state. Clinical trial information: NCT05392946. Research Sponsor: Bristol Myers Squibb (BMS).

Long-term outcomes with sustained minimal residual disease (MRD) negativity in belantamab mafodotin–treated patients (pts) with relapsed/refractory multiple myeloma (RRMM): An update from DREAMM-8.

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

Isatuximab plus pomalidomide-dexamethasone in relapsed/refractory multiple myeloma: Subgroup analysis by prior anti-CD38 exposure from the phase 3 IRAKLIA trial.

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Background: With the growing use of anti-CD38 therapies in early multiple myeloma (MM) management, there is a need for data in patients previously exposed to anti-CD38 therapy to guide decision making. In the Phase 3 IRAKLIA trial (NCT05405166), patients with relapsed/refractory MM (RRMM) received the anti-CD38 monoclonal antibody isatuximab (Isa) subcutaneously (SC) delivered via an innovative on-body injector (OBI) or intravenously (IV), with pomalidomide and dexamethasone (Pd). In this post hoc analysis, we examined outcomes in IRAKLIA patients with vs without prior anti-CD38 exposure. **Methods:** RRMM patients ≥ 18 years with ≥ 1 prior line of therapy including lenalidomide and a proteasome inhibitor were randomized to receive Isa SC (n=263) or IV (n=268) weekly in Cycle 1, then every 2 weeks, with Pd. Patients with prior anti-CD38 exposure < 9 months (mos) before randomization or intolerance to anti-CD38 were excluded. Refractory patients were defined as those who failed to achieve minimal response on treatment or had progression within 60 days after last dose. Patients receiving Isa SC or IV were pooled. **Results:** Overall, 67 patients (12.6%) had prior anti-CD38 exposure with a median washout period of 20.2 mos, of which 26 (38.8%) were anti-CD38 refractory. Baseline characteristics were largely consistent between patients with or without prior anti-CD38 exposure; the median follow-up for the overall population was 12 mos. Patients with prior anti-CD38 exposure had an overall response rate (ORR) of 52.2%, 12-mo progression-free survival (PFS) rate of 40.6%, and median PFS of 8.5 mos. In patients without prior exposure, an ORR of 73.5%, 12-mo PFS of 68.8%, and non-estimable (NE) median PFS were reported. Anti-CD38 non-refractory vs refractory patients had an ORR of 48.8% vs 57.7%, 12-mo PFS of 38.9% vs 42.2%, and median PFS of 9.0 vs 7.5 mos. Patients with a longer washout period ($>$ median of 20.2 mos) had an ORR of 63.6%, 12-mo PFS of 61.8% and NE median PFS, whereas patients whose prior anti-CD38 therapy ended more recently ($\leq$ median of 20.2 mos) had an ORR of 41.2%, 12-mo PFS of 19.2%, and median PFS of 6.7 mos. The safety profile of Isa + Pd was similar in patients with vs without prior anti-CD38 exposure. **Conclusions:** Isa + Pd demonstrated clinical benefit across anti-CD38-naïve, anti-CD38-exposed, and anti-CD38-refractory patients. A washout period $>$ median of 20.2 mos resulted in outcomes comparable to those in anti-CD38-naïve patients, and outcomes were consistent between anti-CD38-exposed and anti-CD38-refractory patients after a > 9 -mo washout period. Efficacy of Isa + Pd in patients with prior anti-CD38 exposure from the IRAKLIA trial presents an opportunity to address an unmet need in a difficult-to-treat patient population. Clinical trial information: NCT05405166. Research Sponsor: Sanofi.

Final analysis of daratumumab, carfilzomib, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma.

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Background: Frontline therapy for patients with multiple myeloma (MM) has mainly consisted of a proteasome inhibitor and an immunomodulatory imide drug (IMiD). Anti-CD38 monoclonal antibodies are fast becoming incorporated into frontline regimens, but many patients experiencing relapse today remain naïve to this drug class. While quadruplet therapies have become a standard-of-care in the newly diagnosed setting, they have not been well studied in patients with relapsed/refractory MM (RRMM). Here, we report the final analysis of a phase 2 Multiple Myeloma Research Consortium study of daratumumab combined with carfilzomib, pomalidomide, and dexamethasone in RRMM (NCT01665794). **Methods:** Eligible patients had documented MM with 1–3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug. Prior exposure to a CD38-directed monoclonal antibody was exclusionary. Dose and frequency were described previously. The primary endpoint was the rate of near complete response (nCR) after 4 cycles of DaraKPd; secondary endpoints included progression-free survival (PFS) and overall survival (OS). **Results:** A total of 28 patients were treated with DaraKPd. Patients had received a median of 1 prior line of therapy (range 1–3), including 24 (85.7%) with prior autologous stem cell transplant, and 82% that were refractory to lenalidomide. The study reached the statistical threshold for efficacy (nCR of 39%; 95% CI 22–59%), and the study was stopped early as a result. At a median follow-up of 70.2 months, the median progression-free survival (mPFS) was 38.3 months (95% CI 18.4 mo–not reached [NR]) and median OS (mOS) was not reached. The 36-month PFS and OS were 54% (95% CI 35–70%) and 75% (95% CI 57–87%), respectively. High-risk cytogenetics, as defined by the presence of t(4;14), t(14;16), t(14;20), deletion 17p, and 1q gain or amplification, were present in 18 (64%) patients. The mPFS in the high risk group was 42.8 mo (18.4–NR) and mOS was not reached. For patients with standard-risk cytogenetics, neither the mPFS nor mOS were reached. Of the 26 patients evaluable for MRD negativity by flow cytometry (limit of detection 10^{-5}), 17 (65%) achieved MRD-negativity and 11 (42%) had sustained MRD negativity for ≥ 1 year. Among patients with MRD-negativity as best response, mPFS was 69.4 mo (18.9–NR) compared to 14.0 mo (1.2–NR) in patients with MRD positivity ($p = 0.002$). There were no new safety signals or treatment-related deaths. **Conclusions:** With nearly 6 years of follow-up, DaraKPd in lenalidomide-exposed and anti-CD38 monoclonal antibody-naïve RRMM showed deep and durable responses, with a mPFS of 38.3 months and 36-month OS of 75%. These long-term follow-up data support DaraKPd as a safe and effective treatment in patients with RRMM. Clinical trial information: NCT01665794. Research Sponsor: Multiple Myeloma Research Consortium; Amgen; Bristol Myers Squibb.

Prediction of progression in MGUS using transformer-based survival time-series modeling.

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Background: Monoclonal gammopathy of undetermined significance (MGUS) is common, yet only a minority progress to malignant plasma-cell disorders. Mayo risk stratification uses baseline factors and is commonly implemented/validated in a Cox proportional hazards (CoxPH) framework, which may miss prognostic longitudinal patterns. **Methods:** We assembled 15,158 MGUS patients with longitudinal laboratory data and progression outcomes (smoldering multiple myeloma, multiple myeloma, AL amyloidosis, or Waldenström macroglobulinemia). We compared a Mayo-factor Cox proportional hazards (CoxPH) baseline versus STRaTS, a transformer-based survival model, to predict progression risk at 3-, 5-, and 10-year horizons. STRaTS leveraged longitudinal trajectories of routine labs including hemoglobin, platelets, differential counts (neutrophils/lymphocytes/monocytes), immunoglobulins (IgG/IgA/IgM), free light chains (kappa/lambda), M-spike, and creatinine. To minimize bias, we used laboratory results collected from 1–3 years after diagnosis and started follow-up at year 3; patients progressing before year 3 or lacking follow-up beyond year 3 were excluded. A total of 7,305 patients met eligibility and were split into train/validation/test cohorts of 4,383/1,461/1,461. Discrimination was assessed by concordance index (C-index). Clinical operating performance was evaluated on a held-out test cohort by comparing sensitivity and specificity at the same proportion of patients selected for intensified surveillance (same workload). **Results:** Among MGUS patients with complete baseline Mayo factors (N=3,388), Kaplan–Meier–estimated 3-/5-/10-year cumulative progression risk was 0.1/0.4/3.4% (Low), 3.0/4.3/7.9% (Low-Intermediate), 4.4/6.4/14.1% (High-Intermediate), and 8.9/12.5/16.9% (High). On a held-out test cohort, STRaTS demonstrated superior discrimination versus the Mayo-factor CoxPH (C-index 0.75 vs 0.538; $p < 0.0001$). Both models were trained and evaluated on identical train/test splits. At the same surveillance workload, STRaTS achieved higher sensitivity with comparable specificity; when 40.3% of patients were selected for closer surveillance, 3-year sensitivity was 81.0% for STRaTS versus 47.6% for CoxPH (Table). **Conclusions:** Among MGUS patients who remain progression-free at 3 years, transformer-based survival modeling of longitudinal laboratory trajectories provides more accurate individualized conditional progression risk estimates and improved workload-matched identification of progressors compared with the conventional Mayo/Cox approach. Research Sponsor: None.

Sensitivity/specificity (%).			
Operating Point	Flagged %	STRaTS Sens / Spec (%)	CoxPH Sens / Spec (%)
Int+High, 3y	40.3	81.0 / 58.5	47.6 / 58.9
Int+High, 5y	40.3	81.2 / 60.4	46.9 / 58.8
Int+High, 10y	40.3	25.0 / 56.3	23.8 / 58.7
Two-Group High (≥ 2 factors), 5y	5.6	37.4 / 93.4	35.4 / 93.1

Early detection of multiple myeloma and MGUS progression risk using artificial intelligence and routine laboratory data.

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Background: Multiple myeloma (MM) is a malignant plasma cell disorder that often presents with non-specific symptoms, resulting in delayed diagnosis and poorer outcomes. While artificial intelligence (AI) models using routine laboratory data have shown promise for MM detection, their ability to distinguish monoclonal gammopathy of undetermined significance (MGUS) from early MM and to identify patients at risk of progression remains limited. **Methods:** We conducted a retrospective study using routinely collected clinical and laboratory data from 89 patients evaluated at the Lincolnshire Hospital Group between 2003 and 2025. The cohort included confirmed MM cases, MGUS patients, and non-myeloma controls. Predictive features included hemoglobin, serum creatinine, calcium, albumin, immunoglobulin levels, paraprotein concentration, and derived laboratory indices. After rigorous data cleaning and preprocessing, eight supervised machine learning models were trained using a training-testing split. These included six machine learning algorithms (Lasso, gradient boosting, random forest, elastic-net, ridge regression, and support vector) and two baseline algorithms (Naïve (Mean) and Seasonal-Naïve). The training set included 69 patients (82%), and the test set included 20 patients (18%). Model performance was evaluated using precision, recall, F1 score, and regression evaluation metrics such as R^2 (R-squared) and MAE (Mean Absolute Error), with a specific focus on MGUS-MM differentiation. **Results:** The developed AI models demonstrated reliable performance in distinguishing MM from non-myeloma controls and showed improved discriminatory ability between MGUS and MM compared with standard laboratory threshold-based assessment. Specific laboratory feature patterns were associated with progression-consistent phenotypes, enabling risk stratification within the MGUS population. The best-performing model, Lasso Regression, achieved 0.01 MAE (months) and a nearly perfect score of 1.00 for R^2 . This meant the best prediction done by the model had a 0.47 months error, i.e. 14 days difference from the actual transformation date. Gradient Boosting and Random Forest achieved 1.04 and 1.15 MAE, and 0.90 and 0.95 R^2 , respectively. The results were implemented as a prototype clinical decision-support tool capable of generating rapid risk predictions using routinely available laboratory data. **Conclusions:** This study advances existing AI-based diagnostic approaches by addressing the clinically important challenge of early MM detection and MGUS risk stratification. AI-driven analysis of routine laboratory data may support earlier identification of patients at risk of progression, enabling improved monitoring, timely referral, and enhanced clinical decision-making. Research Sponsor: None.

Artificial intelligence predicted natural killer cell fitness to guide daratumumab and transplant strategies in newly diagnosed multiple myeloma.

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Background: Daratumumab (Dara) requires CD16-expressing natural killer (NK) cells for anti-myeloma activity. The use of bone marrow transplant (ASCT) results in prolonged immunosuppression, including lower levels of NK-cells. We evaluated if artificial intelligence (AI) predicted CD16 from routine hematoxylin and eosin (H&E) stained bone marrow biopsy slides could be used to guide Dara and transplant treatment strategies. **Methods:** We analyzed 212 newly diagnosed patients from the HealthTree registry treated with VRd (n=135; median follow-up 24.5 months (mo)) and D-VRd (n=77; 16.6 mo). H&E slides were processed using GigaTIME, a foundation model via zero-shot inference. Patients were dichotomized at median predicted CD16 and stratified by ASCT status. Subgroups: transplant-eligible (TE: age<65, ASCT; n=53), deferred (TD: age<70, no ASCT; n=34), and ineligible (TI: age≥70; n=17). Primary endpoint: time to next treatment (TTNT). Multivariate Cox regression adjusted for age, cytogenetic risk tested interaction between CD16, treatment and ASCT. **Results:** D-VRd achieved superior outcomes vs VRd (23.4% event rate vs 74.8%, $p<0.001$) despite lower ASCT use among D-VRd treated patients (50.6% vs 71.1%, $p=0.005$). In the VRd group, AI-predicted CD16 was highly prognostic in non-transplanted patients: High-CD16 achieved median TTNT 33.1 vs 5.1 mo for Low-CD16 ($p=0.0053$). ASCT rescued Low-CD16 patients (median 5.1 to 26.7 mo, $p<0.001$). Conversely, in D-VRd, CD16 did not stratify outcomes ($p=0.48$), indicating that Dara can rescue low-immune-fitness disease. Specifically, Dara rescued low CD16 non-transplanted patients from progression (86.8% 18-mo event-free survival for D-VRd versus 28.6% 18-mo event-free survival for VRd; $p<0.001$). High CD16 patients on D-VRd without ASCT achieved 86.3% event-free survival, non-inferior to ASCT (82.2%, $p=0.21$), supporting transplant deferral. The CD16×treatment×ASCT interaction was significant (HR 0.06, $p=0.045$). Among transplant-deferred patients, D-VRd improved 18-mo event-free rates vs VRd (70.5% vs 40%, $p=0.029$), with the largest benefit in Low CD16 ($p=0.016$). TI patients on D-VRd achieved 100% event-free at 18 mo vs 38.2% on VRd ($p=0.011$). **Conclusions:** We validated that AI-quantified CD16 from routine H&E guides Dara and transplant strategies in NDMM (n=212). The CD16×treatment×ASCT interaction (HR=0.06, $p=0.045$) confirms that CD16 predicts treatment benefit, not just prognosis. In VRd, low CD16 identifies a high-risk group (median TTNT 5.1 mo) needing intensification. D-VRd rescues low-immune-fitness patients (18-mo event-free survival: 86.8% vs 28.6% with VRd, $p<0.001$) and enables safe transplant deferral in high-fitness patients (82.2% with ASCT vs 86.3% without, $p=0.21$). This novel strategy enables precision medicine using standard H&E slides, with immediate clinical implications. Research Sponsor: None.

AI-enabled multimodal adjudication of revised IMWG progression after BCMA CAR-T.

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Background: Real-world ascertainment of clinically meaningful relapse after BCMA CAR-T is challenging because progression signals are distributed across laboratories, imaging, pathology, and clinician actions and are frequently embedded in unstructured external reports. The revised IMWG criteria (Kumar et al., IMS 2025) provide standardized definitions for imaging-based progression (PET/CT and WB-MRI) enabling automated recognition of radiologic and serologic progression thresholds. We developed an AI-enabled multimodal framework to automate real-time derivation of recognized IMWG progression across fragmented care settings. **Methods:** We analyzed 183 BCMA CAR-T treatment episodes with longitudinal routine laboratory data and independent dual-reviewer adjudication of progression dates. Automated detection evaluated every M-protein and FLC measurement longitudinally in a continuous IMWG rules engine, in addition to flagging new hypercalcemia. In addition, initiation of a new line of therapy (considered a progression event), together with large-language-model extraction of radiologic progression from PET/CT, WB-MRI, CT, X-ray, and MRI brain/spine reports. Performance was assessed using accuracy and specificity. **Results:** Serologic progression from real-world lab feeds was detected with high reproducibility, with FLC and M-protein achieving high accuracy (96.5% and 98.5%, respectively) and specificity (>97%), indicating minimal premature triggering across serial measurements. Hypercalcemia was rare but highly specific for progression. Radiology-based AI extraction achieved high accuracy (91%) and specificity (92.1%), enabling reliable identification of imaging-defined relapse. Initiation of a new line of therapy occasionally occurred before formal serologic IMWG thresholds were met, reflecting clinician-recognized relapse or that driven by non-serologic disease. Notably, 19% of adjudicated relapses were triggered by radiologic or marrow criteria when serologic IMWG thresholds were absent or lagging, including 12.5% radiology-only and 5.8% marrow-only events, aligned with our published data for post CART relapses (Abuhelwa et al Front. Oncol 2025). **Conclusions:** Automated lab-only approaches systematically underestimate true IMWG progression after BCMA CAR-T. An AI-enabled multimodal adjudication framework aligned with the revised IMWG criteria enables scalable, real-time, and reproducible progression capture for clinical trials and real-world datasets, supporting rapid endpoint determination, regulatory-grade retrospective analyses, and biologically faithful reconstruction of relapse patterns after CAR-T. Research Sponsor: None.

Echo cancer advisor: A modular AI framework for interpretable, patient-specific oncology decision support.

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Background: Oncology increasingly relies on large, heterogeneous datasets spanning genomics, clinical records, imaging, and treatment history. Large language models (LLMs) show promise for synthesizing such information, yet currently suffer from limited transparency, hallucination risk, and poor alignment with real-world clinical reasoning. There is a critical need for AI systems that can integrate multimodal data while preserving interpretability, traceability, and clinician control. **Methods:** We developed a modular AI decision-support system to assist oncologists in complex clinical reasoning tasks. Unlike monolithic LLM approaches, it decomposes clinical questions into atomic sub-tasks that are executed through structured, auditable pipelines, while integrating curated clinical data (EHR, genomics, pathology), external knowledge bases, and computational analyses via a function-oriented architecture. Each step is independently validated, logged, and audited to ensure correctness. It uses a hybrid local/cloud architecture and was evaluated on real-world oncology use cases in Moffitt Cancer Center's Multiple Myeloma (MM) cohort, which contains three data modalities: clinical, molecular, and pre-clinical. Clinical data resides in a PHI-compliant Snowflake data warehouse (Moffitt Cancer Analytics Platform, MCAP), including longitudinally-resolved treatment and outcome information from clinical notes, labs, pathology and radiology reports. CD138-enriched bone marrow samples from 1,260 MM patients were molecularly profiled using RNA-seq (n=1,376 biopsies) and whole exome sequencing (WES, n=1,427), whereas 549 tumor samples from MM patients were tested for ex vivo drug sensitivity. **Results:** This system successfully decomposed complex clinical questions into atomic sub-questions and generated appropriate database queries and software tool calls to retrieve relevant information across heterogeneous data sources. Independently, the system integrated clinical data—including physician notes, pathology reports, laboratory values and pharmacy records—to reconstruct longitudinal patient histories achieving 80% concordance with expert manual abstraction, while reducing case synthesis time from hours to minutes. Importantly, the system preserved transparency by explicitly exposing intermediate reasoning steps and highlighting missing or ambiguous data requiring clinician judgment. **Conclusions:** We propose a shift from generative AI toward structured, interpretable clinical reasoning systems. By emphasizing modularity, auditability, and human-in-the-loop design, we offer a scalable path toward trustworthy AI deployment in oncology. This framework supports precision medicine not by replacing clinical judgment, but by amplifying it—providing clinicians with transparent, reproducible, and context-aware decision support. Research Sponsor: None.

Identifying high-risk cytogenetic subgroups in multiple myeloma using large language artificial intelligence models.

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Background: The Revised International Staging System (R-ISS) is the clinical standard for risk stratification in multiple myeloma (MM) and is central to treatment selection and prognostication. However, the cytogenetic abnormalities on which the R-ISS is predicated are typically reported in unstructured formats within bone marrow biopsy reports and clinical notes. Despite the critical importance and relevance of obtaining cytogenetic abnormalities in MM, this information is often missing from large clinical databases, limiting their availability for large scale research and real-world analyses. Here, we created a large language model (LLM)-based algorithm to identify cytogenetic abnormalities from unstructured text and evaluated our model's adaptability by comparing its performance across definitions of high-risk abnormalities. **Methods:** We extracted oncology notes and pathology reports within 2 years of diagnosis from the EHR of adult patients with MM registered within the Department of Veterans Affairs (VA) Cancer Registry System between 2000 and 2024. Two physician reviewers iteratively annotated 1600-character snippets from these texts for abnormalities and their type (gain, deletion, translocation) plus normal cytogenetics. From these annotations we identified items with high-risk cytogenetic abnormalities per current guidelines (del(17p) in > 20% plasma cells; TP53 mutation; gain(1q) and/or del(1p32) plus t(4;14), t(14;16), or t(14;20); monoallelic del(1p32) plus gain(1q); biallelic del(1p32)) and previous guidelines (t(4;14), t(14;16), t(14;20), del TP53/17p, del(1p), gain(1q)). We used few-shot prompting with GPT-OSS 120B to extract cytogenetic results and validated our model on a test set of 985 snippets representing 773 patients at 98 VA centers. **Results:** The test set contained 81 snippets with normal cytogenetics and 464 with abnormalities; 58 were high-risk per current guidelines and 144 per previous guidelines. Our model successfully identified high-risk cytogenetics per current (P: 88.9%, R: 82.8%, F1: 85.7%) and previous guidelines (P: 86.7%, R: 90.3%, F1: 88.4%), as well as type of cytogenetic abnormality (weighted averages; P: 92.3%, R: 92.2%, F1: 92.4%), demonstrating its utility and flexibility for the task as standards change. Applied to a cohort of 7250 unlabeled notes, our model identified high-risk cytogenetics in 501 (6.9%) and any cytogenetic information in 5385 (74.3%). **Conclusions:** Our model demonstrated the successful capture of cytogenetic information across multiple definitions of high-risk cytogenetic abnormalities, providing a fast, adaptable framework for extraction that traditionally required repeated large-scale human efforts. Leveraging an LLM for this task enables scalable MM risk stratification while reducing clinician burden and supporting rapid adaptation to evolving cytogenetic risk definitions. Research Sponsor: VA Office of Research and Development.

RP2R dose selection of Tal + Tec for the treatment of EMD patients in the RedirecTT-1 study.

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Background: Talquetamab (Tal, anti-GPRC5D) and Teclistamab (Tec, anti-BCMA) are first-in-class bispecific antibodies approved as monotherapies for triple-class exposed relapsed/refractory multiple myeloma (RRMM). Extramedullary disease (EMD) is an aggressive MM subtype with poor outcomes and high unmet need. RedirecTT-1 (NCT04586426) is a Phase 1b/2 dose escalation/expansion study evaluating Tal + Tec in RRMM patients (pts) including EMD. We present data supporting selection of the recommended Phase 2 regimen (RP2R) for treatment of EMD pts, based on efficacy, safety, and exposure-response (E-R) analyses from Phase 1. Phase 2 allowed switching to a Q4W regimen after cycle 6 or cycle 4 if the response was $\geq$ VGPR. **Methods:** Phase 1 evaluated 6 dose regimens of Tal (0.2–0.4 mg/kg QW, 0.8 mg/kg Q2W, 0.8 mg/kg Q4W) + Tec (0.75–1.5 mg/kg QW, 1.5–3 mg/kg Q2W, 3 mg/kg Q4W). Responses were investigator-assessed per IMWG criteria. CRS and ICANS were graded by ASTCT criteria; all other adverse events were graded by CTCAE v5.0. Model-based E-R analyses for efficacy were conducted with reported efficacy endpoints (ORR, $\geq$ VGPR, $\geq$ CR). First cycle PK metrics (C_{avgC1} , $C_{troughC1}$) were used due to time-varying clearance of Tal and Tec. **Results:** At the clinical cutoff for this analysis (18 March 2025), Phase 1 enrolled 114 pts (38 EMD) with a median follow-up of 31.6 months. EMD pts treated with QW regimens of Tal 0.2–0.4 mg/kg + Tec 0.75–1.5 mg/kg (n=13), which comprised of multiple dose levels (1–9 pts per cohort), achieved an ORR of 33–100% ($\geq$ CR, 0–22.2%). EMD pts treated with the Q2W regimen using Tal 0.8 mg/kg and Tec 1.5 mg/kg (n=4) achieved an ORR of 50% ($\geq$ CR, 25%), while EMD pts treated with the Q2W regimen including Tal 0.8 mg/kg + Tec 3.0 mg/kg (RP2R, n=18) demonstrated high and deep response rates (ORR, 61.1%, $\geq$ CR, 44.4%) with a manageable safety profile. EMD pts treated with the Q4W regimen of Tal 0.8 mg/kg + Tec 3.0 mg/kg (n=3) achieved an ORR of 100%, where 2 achieved $\geq$ VGPR, but none achieved $\geq$ CR. The RP2R generally provided higher and deeper responses in EMD pts compared to non-RP2R regimens. The efficacy E-R analysis for EMD pts showed a positive E-R relationship between exposure (C_{avgC1} and $C_{troughC1}$) and $\geq$ CR. Pts with exposures above the median for both Tal and Tec showed higher CR rates. At RP2R, C_{avgC1} and C_{trC1} exceeded median exposures across all Phase 1 dose regimens for both antibodies. The overall safety profile of Tal + Tec at the RP2R was manageable and consistent with each agent as monotherapy, while enabling deeper and more durable responses than observed across non-RP2R regimens. **Conclusions:** The totality of efficacy, safety and E-R analyses support advancement of a Tal + Tec regimen for further clinical development in RRMM pts with EMD who have received a PI, an IMiD, and an anti-CD38 mAb, and offers flexibility of switching to Q4W for responders. Clinical trial information: NCT04586426. Research Sponsor: Johnson & Johnson.

An integrated population pharmacokinetic/pharmacodynamic (popPK/PD) model to select the linvoseltamab (LINVO) dosing regimen in patients with high-risk smoldering multiple myeloma (HR-SMM).

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Background: LINVO is a BCMA $\times$ CD3 bispecific antibody approved for triple-class exposed relapsed/refractory (RR) multiple myeloma (MM) after ≥ 3 therapies (EU) or ≥ 4 prior lines of therapy (USA). LINVO 200 mg was approved based on the deep and durable responses and manageable safety profile observed in the LINKER-MM1 study (objective response rate [ORR] 71%; NCT03761108). LINVO 200 mg demonstrated promising efficacy and a generally manageable safety profile as an early intervention in HR-SMM (ORR 100%; Phase [Ph] 2 LINKER-SMM1 NCT05955508; IMS 2025 OA-68) and as frontline therapy in newly diagnosed (ND) MM (ORR 86%; Ph 1/2 LINKER-MM4 NCT05828511; ASH 2025 #697). We present results from a semi-mechanistic popPK/PD model of LINVO integrating data from pts with RRMM, NDMM, and HR-SMM, to support full dose selection for a Ph 3 HR-SMM study. **Methods:** A popPK/PD model was developed from LINKER-MM1 RRMM data to predict LINVO concentration (conc) and disease burden dynamics (soluble BCMA, total [involved + uninvolved] free light chain [FLC] conc). Free LINVO conc was a strong predictor of ORR and progression-free survival in the LINKER-MM1 model. The model was updated with data from LINVO administration in pts with NDMM and HR-SMM. Based on baseline disease characteristics in pts with HR-SMM, the model was used to predict free and total LINVO conc for regimens with full doses of 50, 100, and 200 mg in a clinical trial simulation setting. The model assumed that T-cell-mediated tumor killing was dependent on free LINVO forming the T-cell + drug + MM cell complex. The variability in observed response rates across studies was presumed to arise due to differences in disease burden, MM plasma cell proliferation, and T-cell fitness, with the killing rate expected to be more similar between HR-SMM and NDMM than between HR-SMM and RRMM. **Results:** The dose regimen chosen for evaluation in a Ph 3 HR-SMM study comprised a 200 mg dose given weekly in cycle (C) 1 with the frequency decreasing to every 2 weeks after C1, every 4 weeks after C6, and every 8 weeks after C13. Following initial weekly dosing in this regimen, the free LINVO conc predicted in HR-SMM matched the free LINVO conc predicted in the higher efficacy arm of LINKER-MM4 and the higher efficacy arm in Ph 2 of LINKER-MM1. The model predicted that the 200 mg dose regimen would achieve deep responses (measured by substantial reduction in FLC conc) as rapidly as Week 8, and continue through Week 30, despite the reduced dosing frequency. **Conclusions:** The totality of evidence, including efficacy and safety data in pts with SMM, dose-ranging data (PK/PD, safety, and efficacy) in pts with NDMM and RRMM, and exploratory analyses integrating exposure and response markers across studies, supports selection of the less intensive LINVO 200 mg dose regimen (compared with NDMM and RRMM) in the Ph 3 HR-SMM study. Clinical trial information: NCT03761108; NCT05828511; NCT05955508. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Comparative efficacy of linvoseltamab versus teclistamab in triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM): Updated matching-adjusted indirect comparison (MAIC) with longer follow-up.

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Background: Linvoseltamab and teclistamab are anti-B-cell maturation antigen (BCMA)×CD3 bispecific antibodies evaluated in the LINKER-MM1 and MajesTEC-1 trials, respectively, and approved for TCE RRMM. In the absence of head-to-head trials, a previous MAIC assessed their relative efficacy at ~14-month median follow-up (mFU). We present updated results with longer follow-up for both trials. **Methods:** After excluding 10 patients (pts) with prior BCMA antibody–drug conjugate exposure from LINKER-MM1 to align with MajesTEC-1 eligibility, pt-level data from LINKER-MM1 (linvoseltamab 200 mg, N=107; data cut-off [DCO] July 2024; mFU 21.3 months) and aggregate data from MajesTEC-1 (N=165; DCO August 2023; mFU 30.4 months) were used. LINKER-MM1 pts were weighted to match MajesTEC-1 using pre-specified prognostic factors, as described previously (Lee et al., *Clin Lymphoma Myeloma Leuk* 2025;25:897–909). MAICs were rerun for objective response rate (ORR), very good partial response or better ($\geq$ VGPR) rate, complete response or better ($\geq$ CR) rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and time to next treatment (TTNT). Treatment effects were estimated using odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs). Restricted mean survival time (RMST) was evaluated at 30 months. **Results:** In both unadjusted comparisons and MAICs adjusted for 6 key prognostic factors (cytogenetic risk, age, refractory status, ISS stage, ECOG score, extramedullary disease/plasmacytoma status; effective sample size 82.5), linvoseltamab showed numerically higher ORR, $\geq$ VGPR, and $\geq$ CR rates and significantly longer DOR, PFS, OS, and TTNT vs teclistamab (Table). Compared with prior MAICs with shorter follow-up, adjusted HRs for DOR and TTNT further decreased in favor of linvoseltamab, while other results remained stable. **Conclusions:** With longer follow-up, linvoseltamab continued to demonstrate comparative efficacy advantages vs teclistamab, reinforcing its potential as an effective treatment option for TCE RRMM. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Outcome, linvoseltamab vs teclistamab	Unadjusted	Adjusted for 6 key prognostic factors
	OR (95% CI)	OR (95% CI)
ORR	1.44 (0.97–2.13)	1.50 (0.97–2.32)
$\geq$ VGPR	1.19 (0.83–1.72)	1.17 (0.79–1.74)
$\geq$ CR	1.29 (0.91–1.82)	1.21 (0.83–1.76)
	HR (95% CI); RMST difference, months (95% CI)	HR (95% CI); RMST difference, months (95% CI)
DOR	0.58 (0.36–0.96)*; 3.66 (0.77–6.55)*	0.54 (0.31–0.92)*; 4.06 (1.13–6.98)*
PFS	0.57 (0.40–0.82)*; 5.13 (2.01–8.25)*	0.55 (0.36–0.82)*; 5.43 (2.04–8.81)*
OS	0.68 (0.47–0.98)*; 2.99 (0.22–5.75)*	0.64 (0.43–0.97)*; 3.06 (0.08–6.04)*
TTNT	0.42 (0.28–0.62)*; 7.10 (4.27–9.94)*	0.41 (0.27–0.64)*; 7.12 (4.15–10.09)*

*p<0.05. OR >1, HR <1, or RMST >0 indicate better efficacy with linvoseltamab vs teclistamab.

Updated two-year overall survival and toxicity outcomes of BCMA CAR-T therapy compared with teclistamab in multiple myeloma.

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Background: B-cell maturation antigen (BCMA) targeted chimeric antigen receptor T-cell therapy (CAR-T) and bispecific antibodies have transformed the treatment landscape for relapsed or refractory multiple myeloma. In a prior real-world study, CAR-T therapy was associated with improved short-term overall survival compared with teclistamab; however, follow-up was limited to less than one year. Longer-term comparative outcomes between these modalities remain insufficiently characterized. This sequel study evaluates the updated two-year overall survival and toxicity outcomes. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, comprising data from over 70 healthcare institutions in the United States, to identify patients with multiple myeloma treated between 2021 and 2023 with either CAR-T therapy (ciltacabtagene autoleucel [cilta-cel] or idecabtagene vicleucel [ide-cel]) or teclistamab. Patients who received other bispecific antibodies, including elranatamab, talquetamab, or linvoseltamab, were excluded. Two mutually exclusive cohorts were defined: patients who received CAR-T therapy without prior or subsequent teclistamab and patients who received teclistamab without prior or subsequent CAR-T therapy. Propensity score matching was performed to balance baseline demographics, comorbidities, prior therapies, and laboratory values. HR and 95% CI were estimated using Cox proportional hazards models for two-year overall survival, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). **Results:** A total of 351 CAR-T cell therapy recipients and 507 teclistamab recipients were included. After propensity score matching, 227 patients were retained in each cohort, with well-balanced baseline characteristics, including demographics (mean age: 65 years, White: 74%, male: 53%), comorbidities, and prior multiple myeloma treatments, including immunomodulatory drugs, proteasome inhibitors, dexamethasone, and anti-CD38 antibodies. Mean follow-up durations were comparable between the CAR-T and teclistamab cohorts at 524 and 438 days, respectively. CAR-T therapy was associated with significantly improved two-year overall survival compared with teclistamab (HR: 0.61, 95% CI: 0.43–0.87, $p=0.005$). In contrast, CAR-T therapy was associated with higher risks of CRS (HR: 1.48, 95% CI: 1.12–1.96, $p=0.003$) and ICANS (HR: 2.02, 95% CI: 1.20–3.41, $p=0.007$). **Conclusions:** In this extended two-year real-world analysis, CAR-T therapy was associated with superior overall survival compared with teclistamab, albeit with increased immune-mediated toxicities. These findings build upon prior short-term data and underscore the need for prospective studies directly comparing BCMA-targeted treatment strategies across longer follow-up intervals. Research Sponsor: None.

Iberdomide (Iber) maintenance following upfront autologous stem cell transplant (ASCT) in multiple myeloma (MM).

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Background: Lenalidomide (Len) maintenance after ASCT has been a standard of care for patients (pts) with MM. Historically, ~30% of pts discontinue Len within 1 year (yr) due to toxicity and there is a need for more effective and better tolerated maintenance strategies. Iber is a potent, oral cereblon E3 ligase modulator under evaluation in the relapsed/refractory and newly diagnosed settings. We report the results of the primary analysis of a Phase II trial of Iber maintenance following upfront ASCT. **Methods:** Pts ≥ 19 yrs of age with MM, within 1-yr of initiation of induction therapy and in a $\geq$ partial response (PR) at day 80-110 post-ASCT, were accrued. Iber was administered 1.0 mg orally days 1-21 of a 28-day cycle, continued until progressive disease (PD) or toxicity. Up to 2 dose reductions (0.75 mg/day then 0.6 mg/day) were allowed. Growth factor support was not permitted. Minimal residual disease (MRD) assessment by flow cytometry (10^{-5}) was performed at registration, post-cycle 12 and post-cycle 24. An optimal Simon two-stage design with type I and II errors of 0.1 was chosen to test whether the proportion of pts who are progression-free and on treatment at 1 yr is $<60\%$ against the alternative of $\geq 80\%$. If ≥ 27 out of 38 pts were progression-free (by 2016 IMWG criteria) and on treatment at 1 yr, Iber would be considered to have promising activity. **Results:** 38 pts (55% males, median age 61 yrs (range: 41-77)) received Iber. R-ISS at diagnosis was stage I (34%), II (39%), III (8%) and unknown (18%), with 34% having high-risk disease per 2025 IMS/IMWG criteria. All pts received triplet or quadruplet induction therapy, with 97% receiving Len and 84% receiving daratumumab. At day 80-110 post-ASCT, all pts had $\geq$ very good PR, with 22 (58%) $\geq$ complete response (CR) and 33 (87%) MRD-negative (neg). The median number of administered treatment cycles is 18 (range: 1-45), with 18 (47%) pts having ≥ 1 dose reduction, most commonly due to neutropenia (n=12). The most common grade (gr) 3/4 adverse event was neutropenia (gr 3 (n=19), gr 4 (n=5)). Within yr 1, 29% (11/38) discontinued Iber due to neutropenia (n=5), rash (n=1), infection (n=1), pt choice (n=1), or PD (n=3). After 1 yr, 6 pts discontinued due to neutropenia (n=4) and PD (n=2). While on Iber, 19 pts had deepening of response to stringent CR and 3 pts converted from MRD-positive to MRD-neg. The post-cycle 12 and 24 MRD-neg rates are 85% (23/27) and 100% (14/14), respectively. **Conclusions:** Iber demonstrated promising activity with dose reductions/discontinuations mainly due to neutropenia. Strategies including lower starting dose, growth factor support and more flexible management of neutropenia may enable more pts to remain on treatment. Longer follow-up will permit evaluation of sustained MRD-negativity and PFS, but overall, these results provide rationale for further exploration of Iber-based post-ASCT maintenance strategies. Clinical trial information: NCT05177536. Research Sponsor: Bristol Myers Squibb.

Association between survival outcomes in patients with multiple myeloma and treatment facility volume.

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Background: Oncology research previously demonstrated a volume-outcome relationship, where patients treated at healthcare centers with higher (vs lower) treatment volumes have improved survival. In multiple myeloma (MM), evidence supporting this association remains limited. Most patients with MM are treated at lower volume centers; it is important to recognize and prioritize partnerships between higher and low-volume centers. **Methods:** Adults (≥ 18 years) receiving ≥ 1 active MM therapy—IMiD, PI, anti-CD38 mAb, CAR-T, ASCT—from 2017 – 2023 with ≥ 6 -month pre-index enrollment were identified in Komodo Health’s Healthcare Map. Patients lacking facility data or treated outside their diagnosing site were excluded. Facilities were segmented based on volume, defined as the average number of new patients with MM per year: ≤ 1 (very low), 1–5 (low), > 5 –10 (medium volume), > 10 (higher volume). Outcomes included overall survival (OS) and event-free survival (EFS), the latter separately defined as time to 1) therapy change and 2) first symptomatic progression (based on CRAB criteria). Multivariable mixed-effects Cox models were adjusted for diagnosis year, demographics, comorbidities, payer type and treatment exposure. Subgroup analysis of patients initiating 2L therapy was also conducted. **Results:** 18,646 MM patients and 2,049 facilities were identified. Volume distribution was highly skewed: 81.0% were treated at very low volume centers and ~1.9% were treated at higher volume centers. Higher volume centers had the highest use of ASCT (63.7%) and CAR-T (2.1%). Among all patients, use of IMiD-, PI-, and anti-CD38-based regimens were 51.42%, 63.55% and 35.69%, respectively. Although median OS was not reached for any of the segments, higher volume centers had the highest unadjusted median EFS using therapy-based (771 days) and CRAB-defined progression (213 days) definitions ($p < .001$ vs all other segments). After adjustment, lower-volume segments (very low, low and medium volume centers) had shorter median OS (HRs: 1.03–1.26, 95% CI 0.88–1.46) than higher volume centers. However, compared with higher volume centers, median EFS was similar in lower-volume segments (HRs: 0.97–1.09, 95% CI 0.86–1.23). Among 2L patients, OS models and CRAB-defined EFS showed similar volume-related patterns compared with adjusted overall results. **Conclusions:** Higher-volume centers had more experience with novel therapies and combination of therapies. Experience from high volume centers can effectively be used to partner with smaller volume centers to advance MM care and be able to improve outcomes for patients. Research Sponsor: Pfizer, Inc.

Adjusted EFS and OS hazard ratios by treatment facility segment.				
Facility Volume Segment	Change in Therapy EFS		OS	
	Overall	95% CI	Overall	95% CI
Higher volume	Ref	Ref	Ref	Ref
Medium volume	0.97	(0.86, 1.09)	1.03	(0.88, 1.21)
Low volume	1.03	(0.92, 1.16)	1.15	(0.99, 1.34)
Lower volume	1.09	(0.97, 1.23)	1.26	(1.09, 1.46)

Gaps in access to chimeric antigen receptor T-cell (CAR-T) therapy post leukapheresis: Waiting time and post-leukapheresis treatment patterns in relapsed/refractory multiple myeloma (RRMM)—Real-world evidence from U.S. claims.

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Background: B-cell maturation antigen (BCMA)-directed CAR-T therapy is a highly effective treatment with potential for long-term remission of RRMM with improved outcomes vs daratumumab-based regimens. CAR-T suitability may be limited by delays/manufacturing failure and changes in pt condition, financial situation, or access to specialized treatment centers. We characterized pts with RRMM who underwent leukapheresis to prepare for CAR-T and pt treatment waiting time, to understand the delays incurred prior to CAR-T infusion. **Methods:** A real-world study in the US using the PharMetrics Plus claims database (July 2020–September 2024) was performed. Eligible pts were aged ≥ 18 years with RRMM, had their first leukapheresis claim (index date) during the index period (March 2021–August 2024), were continuously enrolled in medical/pharmacy benefits for ≥ 180 days prior to and ≥ 30 days after index date, and were not clinical trial participants. Pt characteristics, rate of CAR-T receipt, and time to CAR-T receipt were assessed during the variable follow-up. **Results:** Overall, 337 pts who received leukapheresis were identified. Median (interquartile range) age was 62 (55–67) years, and 59.1% of pts were male. Mean National Cancer Institute (NCI) comorbidity index was 0.52. Most pts received care in the Midwest (31.8%) or Northeast (24.6%) regions. Most pts (95.9%) received leukapheresis in an outpatient setting. Median available follow-up time was 255 days (mean 337 days). During follow-up, 183 pts (54.3%) did not receive CAR-T after leukapheresis. Among pts who had ≥ 12 months of follow-up ($n=143$), the proportion of pts who did not receive CAR-T was similar at 53.1% ($n=76$). Among pts who received CAR-T during the follow-up ($n=154$; 45.7%), the median waiting time was 54.0 days (mean 56.7 days). The cohort of pts who did not receive CAR-T had a higher proportion of females (48.6%/31.8%), were more likely to have Medicaid (29.5%/7.8%), had higher NCI comorbidity index (scores 0.55/0.47), and most commonly received care in the Northeast (35.5%/11.7%) while pts who received CAR-T most commonly received care in the Midwest (23.0%/42.2%). The most common first classes of multiple myeloma medications after leukapheresis but prior to CAR-T infusion in pts who did/did not receive CAR-T were an alkylating agent (65.6%/36.1%), proteasome inhibitor (40.3%/30.6%), steroid (38.3%/39.3%), immunomodulatory drug (22.7%/27.3%), anti-CD38 (20.8%/20.8%), and stem cell transplant (0%/17.5%). **Conclusions:** Over half of pts receiving leukapheresis did not receive CAR-T infusion, highlighting a persistent gap between eligibility and treatment delivery. These data emphasize an urgent need for broadly accessible BCMA-targeted therapies that provide deep and durable responses. Research Sponsor: GSK.

Targeting cfDNA and NETs with DNase I to augment CAR T-cell function and antitumor efficacy.

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Background: Chimeric antigen receptor (CAR) T-cell therapy induces high initial response rates in B-cell malignancies; however, limited persistence and early relapse remain major clinical challenges. Accumulation of cell-free DNA (cfDNA) and neutrophil extracellular traps (NETs) within the tumor microenvironment represents a potential mechanism of CAR T-cell dysfunction through induction of exhaustion, immunosuppression and impaired expansion. We hypothesized that enzymatic degradation of extracellular DNA using DNase I could enhance CAR T-cell persistence and antitumor efficacy. **Methods:** The effects of cfDNA and NETs on human CD19 CAR T-cell function were evaluated using sequential killing assays, proliferation assays, and flow cytometry-based phenotyping. DNase I was assessed for its ability to reverse cfDNA/NET-mediated suppression and prevent exhaustion. In vivo efficacy, expansion, and persistence of CAR T cells were studied in xenogeneic B-cell acute lymphoblastic leukemia (Nalm-6) and Burkitt lymphoma (Raji) mouse models. Longitudinal in vivo tracking of CAR T-cell expansion was performed using bioluminescence imaging and serial peripheral blood analysis. Translational relevance was further explored through compassionate-use administration of DNase I in combination with CAR T-cell therapy in a pediatric patient with relapsed/refractory Burkitt lymphoma. **Results:** cfDNA and NETs suppressed CAR T-cell proliferation and cytotoxicity while promoting upregulation of exhaustion markers, including PD-1, LAG-3, and TIM-3. DNase I efficiently degraded extracellular DNA, preserved CAR T-cell effector function, improved CD8:CD4 ratios, and reduced exhaustion across multiple rounds of tumor rechallenge in vitro. In vivo, DNase I significantly enhanced CAR T-cell expansion and persistence following infusion, as demonstrated by longitudinal tracking studies. Combination therapy resulted in improved tumor control, delayed relapse upon rechallenge, and prolonged survival in both NALM-6 and Raji xenograft models. In a single pediatric patient with highly refractory Burkitt lymphoma, DNase I co-administration was associated with marked CAR T-cell expansion and progressive reduction in tumor burden after prior CAR T-cell failure. **Conclusions:** Extracellular DNA and NETs constitute a critical barrier to durable CAR T-cell efficacy. DNase I enhances CAR T-cell persistence and antitumor activity by eliminating cfDNA/NET-driven immunosuppression, supporting further clinical evaluation of DNase I as a combinatorial strategy to improve CAR T-cell therapy outcomes. Research Sponsor: None.

Evaluating the impact of a statewide intervention on multiple myeloma bispecific T-cell engaging antibody (BsAb) therapy uptake in Florida (FL).

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Background: BsAbs are highly effective, off-the-shelf T-cell engagers recently approved for relapsed/refractory multiple myeloma (MM) but remain underutilized in real-world settings. In partnership with the Florida Society of Clinical Oncology (FLASCO), a statewide initiative was launched to expand BsAb access through peer-led regional discussions focused on operational barriers, care transitions, and therapy management strategies. This study assessed the real-world impact of these interventions on BsAb utilization in FL. **Methods:** Multidisciplinary discussion forums were held in 4 FL metropolitan areas (Jan–Apr 2024). We conducted single and controlled interrupted time series (ITS) analyses using IQVIA eLAAD claims data (Apr 2023 – Sep 2025) including adult patients with a diagnosis of MM, evidence of claim activity, and provider state information. Fifth line or later (5L+) status was estimated as 3.3% of MM prevalence (Nikolaou et al.) BsAb utilization (% of MM 5L+ patients receiving a BsAb) was evaluated using segmented regression to estimate pre- and post-intervention trends, excluding the intervention period. We reported BsAb utilization by comparing FL with all other states, between community versus academic settings, and assessing the number of sites administering BsAb. **Results:** Before the intervention, BsAb utilization among MM 5L+ patients in FL rose from 8.2% (Apr 2023) to 11.2% (Dec 2023) (0.3 pp/mo; $p=0.23$), compared with a rise from 6.7% to 16.3% (1.3 pp/mo; $p<0.0001$) across all other states over the same time period. Post-intervention, BsAb utilization in FL increased from 22.8% (May 2024) to 35.9% (Sep 2025), reflecting a 7.0% immediate increase and 0.8 pp/mo sustained growth, exceeding the post-intervention trend observed across all other states (23.5% to 30.3%; 0.5 pp/mo). Overall, although pre-intervention BsAb utilization in FL was lower than all other states, FL demonstrated a 1.2 pp/month higher post-intervention utilization trend ($p<0.001$; Table). Post-intervention, FL community sites showed a 0.13 pp/mo higher BsAb utilization trend than academic sites, and the number of community sites administering BsAb increased from 5 to 9, with no change among academic sites. **Conclusions:** This study suggests that the FLASCO-led, collaborative model increased BsAb utilization in FL community oncology sites and offers a framework for broader community adoption across other states. Research Sponsor: Pfizer.

Parameter estimates from ITS model(s).						
	FL (%)		Other US States (%)		Difference CITS: FL - Other US States (%)	
		p-value		p-value		p-value
Intercept (Apr 2023)	8.6	<.0001	7.7	<.0001	0.9	0.52
Monthly change pre-intervention (Apr - Dec 2023)	0.3	0.23	1.3	<.0001	-0.9	0.002
Immediate change post-intervention (May 2024)	7	0.01	0.2	0.87	6.8	0.01
Monthly change post-intervention (May 2024 – Sep 2025)	0.8	<.0001	0.5	<.0001	1.2	0.0003

Immune effector cell–associated enterocolitis (IEC-EC) incidence and characterization in cilta-cel–treated patients with RRMM in CARTITUDE clinical studies.

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Background: Ciltacabtagene autoleucel (cilta-cel) shows benefit for patients (pts) with relapsed/refractory multiple myeloma (RRMM). A recently recognized uncommon adverse reaction, IEC-EC is characterized by severe/persistent diarrhea typically 1–3 months post CAR-T cell infusion. Here we summarize incidence and features of IEC-EC in clinical trials of cilta-cel for RRMM. **Methods:** 483 pts across RRMM studies (CARTITUDE-1, -2, -4, and CARTIFAN-1) were evaluated for evidence of IEC-EC. The clinical picture and nomenclature for IEC-EC were described in the real-world setting after infusion of most pts. As such, retrospective analysis was performed to identify cases consistent with IEC-EC, defined as prolonged (≥ 3 weeks) and severe ($\geq$ grade 3) diarrhea after cilta-cel infusion, without clear infectious etiology. Correlative biomarker analyses included peripheral CAR-T cell expansion/persistence, immune cell composition, and cytokines/inflammatory markers. Centralized pathomorphological review and immunohistochemical analysis of available biopsies was conducted. **Results:** Across RRMM studies, 6/483 (1.2%) pts demonstrated the clinical picture of IEC-EC, presenting 12–214 days after receiving cilta-cel (median onset 67 days post infusion). Best response was CR/SCR for all subjects. Pts received therapies including steroids (4/6). Four pts experienced symptom resolution within 123–227 days; 2 had persistent symptoms until death (causes: multiorgan failure and COVID19). Pts with IEC-EC had lower levels of B cells and higher levels of CAR+ T cells and inflammatory cytokines (eg, IL-6) at onset compared to a GI symptom-free control group at comparable time; while all cilta-cel–treated pts experienced B cell depletion, pts with IEC-EC had more prolonged deficiency. Histological analyses of GI biopsies from 5 pts with IEC-EC revealed plasma cells, normally present in the GI tract, were absent. CAR-T cells were detected and localized to the lamina propria and were not observed juxtaposed with epithelia, making it unlikely direct damage to epithelia was caused by CAR-T cells. Histologic damage was greater in the small intestine (predominantly duodenum) than the colon. **Conclusions:** Retrospective analysis of cilta-cel trials identified a low IEC-EC incidence (1.2%). Findings support a reactive mechanism involving plasma cell depletion and immune dysregulation rather than direct CAR-T cell cytotoxicity and highlight the importance of upper endoscopy to identify injury patterns in the small intestine that may be less pronounced in the colon. Although the pathophysiology is not fully defined, increased awareness and earlier diagnosis may improve understanding of management and enhance likelihood of IEC-EC reversibility. Research Sponsor: Johnson & Johnson; Legend Biotech USA Inc.

Influence of genomic and clinical high-risk features on outcomes after BCMA-directed bispecific antibody therapy in relapsed/refractory multiple myeloma.

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Background: The definition of high-risk (HR) multiple myeloma (MM) is broad and encompasses established molecular features such as gain(1q) and del(17p), and the presence of extramedullary disease (EMD), plasma cell leukemia (PCL), and focal lesions (FLs), particularly when located in the humeri and femora. While the prognostic relevance of these factors has been widely studied, most data were generated in the pre-T-cell-redirecting therapy era. Their role in patients treated with bispecific antibodies (bsAb) remains poorly defined. Here, we investigated the prognostic value of FL and other high-risk features in relapsed/refractory (RR) MM patients receiving BCMA-directed bsAb therapy. **Methods:** We included 152 RRMM patients (59% male) with a median age of 72 years at bsAb initiation, and a median of 5 (2–12) prior lines of therapy. All patients received at least one full cycle of BCMA targeting bsAb therapy. Functional imaging (PET and/or DWI) was performed within 3 months of bsAb initiation. HR status was defined according to the IMS/IMWG consensus. Progression free (PFS) and overall survival (OS) were estimated using Kaplan Meier analysis. To address the combined impact of prognostic factors, we calculated conditional inference trees. **Results:** Patients with FLs involving the appendicular skeleton (humeri/femora/ribs/shoulders, n=85) showed a trend toward shorter median PFS (20 months, p=0.061) and significantly shorter median OS (20 months, p=0.01), compared to patients without FLs (n=54) or with FLs confined to the spine and/or pelvis (n=13, median PFS and OS not reached [NR]). EMD and PCL were observed in 41 (27%) and 10 (7%) patients, respectively. Patients with PCL had the poorest outcomes, with both median PFS and OS <2 months. EMD was also strongly prognostic, with significantly shorter PFS (11 vs 28 months) and OS (17 months vs NR) compared to patients without EMD. Similarly, HR disease as defined by IMS/IMWG criteria was associated with worse outcomes (PFS 14 months, OS 19 months). Conditional inference tree analyses for PFS identified PCL, EMD and del(17p) as the most relevant prognostic variables. For OS, PCL again emerged as the strongest predictor, whereas EMD was only prognostic in the presence of gain(1q). Notably, gain(1q) also modified the impact of other clinical parameters: both a higher number of prior therapy lines (>5) and prior BCMA exposure were prognostic only in patients without gain(1q). **Conclusions:** Here, we show that EMD, PCL, and FLs of the appendicular skeleton are associated with inferior outcomes in RRMM patients treated with BCMA-directed bsAbs. Notably, the prognostic impact of these tumor growth patterns appears to be strongly influenced by the presence of genomic HR features, underscoring the central role of chromosomal aberrations as key modifiers of clinical risk even in the era of T-cell-redirecting immunotherapies. Research Sponsor: None.

Age-stratified late outcomes following bispecific antibody therapy in multiple myeloma: A real-world 6-month landmark analysis.

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Background: Multiple myeloma (MM) predominantly affects older adults, with a median age at diagnosis of 69 years. Underrepresentation of older adults in clinical trials of Bispecific antibodies (BsAbs) and limited statistical power preclude definitive conclusions about treatment outcomes in this demographic. Some real-world studies report comparable outcomes for BsAbs in older and frail patients, but these are small and heterogeneous. Consequently, limited data exist on the safety and efficacy of BsAbs in older MM patients, especially late outcomes. To address this gap, we conducted a retrospective study comparing the post-6-month outcomes of BsAbs in older adults (≥ 65 years) with those in younger patients. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. We identified MM patients (ICD-10-CM: C90) aged ≥ 18 years who received any BsAbs (teclistamab, elranatamab, talquetamab, blinatumomab, epcoritamab, mosunetuzumab), stratified by age into two cohorts: (1) age ≥ 65 years ($N = 1913$), and (2) age between 18 and 64 years ($N = 948$). The index event was date of initial administration of BsAbs. Outcomes were analysed within a time window starting 180 days after index event, and patients with outcomes outside the window were excluded. Compared outcomes using Kaplan-Meier survival analysis. Calculated hazard ratios (HRs) and log-rank p -values. **Results:** After propensity score matching (1:1), each cohort had 736 patients. Median age was 75 years (maximum age 90 years) in cohort 1 vs 57 years in cohort 2. Female (41.7% vs 43.2%), White (60.6% vs 58.6%), African American (22.6% vs 23.4%). All comorbidities and prior therapies, including stem cell transplant (35.2% vs 35.1%), ide-cel CAR-T (6.3% vs 6.7%), and cilta-cel CAR-T (1.4% vs 1.4%), were balanced between groups. Median follow-up was 305.5 days in cohort 1 and 316 days in cohort 2. All-cause mortality did not differ significantly between groups ($HR = 1.212$, $p = 0.229$). ER visits ($HR = 1.345$), neutropenia ($HR = 1.311$), thrombocytopenia ($HR = 1.559$), sepsis ($HR = 1.398$), pneumonia ($HR = 1.122$), and opportunistic infections ($HR = 1.119$) were slightly higher, in contrast, anemia ($HR = 0.841$), blood transfusion ($HR = 0.812$), and hypogammaglobulinemia ($HR = 0.927$) were lower in the older cohort but none were statistically significant ($p > 0.05$). **Conclusions:** In this large, real-world study, outcomes of BsAbs among patients aged ≥ 65 years were comparable to those of younger patients, without a significant increase in mortality or toxicities. Our findings, although retrospective, suggest that BsAbs can be safely administered in select patients aged ≥ 65 years, and advanced age should not, in itself, preclude treatment. Careful assessment and optimization of comorbidities and performance status could ensure that these patients benefit from effective treatments with minimal toxicity. Research Sponsor: None.

Ciltacabtagene autoleucel in lenalidomide-refractory multiple myeloma responding to bridging therapy: CARTITUDE-4 cytogenetic subgroup analysis.

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Background: CARTITUDE-4 (NCT04181827) showed significant overall (OS) and progression-free survival (PFS) benefits of ciltacabtagene autoleucel (cilta-cel) in patients with lenalidomide-refractory multiple myeloma (MM) after 1–3 lines of therapy. Emerging data underscore the importance of successful bridging therapy (BT); deeper responses (partial response or better, $\geq$ PR) during BT were associated with better survival and safety outcomes in patients treated with cilta-cel. Here, we present efficacy and safety in patients who received cilta-cel as study treatment with high- and standard-risk cytogenetics who responded to BT.

Methods: CARTITUDE-4 as-treated set comprised patients who received a single cilta-cel infusion as study treatment after apheresis, $\geq$ 1 BT cycle, and lymphodepletion. High-risk cytogenetics were defined as positivity for del(17)p, t(14;16), t(4;14) or gain/amp(1q); standard-risk patients were negative for these mutations. Responses to BT were assessed based on International Myeloma Working Group criteria. Efficacy and safety from as-treated patients with $\geq$ PR to BT were analyzed in high- and standard-risk cytogenetics subgroups. **Results:** Of 176 patients who received cilta-cel as study treatment (median follow-up, 33.6 months), 64 patients had high-risk cytogenetics and achieved $\geq$ PR to BT. In these patients, median PFS and OS were not reached; 30-month PFS and OS rates were 65.1% (95% CI, 51.4–75.8) and 87.2% (95% CI, 76.1–93.4), respectively. In 40 patients with standard-risk cytogenetics and $\geq$ PR to BT, median PFS and OS were not reached; 30-month PFS and OS rates were 85.0% (95% CI, 69.6–93.0) and 92.5% (95% CI, 78.5–97.5), respectively. Safety analysis included 64 patients with high-risk and 40 with standard-risk cytogenetics. In the high-risk subgroup, cytokine release syndrome was reported in 73.4% of patients, serious nonhematological adverse events in 64.1%, grade 3/4 infections in 43.8%, and immune effector cell-associated neurotoxicity syndrome in 7.8%. Corresponding rates in the standard-risk subgroup were 70.0%, 57.5%, 30.0%, and 0. Nonrelapse mortality (NRM) occurred in 9 patients (high-risk, 7; standard-risk, 2); there were 4 infection-related deaths in the high-risk population. No cases of immune effector cell (IEC)-parkinsonism were reported in high- and standard-risk subgroups. **Conclusions:** This analysis showed survival and response benefits of cilta-cel in patients with high- and standard-risk cytogenetics who had achieved $\geq$ PR to BT, with $>85\%$ of patients alive at 30 months. No patients had IEC-parkinsonism, and infections were a key cause of NRM. These data highlight the profound benefit that cilta-cel can provide to patients with high- and standard-risk cytogenetics when MM is well controlled at time of infusion. Clinical trial information: NCT04181827. Research Sponsor: Johnson & Johnson; Legend Biotech USA Inc.

CAR T-cell detection and clonality assessment in immune effector cell–associated enterocolitis following ciltacabtagene autoleucel.

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Background: Ciltacabtagene autoleucel (cilta-cel) is an FDA approved chimeric antigen receptor (CAR) T cell therapy for relapsed/refractory multiple myeloma (RRMM). Cilta-cel is associated with gastrointestinal (GI) toxicities including immune effector cell (IEC)-associated enterocolitis. The pathophysiology of IEC-associated enterocolitis is poorly understood and may represent a clonal CAR T cell lymphoproliferative disorder. **Methods:** Retrospective review of patients with RRMM treated with standard of care (SOC) cilta-cel at a single center between 07/21/2022–10/31/2025. Baseline characteristics, outcomes, and GI toxicities were collected. CAR transgene was detected via digital droplet polymerase chain reaction (ddPCR) in GI tissue and peripheral blood samples. CAR T cell clonality was assessed via T cell receptor (TCR) fragment analysis and TCR Beta Constant Region 1 (TRBC1) assessment via IHC or flow cytometry. **Results:** In total 201 patients were included of whom 20 (10%) exhibited GI toxicity. Diarrhea accounted for most cases (15/20). CAR T cells were detected in 5/20 (25%) GI biopsies (Table 1). A clonal CAR T-cell lymphoproliferative disorder affected predominantly the duodenum, evidenced by TRBC1-restricted CD4- or CD8-positive T cells in lamina propria. The cells were positive for CD3 and TCRalpha while negative for CD103 and TCRdelta. MUM1, CD138 and BCMA demonstrated absence of plasma cells in all samples. TCR fragment analysis identified clonal TCR rearrangements in 3/5 evaluable cases. The remaining 2 cases showed equivocal fragment analysis with prominent but subthreshold peaks, likely reflecting low tumor burden. Symptoms resolved in 13/15 patients without detectable CAR T cells compared to 1/5 patients with detectable CAR T cells. Of the remaining 4/5 patients, 2 died and 2 had ongoing symptoms at time of last follow-up. **Conclusions:** GI toxicity was observed in 10% of patients treated with cilta-cel. CAR T-cell infiltration, predominantly duodenal, was detected in 25% of symptomatic patients consistent with IEC-associated enterocolitis. TRBC1-restricted CAR T cell populations were detected in all cases supporting the presence of a clonal CAR T cell lymphoproliferative disorder. At the meeting we will present additional translational studies from GI and peripheral blood CAR T cells including whole genome sequencing, spectral flow cytometry, and single cell RNA sequencing. Research Sponsor: None.

Clinical and pathologic features of IEC-associated enterocolitis.

ID	Onset (Day)	Outcome	Site	CAR	ddPCR	TRBC1/CD3 IHC	TCR Fragment Analysis
1	60	Death	Duodenum	25.12%	NA	7.30%	Clonal
2	42	Ongoing	Duodenum, Jejunum	6.60%	1.30%	84.70%	Borderline clonal
3	169	Death	Duodenum	14%	0.25%	31.60%	Clonal
4	111	Ongoing	Duodenum, Antrum, Ileum, Colon	22.40%	1.32%	88.40%	Clonal
5	39	Resolved	Duodenum	1.70%	0.03%	26.20%	Borderline clonal

How long is long enough? Outcomes with finite-duration bispecific antibody therapy in multiple myeloma.

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Background: Bispecific antibodies (BsAbs) have shown unprecedented efficacy in relapsed/refractory multiple myeloma (RRMM), and finite-duration therapy is an increasingly common yet poorly studied strategy. We aimed to analyze outcomes in MM patients (pts) treated with finite-duration teclistamab (tec) or talquetamab (tal). **Methods:** This single-institution retrospective cohort study included pts treated with tec or tal monotherapy at UCSF from 7/2021 to 1/2025 for RRMM, excluding pts with prior BsAb exposure and pts receiving BsAbs as a bridge to CAR-T. Patient-, disease-, and treatment-related characteristics were collected and summarized descriptively. To assess the impact of treatment duration while mitigating immortal time bias, we conducted 6- and 9-month landmark analyses of PFS, comparing pts who discontinued treatment before the landmark with pts still on treatment. Patients with PD or death before the landmark were excluded. Multivariate analyses (MVA) of survival outcomes used Cox regression with the following covariates: age, IMS-IMWG risk, ISS stage, extramedullary disease (EMD), ECOG score, and prior BCMA exposure. **Results:** In total, 120 consecutive pts were included with median follow-up 13.7 mos. Forty stopped therapy early for reasons other than PD (finite) and 80 did not (non-finite). Among finite pts, median treatment duration was 4.7 mos (range 0.2–32.4), 24 stopped due to toxicity, and 16 due to sustained remission. Clinical characteristics including age, ISS, IMS-IMWG risk, and ECOG were balanced between groups, but finite pts had less EMD (7.5% vs 25.0%, $p=0.03$) and triple-class refractory status (52.5% vs 73.8%, $p=0.03$) than non-finite pts. ORR was 97.5% (60% CR+) and 73.4% (29.1% CR+) in finite and non-finite pts, respectively. For finite, non-finite, and all pts, respectively, median PFS was not reached (NR) with 24-mo PFS 63%, 7.9 mos, and 16.53 mos, while median OS was NR, 24.8 mos, and NR. For landmark analysis of patients alive and progression-free at 6 mos, 22 were off therapy and 55 pts remained on therapy at 6 mos and median PFS was NR and 29.5 mos, respectively (univariate regression HR 0.71 [0.32–1.57], $p=0.4$). On MVA, the hazard ratio also favored the on-therapy group (HR 0.51 [0.21–1.22], $p=0.13$). At the 9-month landmark, 20 pts were off therapy and 42 pts were on, with univariate regression HR 1.71 (0.58–5.11, $p=0.3$) and MVA HR 1.1 (0.32–3.76, $p=0.87$). **Conclusions:** Finite-duration BsAb therapy was associated with durable responses in selected patients, although this group had more favorable baseline disease characteristics. In adjusted landmark analyses, early discontinuation before 6 months was associated with numerically shorter PFS without statistical significance, while PFS was comparable at the 9-month landmark. Randomized-controlled trials are required to define optimal treatment duration. Research Sponsor: None.

Clinical outcomes following CAR T-cell therapy in relapsed or refractory multiple myeloma patients with baseline renal dysfunction: A TriNetX analysis.

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Background: Renal dysfunction is common in relapsed or refractory multiple myeloma (RRMM) and has historically limited eligibility for chimeric antigen receptor T-cell (CAR-T) therapy. However, real world data evaluating early complications and long-term outcomes in this population remains limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, including adult RRMM patients treated with idecabtagene vicleucel or ciltacabtagene autoleucel. Patients with baseline renal dysfunction (creatinine ≥ 2.0 mg/dl, not on dialysis) were compared with those with preserved renal function (creatinine ≤ 1.0 mg/dl) after propensity matching. Early post-CAR-T complications: cytokine release syndrome (CRS) and disseminated intravascular coagulation (DIC) were assessed from day 0 to 15 post CAR-T therapy. Mortality was evaluated at 6 months, 1 year and 3 years. A secondary exploratory analysis assessed renal recovery at 90 days in patients with renal dysfunction following CART-cell infusion using creatinine based (≤ 1.9 mg/dl) and eGFR based (≥ 50 mL/min/1.73 m²) definitions. **Results:** 84/777 (10.8%) RRMM patients who received CAR T-cell therapy had baseline renal dysfunction. After propensity matching, 79 patients were included in each cohort, demographics in Table 1. 0–15 day CRS incidence was similar in patients with and without renal dysfunction (36.5% vs 33.3%), and no patients developed DIC or required dialysis at any point of time. Mortality was significantly higher in patients with renal dysfunction at 6 months (40% vs 13.2%), 1 year (45.3% vs 15.8%), and 3 years (52% vs 21.1%). Among patients with baseline renal dysfunction and available 90 day follow-up (61/79); renal recovery occurred in 48/61 (78.7%) by creatinine and in 38/61 (62.3%) by eGFR criteria. **Conclusions:** Baseline renal dysfunction was not associated with increased CRS incidence or progression of renal disease needing dialysis but was associated with higher long-term mortality, likely reflecting greater myeloma burden. Most patients with baseline renal dysfunction demonstrated renal recovery within 90 days, though they remain underrepresented among CAR-T recipients, highlighting a potential treatment gap. Research Sponsor: None.

Baseline characteristics of both cohorts.

Demographic parameter	Baseline renal dysfunction cohort, N=79(n, %)	Preserved renal dysfunction cohort, N=79, (n, %)
Race		
White	54 (68.4%)	58 (73.4%)
Black or African American	14 (17.7%)	15 (19%)
Sex		
Female	26 (32.9%)	26 (32.9%)
Male	53 (67.1%)	53 (67.1%)
Lab Parameters	Baseline renal dysfunction cohort, Mean $\pm$ SD	Preserved renal dysfunction cohort, Mean $\pm$ SD
Hemoglobin	9.5 $\pm$ 1.7	10.3 $\pm$ 2.2
Hematocrit	28.4 $\pm$ 5.0	31.0 $\pm$ 6.4
Urea Nitrogen	27.2 $\pm$ 13.1	14.6 $\pm$ 5.5
Bicarbonate	21.8 $\pm$ 3.7	24.6 $\pm$ 3.1
Ferritin	1587.7 $\pm$ 3073.6	628.8 $\pm$ 1099.9

Expansion of a highly activated (HLA-DR+/CD38+) CAR T cell population after mezigdomide exposure post–idecabtagene vicleucel infusion in relapsed multiple myeloma.

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Background: Herein, we report CAR T subsets from peripheral blood (PB) mononuclear cell (PBMC) samples from the NCT06048250 Phase 1 trial of mezigdomide (mezi) post idecabtagene vicleucel (ide-cel) in patients with RRMM. Prior studies used PCR for CAR T quantification but have not directly immunoprofiled CAR T. Additionally, we identified a highly activated CAR T cell subpopulation with HLA-DR and CD38 expression. These HLA-DR+/CD38+ T cells correlate with inflammation and disease activity in HLH and viral infections but have not been characterized in CAR T. **Methods:** Mezi was given orally on 21/28 day cycles after ide-cel infusion until disease progression, intolerance, or 12 cycles, whichever comes first. Immunoprofiling of PBMCs were performed at baseline (within two weeks prior to mezi start day of cycle 1 day 1 [C1D1]), C1D8 (early), and cycle 3 day 1 (C3D1; late) using Cytex Aurora spectral flow cytometry with 29-markers in 6 patients (3 in the DL-1 cohort receiving 0.3 mg and 3 in the DL-2 cohort receiving 0.6 mg). Changes in cell populations were measured as frequencies. The parent population was CD3+ BCMA CAR T+ cell for CAR T subsets, CD8+ T cells for CD8 subsets, CD3+ cells for the remainder of the T cell subsets, CD3- CD19+ cells for the B cell subsets, CD3- CD19-CD33+ for the monocyte subsets, and CD3- CD19-CD56+ for the NK cell subsets. Comparisons between groups were assessed using the Wilcoxon test. Mezi was started between D+60 to D+120 post ide-cel. Herein, we report the early translational data for this cohort. **Results:** As of 12/29/25, we enrolled 7 patients: 6 patients had evaluable PB immunoprofiling data. Median age was 81 years old (range: 38–85 years) and a median 5 prior lines of therapy (range 4–7). The median time from CAR T to mezi C1D1 was 108 days (range: 48–112). There was a trend towards increased BCMA CAR T cells at C1D8 ($P=0.22$) and increased BCMA CAR T % was associated with ^{3} CR ($P=0.04$). Early increases in HLA-DR+/CD38+ T cells ($P=0.03$) and HLA-DR+/CD38+ CAR T cells ($P=0.02$), CD8+ effector memory cells ($P=0.03$), BTLA+ T cells ($P=0.03$), CTLA-4+ T cells ($P=0.02$), monocytes (parent: PBMCs; $P=0.04$; higher in the DL-2 cohort, $P=0.03$), and activated B cells ($P=0.04$) compared to baseline were noted. Early decreases in CD8+ TEMRA ($P=0.02$), TIGIT+ T cells ($P=0.04$), monocyte-myeloid-derived suppressor cells (M-MDSCs; $P=0.02$), total B cells ($P<0.05$), memory B cells ($P<0.05$), and naïve B cells ($P<0.05$) were noted. The DL-2 cohort had higher increases in helper T cells ($P=0.007$) and CD4:CD8 ratio ($P=0.03$) at C1D8. **Conclusions:** Preliminary results show that mezi induced a decrease in suppressive cells, a shift in T- cells from exhausted to activated phenotype, and expansion of highly activated HLA-DR+/CD38+ CAR T cells. Future studies should investigate whether it is correlated with efficacy. FP and MJ contributed equally to this work. Clinical trial information: NCT06048250. Research Sponsor: Bristol-Myers Squibb; American Society of Clinical Oncology and Conquer Cancer; 2024YIA-1400257601.

CAR-T in the older adults: Real-world survival and toxicity in patients ≥ 75 years with relapsed/refractory multiple myeloma.

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Background: CAR-T cell therapy targeting BCMA has transformed the treatment landscape for relapsed/refractory multiple myeloma (RRMM). However, pivotal clinical trials have limited representation of patients aged ≥ 75 years, leaving the safety and effectiveness of CAR-T therapy in this older population undercharacterized. In this study, we sought to evaluate the real-world outcomes of CAR-T therapy in patients aged ≥ 75 years with RRMM. **Methods:** A retrospective cohort study was conducted using the TriNetX database, which includes data from a large network of healthcare institutions in the US. Adult patients with RRMM who received CAR-T therapy were identified and stratified into two age based cohorts: ≥ 75 years and < 75 years. Propensity score matching (1:1) was performed based on race, gender, comorbidities, and high risk cytogenetics if available. Outcomes included incidence of immune effector cell-associated neurotoxicity syndrome (ICANS), cytokine release syndrome (CRS), tocilizumab (Toci) use, sepsis, 30-day intensive care unit (ICU) admission rates, 90-day mortality rate, and 1 and 3-year overall survival (OS). Cox proportional hazards multivariate analysis was used to assess the impact of age on OS, controlling for confounders. **Results:** A total of 1,392 patients met study criteria, of which 198 patients were aged ≥ 75 yrs at the time of infusion. The mean age was 62.6 vs. 77.5 yrs in the younger and older cohort, respectively. Prior to propensity score matching (PSM), there were no significant differences in the rates of CRS, ICANS, Toci, sepsis, or 30-day ICU admissions rate post-infusion. Grade 3 or higher CRS/ICANS were infrequent in both cohorts. Additionally, the 90-day mortality rate did not differ significantly between the older and younger cohorts. Following PSM, these findings remained consistent (Table 1). While there was no significant difference in 1-year OS, the 3-year OS was lower in the ≥ 75 cohort (69% vs. 55.4%, log rank $p=0.51$), although the difference was not statistically significant. Cox proportional hazards multivariate analysis, controlling for race, gender, and comorbidities, revealed that age ≥ 75 was not independently associated with OS (hazard ratio [HR] = 1.04, 95%CI 0.65-1.65, $p = 0.87$). **Conclusions:** In this real-world cohort of RRMM patients receiving CAR-T therapy, age ≥ 75 years was not associated with differences in risks of CRS, ICANS, sepsis, 90-day mortality, or 1-year overall survival. While 3-year overall survival was lower in patients ≥ 75 years, possibly due to competing mortality risks, these findings overall suggest that age alone should not preclude BCMA-directed CAR T-cell therapy in select older patients. Research Sponsor: None.

Outcome	<75 years (n=197)	≥ 75 yrs (n=197)	p-value
CRS	53%	46%	0.27
ICANS	12%	8%	0.22
TOCI use	53%	51%	0.82
ICU admission	3.8%	5.1%	0.39
Sepsis	6%	7.9%	0.36
90 day mortality	3.9%	5%	0.28
1-yr OS	86.2%	86.6%	0.86
3-yr OS	69%	55.4%	0.51

Dynamic changes in immune checkpoint and cell populations following lymphodepletion and CAR-T therapy in hematologic malignancies.

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy has significantly improved outcomes in relapsed and refractory hematologic malignancies; however, durable remissions remain limited in patients with high-risk features, including early progression to ≥ 2 extra-nodal sites, high tumor burden, and elevated serum lactate dehydrogenase. Proposed mechanisms of resistance include CAR-T cell exhaustion, impaired expansion and cytotoxicity, antigen loss or downregulation, and inadequate tumor infiltration. In addition, immunosuppressive interactions among myeloid-derived suppressor cells (MDSCs), regulatory T cells, tumor-associated macrophages, and inhibitory immune checkpoints such as PD-1, PD-L1, LAG-3, TIM-3, and VISTA may further limit CAR-T efficacy. Lymphodepleting chemotherapy alters immune homeostasis by affecting T-, B-, and NK-cell populations, modulating co-stimulatory signaling, reducing regulatory populations, and reshaping cytokine networks, influencing both response and toxicity. **Methods:** We conducted a pilot study ($n = 10$) to characterize peripheral immune alterations in patients receiving lymphodepleting chemotherapy followed by CAR-T therapy. Serial peripheral blood samples were collected at pre-defined time points before and after lymphodepletion and CAR-T infusion (D -5, D0 and D28+/-2). Flow cytometry was used to quantify immune cell subsets and evaluate immune checkpoint expression, including PD-1, PD-L1, LAG-3, and VISTA. **Results:** Lymphodepleting chemotherapy resulted in a marked reduction in T cells, B cells, and MDSCs. By D28, most immune populations recovered to pre-lymphodepletion levels; however, granulocytic MDSCs remained relatively suppressed. Preliminary molecular analyses demonstrated trends in both VISTA and LAG-3 expressions on T cells in multiple myeloma patients following lymphodepletion, without significant changes in overall circulating immune cell frequencies. Among patients who experienced disease recurrence ($n = 3$), a trend toward decreased CD45⁺CD3⁺ and CD45⁺CD4⁺ T-cell frequencies on D28 compared with D0 was observed relative to patients achieving complete remission ($n = 7$). **Conclusions:** These preliminary data suggest that lymphodepleting chemotherapy and CAR-T therapy induce dynamic peripheral immune remodeling, including sustained suppression of select myeloid populations and differential immune checkpoint expression. Interpretation is limited by the small sample size and pilot nature of the study. Nonetheless, observed trends in post-infusion T-cell dynamics associated with disease recurrence support further investigation. Larger, longitudinal studies are needed to validate these findings, elucidate mechanisms of resistance, and identify immune biomarkers predictive of response, toxicity, and durable remission following CAR-T therapy. Research Sponsor: None.

Impact of prophylactic cyclophosphamide on ALC and delayed neurotoxicity after cilta-cel.

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Background: Delayed neurotoxicity (DNT) after ciltacabtagene autoleucel (cilta-cel) is associated with severe morbidity and mortality occurring in 10–15% of patients. A high post-infusion peak absolute lymphocyte count (ALC_{peak} $\geq 3 \times 10^9/L$; ALC^{hi}) is correlated with an increased risk of DNT (25–30%). We previously examined prophylactic dexamethasone (PPX DEX) administered for 3 days when ALC^{hi} was reached and found no reduction in ALC expansion, DNT incidence or severity. Here, we report the use of prophylactic cyclophosphamide (PPX CTX) on ALC kinetics and DNT. **Methods:** We conducted a retrospective analysis of patients (pts) treated with cilta-cel at Mayo Clinic (09–12/2025; n = 60). Pts with ALC^{hi} received CTX 500 mg IV/PO once (n = 22). Outcomes and ALC kinetics including ALC_{peak}, ALC D28 (ALC_{D28}), and area under the curve D1–D28 (ALC_{AUC}) were compared with PPX DEX cohort (12/2024–08/2025; n = 50) and a historical cohort without PPX (04/2022–11/2024; n = 116). **Results:** Pre-lymphodepletion (LD) demographics were similar across historical ALC^{hi}, PPX DEX, and PPX CTX groups. Pre-LD CRP was higher in the historical ALC^{hi} cohort; however, baseline ferritin, CRS, and ICANS, and disease burden did not differ significantly between groups. There were no statistically significant differences in time to ALC_{peak} or ALC kinetics among the 3 cohorts. Among pts with ALC $< 3 \times 10^9/L$ treated during the PPX CTX study period, 2 developed cranial nerve palsy (IEC–CNP; 2/38, 5%). Both presented with unilateral facial nerve palsy and were treated with corticosteroids. One pt resolved symptoms by one month, while the second had persistent symptoms at 2 weeks and remains on follow-up. Among ALC^{hi} patients in the PPX CTX cohort, DNT occurred in 4/22 pts (18%), including 1 case of IEC–CNP (5%) and 3 with parkinsonism (IEC–PKS, 14%). Within the PPX CTX cohort, baseline characteristics and post-infusion CRS or laboratory parameters did not differ between patients with and without DNT. Among patients who developed DNT, ALC kinetics were similar across PPX CTX, PPX DEX, and historical cohorts. PPX CTX was well tolerated, with 2 cases of grade 1 nausea reported. The incidence of DNT did not differ significantly between the PPX DEX (14/61, 23%) and PPX CTX (4/22, 18%) cohorts. However, DNT presentations in the PPX CTX cohort appeared milder and were responsive to treatment. Two of three patients (67%) presented with mild symptoms (one with dynamic dysphasia; second with flat affect) that responded to DEX. A third patient presented with typical parkinsonian features (hypomimia, bradykinesia, rigidity) and demonstrated clinical improvement following high-dose CTX. **Conclusions:** PPX CTX was well tolerated. While it did not significantly impact ALC expansion kinetics or DNT rates, first few cases of IEC–PKS suggest that the presentation may be milder and amenable to less toxic treatment. Larger cohorts are needed to refine optimal prophylactic strategies. Research Sponsor: None.

Efficacy and hematopoietic recovery of high-dose melphalan with stem cell rescue as bridging to CAR-T compared with non-intensive bridging in relapsed/refractory multiple myeloma.

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Background: Bridging therapy is required for disease control in relapsed/refractory multiple myeloma (RRMM) patients awaiting CAR-T. Recent data suggest intensive cytotoxic bridging impairs post-CAR-T hematopoietic recovery. We compared melphalan-based therapy with stem cell rescue (MBT) versus talquetamab (T), a GPRC5D-directed bispecific antibody. **Methods:** We performed a retrospective single-center study of RRMM patients bridged with MBT or T prior to CAR-T (June 2021–December 2024) post apheresis. Cytopenias were graded per CTCAE v5.0 during early (within 30 days of CAR-T) and late (beyond 30 days of CAR-T) periods. Kaplan Meier analysis was performed to evaluate survival outcomes. **Results:** Of 242 CAR-T recipients, 34 received bridging either with T (n = 21, 62%) or MBT (n = 13, 38%). MBT patients were younger (61.9 vs 67.2 years; $P = 0.08$); high-risk cytogenetics by FISH were similar (92% vs 85%; $P = 0.58$). Bridging response rates were comparable (92% vs 82%; $P = 0.36$). At 20 months, 64% MBT and 58.7% T patients remained progression-free. Early grade 3–4 neutropenia for MBT vs T: 92% vs 95% ($P = 0.37$); late: 46% vs 33% ($P = 0.84$). Early grade 3–4 thrombocytopenia MBT vs T: 31% vs 24% ($P = 0.28$); late: 15% vs 14% ($P = 0.40$). Early grade 3 anemia MBT vs T: 69% vs 38% ($P = 0.18$); late grade 3–4: 17% vs 10% ($P = 0.35$). Median recovery times (MBT vs T): ANC 10 vs 5 days early ($P = 0.28$), 19 vs 17 days late ($P = 0.11$); platelets 7 vs 7.5 days early ($P = 0.30$), 12 vs 49 days late ($P = 0.20$); hemoglobin 13.5 vs 9 days early ($P = 0.49$), 35 vs 93 days late ($P = 0.65$). CRS rates were comparable: 53.8% vs 63.6% ($P = 0.57$). ICANS occurred only in the T cohort (13.6%) ($p = 0.08$). **Conclusions:** MBT yielded hematopoietic recovery, toxicity, and outcomes comparable to bispecific antibody bridging. These findings contrast with prior studies showing impaired recovery after intensive cytotoxic bridging, likely because stem cell rescue improves hematopoietic reserve. Prospective studies are warranted. Research Sponsor: None.

Racial disparities in utilization of bispecific T-cell engager therapy for relapsed/refractory multiple myeloma: A TriNetX study.

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Background: There have been remarkable advancements in the treatment of multiple myeloma over the past few decades. With the advent of cell redirecting immunotherapies, such as bispecific T-cell engagers (BiTEs), we have significantly improved rates of progression-free survival. As a result, physicians now prefer early utilization of these therapies in Relapsed/Refractory Multiple Myeloma (RRMM) due to their efficacy. This study aims to investigate the utilization and clinical outcomes of bispecific therapy based on race using a real-world database. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, including adult patients (≥ 18 years) with RRMM treated with teclistamab, talquetamab, elranatamab, or linvoseltamab. Outcomes were assessed from 30 days to 5 years following the index diagnosis of RRMM. Propensity score matching (1:1) was performed to balance demographics, comorbidities, prior therapies, transplant status, medications, and laboratory parameters. Kaplan–Meier analyses were used to assess overall survival. Outcomes included hospitalization, overall survival, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) rates. **Results:** A total of 25,225 patients with RRMM were identified. 67.3% were White, 19.5% were Black, and the remainder were classified as other races, including Asian or unknown. Among 1,889 patients treated with bispecific antibodies, 1,256 (66.5%) were White and 403 (21.3%) were Black patients. The median follow-up was 854 days for White patients and 785 days for Black patients. In the unadjusted analysis, mortality was similar between Black and White patients (21.7% vs 23.7%, $p = 0.43$), with no difference in overall survival (HR 0.98; log-rank $p = 0.88$). Hospitalization rates (34.6% vs 39.0%), CRS and ICANS were comparable. After propensity score matching, outcomes remained consistent. Mortality was numerically lower among Black patients (20.3% vs 25.4%), though not statistically significant ($p = 0.11$). Hospitalization, CRS and ICANS did not differ significantly between cohorts. **Conclusions:** Our findings showed no significant difference in mortality or five-year survival probability between Black and White patients. The incidence of multiple myeloma is more than twice as high among Black vs. White people (14 vs. 6.1 per 100,000). Despite this, White patients are disproportionately more likely to receive BiTE therapy than Black patients. This highlights the impact that lack of access has on myeloma outcomes for Black patients, likely driven by systemic inequities such as socioeconomic status, geographic barriers to access therapy, the requirement of a full-time caregiver and lack of knowledge about newer therapies available. Future efforts should focus on expanding access to BiTE therapy to promote equitable care for Black patients. Research Sponsor: None.

cfDNA WGS vs plasma proteomics for minimally invasive MRD assessment in multiple myeloma.

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Background: MRD assessment informs relapse risk in MM but is typically bone marrow-based and invasive. We therefore compared two minimally invasive MRD assays: BM-informed cfDNA whole-genome sequencing (cfWGS) and plasma proteomic MRD (EasyM). **Methods:** 71 longitudinal plasma samples (22 diagnosis, 49 follow-up) from 22 newly diagnosed MM patients across 8 Canadian sites (TFRIM4) had paired cfWGS and EasyM (Rapid Novor Inc). cfWGS MRD used patient-specific mutation lists from diagnostic BM WGS (Abelman et al., medRxiv 2025). EasyM used mass spectrometry to quantify residual M-protein from baseline. The primary endpoint was progression-free survival (PFS). **Results:** Among 22 MM patients (8 male, 14 female; median age at diagnosis 62 years), 8 progressed at a median follow-up of 52.6 months (range: 10–79 months). At 1-year maintenance (n = 18 available), cfWGS MRD+ (6/18) predicted inferior PFS (HR 20.12, 95% CI 2.23–181.60, p = 0.007). EasyM any-detect positivity was frequent (16/18, reflecting delayed clearance) and not prognostic (p = 0.99), with poor agreement vs cfWGS (44.4%, κ = 0.118). An exploratory EasyM clearance threshold of 0.93% (hypothesis-generating) classified 5/18 patients as MRD+ and stratified PFS (HR 8.78, 95% CI 1.55–49.82, p = 0.004), improving agreement with cfWGS (17/18, 94.4%, κ = 0.870). Progression clustered in cfWGS+/EasyM-high patients (EasyM >0.93%; 4/5; median 11.9 months post-collection [1.9–22.8]) and occurred once in cfWGS-/EasyM-low patients (1/12, 27.6 months). The only discordant case (cfWGS+/EasyM-) progressed 8.7 months after collection. Higher quantitative MRD burden was associated with inferior PFS (cfWGS: HR 2.92 per 1 SD, 95% CI 1.29–6.59, p = 0.01; EasyM: HR 5.48 per 1 SD, 95% CI 0.79–37.90, p = 0.085). At ~100 days post-autologous stem cell transplantation (ASCT; n = 16 available), EasyM was uniformly MRD+ (16/16) while cfWGS was MRD+ in 7/16 patients. Applying an EasyM clearance threshold (2.13%; 9 cleared vs 7 residual) improved agreement with cfWGS (14/16; 87.5%; κ = 0.746). Of two discordant cases, one cfWGS+/EasyM-cleared patient relapsed 38.6 months post-collection and one cfWGS-/EasyM-residual patient remained progression-free at last follow-up. At post-ASCT, both assays showed consistent but underpowered associations with PFS (cfWGS HR 6.32, 95% CI 0.70–56.76, p = 0.100; EasyM-clearance HR 2.36, 95% CI 0.39–14.18, p = 0.335). Across all post-treatment samples (n = 49), continuous cfWGS burden correlated with EasyM residual M-protein (ρ = 0.535, p < 0.001). **Conclusions:** BM-informed cfWGS MRD strongly stratified PFS, whereas EasyM required a clearance definition due to near-universal early positivity. Concordant plasma burdens support complementary MRD information. Future work will validate these findings in larger cohorts and quantify the incremental value of combined cfWGS and proteomic MRD for early relapse prediction. Research Sponsor: Terry Fox Research Institute; Paula and Rodger Riney Foundation.

Current threshold of measurable disease in AL amyloidosis clinical trials.

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Background: Eligibility for clinical trials in AL amyloidosis requires measurable disease to ensure that the hematologic response can be adequately assessed, usually set at 5mg/dL. However, there are validated response criteria in low burden disease (dFLC 2–5mg/dL) that correlate with clinical outcomes in the upfront setting (Milani, 2017). Despite validated criteria in low burden disease, most trials maintain a dFLC of 5mg/dL as measurable disease. Shorter survival is seen in patients with high-risk dFLC progression, defined as dFLC >2mg/dL, >20% of baseline value and >50% increase from nadir (Palladini, 2018). Patients with organ progression also have poor outcomes. We examined patients who were excluded from clinical trials to determine if the current measurable disease criteria adequately capture patients who require salvage therapy. **Methods:** We reviewed patients screened for three clinical trials enrolling patients with relapsed/refractory AL amyloidosis: phase I/II trial of carfilzomib (NCT01789242), phase III trial of ixazomib/dexamethasone versus physician's choice (NCT01659658) and phase I trial of etentamig (NCT06158854) to identify patients who failed screening. All clinical trials required measurable disease, defined as dFLC at least 5mg/dL. High-risk dFLC progression (Palladini, 2018) and organ progression (Palladini, 2012/2014) were evaluated at the time of screen failure. **Results:** Among 47 patients screened, 14 (30%) were enrolled: 7 for carfilzomib, 6 on the ixazomib trial, 1 for etentamig (Figure 1). Of 33 excluded patients, 18 (54%) were due to dFLC < 5mg/dL. Among 18 patients excluded due to insufficient dFLC at the time of screening, 6 met criteria for organ progression (cardiac (n=4), renal (n=2)), 6 had high-risk dFLC progression (as defined in background) and 2 had both (Table 1), indicating 10 patients were at high risk of poor outcomes. Four patients were lost to follow-up within 6 months of screening. In the remaining 14 patients, 5 received alternative commercially available therapy within 6 months of screening, 5 enrolled in trials with lower dFLC eligibility, and 1 progressed to dFLC > 5, was rescreened and enrolled on the carfilzomib trial. Among the other 3 patients, none achieved a dFLC of 5mg/dL: 1 died within 12 months, 1 was treated after 12 months and one remains off treatment at 8 months. **Conclusions:** Two thirds of patients with AL amyloidosis failed screening with >50% due to dFLC<5mg/dL. Among those with dFLC<5mg/dL, the majority met criteria for high-risk dFLC progression or organ progression and were treated within 6 months. The current dFLC threshold for measurable disease excludes AL amyloidosis patients requiring therapy from clinical trials and results in trial patients not being representative of real-world practice. In the era of highly effective T cell redirecting therapies, we advocate a lower dFLC inclusion (>2mg/dL) to enable participation of patients with low-burden disease. Research Sponsor: Memorial Sloan Kettering P30 Grant.

Real-world outcomes comparing the use of GLP-1 agonists in patients with multiple myeloma and comorbid obesity: A propensity score–matched analysis from a global federated health research network.

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Background: Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for the treatment of type 2 diabetes and obesity, and emerging evidence suggests their benefits beyond glycemic control, including cardiovascular effects and potential anti-inflammatory and anti-proliferative properties. Therapeutic advances in multiple myeloma (MM) have improved the overall life-expectancy in our patients. However, metabolic comorbidities remain common, likely driven by disease burden, functional decline, ongoing inflammation, and treatment related effects. Our study evaluates the impact of GLP-1 receptor agonists on outcomes in patients with MM, exploring potential interactions between metabolic modulation and disease outcomes. **Methods:** We conducted a real-world retrospective cohort study using the TriNetX Global Collaborative Network, covering January 2000 to December 2025, encompassing data from 168 global healthcare organizations. Patients aged 18 and above with multiple myeloma were identified and then stratified into two groups based on treatment with GLP-1 agonists or not. The two groups were then propensity-matched based on age, sex, race, and various comorbidities. We assessed outcomes including overall mortality, myocardial infarction (MI), ischemic stroke, sepsis, anemia, pancreatitis, venous thromboembolism (VTE), and ED visits. Time-to-event analyses were performed using Kaplan-Meier methods and Cox proportional hazards models. **Results:** We identified 1716 patients with MM and obesity who received GLP-1 receptor agonists, and 13,491 patients with MM and obesity who did not receive GLP-1 therapy. After propensity matching, each cohort consisted of 1712 patients with well-balanced baseline characteristics. We followed these patients for 5 years from treatment initiation. Patients with MM who received GLP-1 had a significantly lower risk of overall mortality (Hazard Ratio [HR]: 0.423, 95% CI: 0.351–0.509, p-value <0.001), MI (Risk Difference [RD]: -3.6 %, 95% CI: -5.4 % to -1.7 %, p-value <0.001), ischemic stroke (RD: -1.7 %, 95% CI: -3.3 % to -0.1 %, p-value = 0.04), sepsis with and without shock (RD: -3.0 %, 95% CI: -4.9 % to -1.1 %, p-value = 0.002), and anemia (RD: -9.6 %, 95% CI: -12.9 % to -6.4 %, p-value <0.001). There was no statistically significant difference in the rates of VTE, ED visits, and pancreatitis between the two cohorts. **Conclusions:** Our study revealed that patients with MM with obesity who received GLP-1 therapy had significantly lower rates of overall mortality, MI, ischemic stroke, sepsis with and without shock, and anemia. Additional longitudinal cohort studies are required to explore the associations between these agents and inform clinical practice guidelines in these patients. Research Sponsor: None.

Duffy-null status and cytopenias following BCMA-directed CAR T therapy in multiple myeloma.

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Background: Anti-BCMA chimeric antigen receptor T-cell (CAR T) therapies are highly effective in relapsed or refractory multiple myeloma (RRMM). The Duffy null phenotype, common among individuals of African ancestry and associated with lower baseline neutrophil counts, may influence hematologic toxicity following CAR T therapy. We evaluated outcomes of anti-BCMA CAR T by Duffy antigen status. **Methods:** We performed a retrospective analysis of 173 RRMM patients receiving ciltacabtagene autoleucel (cilta-cel; n=83) or idecabtagene vicleucel (ide-cel; n=90) between July 2021 and May 2025. Primary endpoints were PFS, OS, and response rate. Secondary endpoints included cytopenias and infections. Analyses were stratified by Duffy status and race/ethnicity and adjusted for age, prior therapies, and baseline ANC. **Results:** Cilta-cel: Duffy null patients (n=11, 13.3%) had comparable baseline characteristics to Duffy positive patients, except lower ANC (1.71 vs 2.44, p=0.01). Duffy null status was associated with prolonged neutropenia, with lower median ANC at day 30 (0.56 vs 1.77, p=0.005) and day 90 (1.06 vs 2.45, p=0.0002), and persistent grade ≥ 3 neutropenia at day 90 in 44.4% vs 4.3% (p=0.002). Infection rates were similar between groups (36.4% vs 41.7%, p=1.0). Response rates were high in both groups (100% vs 92%) and PFS did not differ significantly (HR 0.54, 95% CI 0.12–2.43, p=0.42), with a nonsignificant trend toward improved PFS among Duffy null patients after adjustment (HR 0.38, p=0.24). There were no significant differences in OS. Ide-cel: Duffy null status (n=16, 17.8%) was not associated with delayed cytopenia recovery (day 90 grade ≥ 3 neutropenia 33.3% vs 16.4%, p=0.2). Duffy null patients had higher infection rates (68.8% vs 39.2%, p=0.03) and a trend toward inferior OS (median 19.1 vs 40.4 months, log-rank p=0.11). These patients were more heavily pretreated (median 7 vs 5 prior lines, p=0.04); in multivariable analysis, prior lines of therapy predicted OS (HR 1.13, p=0.046) while Duffy status did not (HR 1.63, p=0.30). Response rates and PFS were similar between groups. Race/ethnicity alone was not associated with cytopenia recovery, infection rates, or survival. **Conclusions:** Duffy null status predicts severe, prolonged cytopenias following cilta-cel, without compromising efficacy or survival. Despite profound neutropenia, similar infection rates suggest benign cytopenia rather than true immunosuppression. Pre-CAR T Duffy phenotyping may prevent unnecessary neutropenia-directed interventions such as growth factors or stem cell boost. In ide-cel recipients, higher infection rates and inferior survival trends likely reflect heavier pretreatment and diminished marrow reserve. Future studies should evaluate Duffy status in earlier treatment lines and assess post-CAR T supportive care utilization by phenotype. Christen Dillard and Erneisha Brown contributed equally to this work. Research Sponsor: None.

The future mortality trends in multiple myeloma (SEER analysis 2000–2030).

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Background: Novel therapies have transformed Multiple Myeloma (MM) from a rapidly fatal diagnosis into a chronic condition. However, this extended survival exposes patients to a new set of competing risks. We utilized the SEER database to quantify the evolving burden of cause-specific mortality in the modern era and project future mortality trends. **Methods:** We identified 129,837 patients diagnosed with MM from 2000–2022 using SEER-17 registries. Patients were stratified by era: Pre-Novel (2000–06), Early-Novel (2007–14), and Modern (2015+). Median overall survival (mOS) and cumulative incidence function of death (CIF) were analyzed using Kaplan-Meier estimates and Gray's test, respectively. Fine-Gray competing risk regression was used to estimate sub-distribution hazard ratios (sHR) for non-cancer death. Non-cancer mortality burden was projected from 2021–2030 using linear regression models based on 2010–2021 trends. **Results:** Median Overall Survival (mOS) improved from 32 months (Pre-Novel era) to 49 months (Early-Novel era) and 63 months (Modern era) ($p < 0.001$). Modern-era patients had lower odds of dying from MM compared to the Pre-Novel era (OR 0.68, 95% CI 0.66–0.71, $p < 0.001$). The 5-year CIF of MM-specific death decreased from 46.5% (Pre-Novel) to 28.0% (Modern) while the non-cancer death remained stable (20.2% vs 20.7%). Among 82,585 total deaths recorded, Myeloma remained the primary cause (62.5%), while non-cancer causes accounted for 37.5%. Cardiovascular disease was the most common specific non-cancer cause, accounting for 11.4% ($n=9,383$) of all deaths. Early decedents (<3 years) had significantly higher odds of dying from Myeloma compared to late survivors (65.1% vs 58.5%; OR 1.32, $p < 0.001$). In contrast, late survivors (≥ 3 years) had significantly higher odds of death from cardiovascular disease (OR 1.16, 95% CI 1.11–1.21, $p < 0.001$) and Infections (OR 1.16, 95% CI 1.05–1.28, $p = 0.003$) as compared to early decedents. In Fine-Gray competing risk models, the modern era was associated with a reduced relative hazard of non-cancer death (sHR 0.80, $p < 0.001$). The population of MM is projected to grow by 34.5% (from ~47,200 to ~63,500) between 2022 and 2030 and annual Myeloma-specific deaths are projected to increase by 6.1% (~2,980) by 2030, annual non-Cancer deaths are projected to rise by 38.8% (~3,600). **Conclusions:** Novel therapies have nearly doubled median survival in MM, narrowing the "mortality gap" as non-cancer causes as now approach half of annual deaths. Despite reduced relative hazards, the absolute non-cancer burden is projected to rise 49% by 2030. This necessitates the need for comprehensive survivorship care for the management of MM. Research Sponsor: None.

Machine learning to identify racial and socioeconomic disparities in the onset and tumor distribution of second primary malignancies in multiple myeloma.

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Background: As survival in Multiple Myeloma (MM) improved with novel therapies, the burden of second primary malignancies (SPM) has emerged as a significant competing risk. While racial disparities in MM outcomes are established, it remains unclear whether the timing and type of SPM differ by race or socioeconomic status. **Methods:** We analyzed 7,513 MM survivors from the SEER Research database (2000–2022) who developed a confirmed, invasive SPM (excluding non-melanoma skin cancers). To account for the shorter follow-up duration in the modern era, latency drivers were assessed using Fine-Gray competing risk models which adjust for censoring. Racial and socioeconomic differences were quantified using logistic regression adjusted for age, sex, and median household income. Random Survival Forests were used to identify predictors of SPM latency with variable importance (VIMP) indicating the contributor for each factor. **Results:** The mean time-to-SPM decreased from 5.18 years (2000–2010) to 2.61 years (2011–2022) ($p < 0.001$). Black patients developed SPMs earlier than White patients (Average Direct Effect: -0.33 years, $p < 0.001$) and at a younger mean age for secondary Prostate cancer (68.5 vs. 71.6 years, $p < 0.001$). In Random Survival Forest modeling, biological age (VIMP=0.15) was the primary predictor of latency, followed by Stem Cell Transplant and Radiation utilization (VIMP=0.03). Multivariable linear regression indicated that patients with low household income ($< \$60k$) developed SPMs 0.34 years faster than wealthier peers ($p = 0.009$). Black patients had significantly lower odds of therapy-related hematologic malignancies (OR 0.62, 95% CI 0.49–0.77; $p < 0.001$) but higher odds of solid tumors (OR 1.62, 95% CI 1.30–2.04; $p < 0.001$). This solid tumor disparity persisted after adjusting for age and income ($p=0.27$) and was driven by Prostate (OR 1.79, 95% CI 1.54–2.09) and Breast cancer (OR 1.31, 95% CI 1.06–1.62). Post-SPM mortality hazard was higher in Black patients compared to White patients (HR 1.15, $p < 0.001$). **Conclusions:** Our findings showed racial and socioeconomic factors impact both the timing and type of SPM in MM survivors. Black and low-income patients develop SPM earlier and are more likely to develop solid tumors, especially prostate and breast. These findings suggests need for surveillance strategies and earlier focused screening for high risk populations to address disparities in MM survivorship. Research Sponsor: None.

Impact of human immunodeficiency virus on in-hospital outcomes among patients hospitalized with multiple myeloma: A National Inpatient Sample study, 2016–2022.

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Background: Outcomes among hospitalized patients with multiple myeloma (MM) and concomitant human immunodeficiency virus (HIV) infection remain incompletely characterized at a national level. We evaluated the association of HIV infection with in-hospital outcomes among MM hospitalizations in the United States. **Methods:** We analyzed 161,303 MM hospitalizations and identified HIV infection using ICD-10 diagnosis codes (B20–B24, Z21). To improve comparability, we restricted analyses to hospitalizations with length of stay (LOS) < 30 days and complete covariate data, then performed 1:1 propensity score matching using demographics, hospital characteristics, Charlson comorbidity category, and key comorbidities. Primary outcome was in-hospital mortality. Secondary outcomes included LOS, total hospital charges, and inpatient complications. **Results:** Of 161,303 MM hospitalizations, 0.4% (n = 681) had HIV infection. After applying analytic restrictions, 458 HIV-positive hospitalizations were matched to 458 HIV-negative hospitalizations with good covariate balance; mean age was 60.0 years. HIV infection was not associated with higher in-hospital mortality (OR 0.68, 95% CI 0.37–1.21; p = 0.191). Median LOS was similar between groups (5 days in both); however, on log-transformed analysis HIV infection was associated with shorter LOS (LOS ratio 0.90; p = 0.033). HIV infection was associated with a nonsignificant trend toward lower total hospital charges (cost ratio 0.88, 95% CI 0.77–1.01; p = 0.061). HIV infection showed nonsignificant trends toward increased venous thromboembolism, including pulmonary embolism (OR 4.05; p = 0.078) and deep vein thrombosis (OR 1.88; p = 0.085). No significant differences were observed for mechanical ventilation or cerebrovascular accident. **Conclusions:** In matched analyses of MM hospitalizations, HIV infection was not associated with increased in-hospital mortality and was associated with shorter LOS despite similar median LOS. Total charges were not significantly different, though a trend toward lower charges was observed. Signals for increased venous thromboembolism warrant further study in larger cohorts. Research Sponsor: None.

Single-cell analysis of plasma cell–centered inflammatory–immunosuppressive niches and response to daratumumab in primary light-chain amyloidosis.

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Background: Primary light-chain amyloidosis (pAL) is a plasma cell disease in which clonal plasma cells produce misfolded immunoglobulin light chains that lead to progressive organ dysfunction. Daratumumab (Dara), an anti-CD38 monoclonal antibody, is the backbone of first-line regimens for pAL; however, ~10–30% of treated patients fail to achieve $\geq$ VGPR. Currently, there remains an unmet need to delineate the immune microenvironmental mechanisms underlying Dara resistance in pAL to enable the identification of predictive biomarkers and therapeutic targets, particularly for patients who lack prognostic cytogenetic markers such as 1q21 gain. **Methods:** We profiled 630,111 single cells obtained from a prospective observational cohort of 30 patients treated with a frontline Dara–bortezomib–dexamethasone regimen, including 11 paired samples collected pre-treatment and post-treatment. Overall, 37.0% of patients showed suboptimal responses ($\leq$ PR) before cycle 6 or initiation of next-line therapy. Plasma cells enriched with CD138⁺ magnetic beads and whole bone marrow were profiled with single-cell RNA-seq. **Results:** At cohort baseline, 93.3% of the patients were Mayo 2004 stage I–IIa, 46.7% harbored the t(11;14) translocation, and 20.0% had 1q21 gain. Suboptimal responders showed two plasma cell–centered immune processes already upregulated at baseline: (i) an inflammatory axis with elevated PTGES2/PTGES3 (PGE₂)–EP2/EP4 (BH-adjusted Wilcoxon $p < 0.05$) signaling between plasma cells and myeloid, NK, and T cells, possibly driven by upstream PTGS2-expressing myeloid-derived suppressor cell-like CD38⁺CD14⁺ monocytes that expanded during treatment; and (ii) an immunosuppressive axis in which non-classical MHC class I on plasma cells increased inhibitory interactions mainly with NK and T cells (including HLA-E–KLRK1, HLA-G–LILRB1, and HLA-F–LILRB1) (BH-adjusted Wilcoxon $p < 0.05$). Compared with patients with 1q21 gain, patients with t(11;14) were associated with higher non-classical MHC class I and PTGES3-dependent prostaglandin signaling and lower PTGES2-dependent prostaglandin signaling. Possibly driven by this microenvironment, myeloid cells downregulated phagocytosis and endocytosis, NK cells showed impaired effector functions, and T cells upregulated exhaustion, accompanied by an enhanced interferon response in suboptimal versus good responders (BH-adjusted Wilcoxon $p < 0.05$). **Conclusions:** This single-cell cohort revealed a baseline inflammatory–immunosuppressive niche in pAL that underpins suboptimal hematologic responses to Dara, characterized by up-regulated non-classical MHC class I and prostaglandin signaling between plasma cells and immune cells and associated with impaired immune effector functions during Dara treatment. Research Sponsor: None.

Copy number aberration profiling using shallow whole-genome sequencing-based LeukoPrint in multiple myeloma.

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Background: Multiple myeloma (MM) is a clonal plasma cell malignancy in which cytogenetic abnormalities are central to prognosis and therapy. Karyotyping is limited by low plasma cell proliferation, and FISH provides only targeted, costly detection. LeukoPrint, a shallow whole-genome sequencing-based assay, enables genome-wide CNA profiling. Supported by prior validation, we launched a prospective multicenter trial (ChiCTR2300077768) to assess the clinical relevance of LeukoPrint-detected CNAs in MM, and report interim results from the first 102 patients. **Methods:** This multicenter, prospective trial aims to enroll 396 newly diagnosed active multiple myeloma patients per IMWG 2014 criteria. As of June 12, 2025, 102 patients from seven hospitals in China were enrolled. LeukoPrint was used to profile CNAs (>1 Mb) from paired bone marrow CD138⁺ plasma cell gDNA and peripheral blood cfDNA collected at diagnosis, post-induction, and relapse. Karyotyping and FISH were performed in parallel when available and compared with LeukoPrint. Risk stratification followed mSMART criteria. **Results:** LeukoPrint identified 863 CNAs (379 chromosomal and 484 sub-chromosomal) in 91 of 102 patients (89.2%). Hyperdiploidy was observed in 33 patients, non-hyperdiploidy in 58, and normal karyotype in 11. The most frequent alterations were 1q gain (53%) and chromosome 13 deletion (50%). Odd-numbered trisomies, often co-occurring, were detected in 51.0% of patients, predominantly in hyperdiploid cases, whereas del(13) was evenly distributed across ploidy groups. Subdiploidy was common (54%) and hyperdiploidy rare (13%) among IGH-translocated cases, suggesting mutual exclusivity of hyperdiploidy and IGH-translocation. LeukoPrint showed 88.4% concordance with FISH for four key prognostic CNAs (1p32-, 1q21+, 13q14-, 17p13-) but detected substantially more abnormalities, including in 80% of FISH-negative patients. It also markedly outperformed karyotyping (90.1% vs. 8.8%), consistent with the limited sensitivity of karyotyping due to the low proliferative activity of plasma cells in MM. Blood-based ctDNA analysis showed good concordance with bone marrow results (81.9%), and CNA dynamics tracked closely with clinical remission, supporting LeukoPrint as a robust tool for diagnosis and treatment monitoring in MM. **Conclusions:** LeukoPrint outperforms FISH and karyotyping, providing a cost-effective, genome-wide CNA platform in MM and demonstrating utility in ctDNA-based liquid biopsy. These results support LeukoPrint as a complementary, and potentially alternative approach to conventional cytogenetics. Clinical trial information: ChiCTR2300077768. Research Sponsor: None.

Extrachromosomal DNA as a shaper of aggressive transcriptional states in multiple myeloma.

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

Enabling blood-based mass spectrometry MRD detection in multiple myeloma without archived serum samples.

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Background: Minimal residual disease (MRD) assessment in multiple myeloma (MM) relies almost exclusively on bone marrow (BM) biopsy, an invasive, costly, and spatially limited procedure that is poorly suited for frequent longitudinal monitoring and may miss focal or extramedullary disease. Blood-based MRD strategies offer a less invasive, lower-cost alternative that could enable more frequent surveillance and earlier detection of disease progression. Mass spectrometry (MS)-based detection of monoclonal immunoglobulin peptides in peripheral blood is a promising MRD approach; however, current methods typically require prior identification of circulating M-protein amino acid sequences from archived serum, limiting applicability in patients without banked samples. We sought to determine whether patient-specific immunoglobulin V(D)J sequences could be reconstructed from BM-derived DNA or RNA, or from peripheral blood RNA, to enable blood-based MRD detection. **Methods:** We analyzed RNA-seq and whole exome sequencing (WES) from BM plasma cells and RNA-seq from peripheral blood mononuclear cells in 75 patients with MM, all of whom had abnormal plasma cells identified by flow cytometry. Immunoglobulin heavy chain (IGH) V(D)J sequences were reconstructed using MiXCR, and the dominant productive clonotype in the BM was selected per patient. Variable-region sequences containing complementarity-determining region 3 (CDR3) and adjacent framework regions were extracted when available. Peripheral blood RNA-seq was evaluated for clonotype recovery without BM sampling. In silico proteolytic digestion was performed to identify peptides compatible with standard MS detection. **Results:** Across 75 patients, dominant IGH clonotypes were reconstructed from 100% of BM sequencing data. From these clonotypes, a mean of 7 RNA-seq-derived peptides and 6 WES-derived peptides per patient were identified, with a mean of 2 peptides shared between platforms. Fifty patients (67%) generated ≥ 10 MS-compatible peptides, and 33 patients (44%) had at least one peptide shared between RNA-seq and WES. Among 51 patients with paired tumor and peripheral blood RNA-seq, dominant clonotypes were detectable in peripheral blood by CDR3 matching in 30 patients (58.8%). **Conclusions:** Patient-specific immunoglobulin clonotypes can be reliably reconstructed from prior BM sequencing data, yielding MS-compatible peptide targets for downstream analysis. In selected patients, clonotype discovery is feasible directly from peripheral blood, potentially reducing the need for invasive BM sampling. This approach overcomes a key limitation of existing MS-based MRD assays by enabling peptide target discovery in patients without archived serum but with available BM sequencing. Additional studies are required to validate MS detection of these peptides and establish a scalable, minimally invasive blood-based MRD platform. Research Sponsor: None.

Circulating tumor DNA *NRAS* and *TP53* mutations to identify ultra-high-risk primary refractory myeloma patients.

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Background: Approximately 5% of newly diagnosed multiple myeloma (MM) patients progress on bortezomib-containing first-line (1L) therapies and develop primary refractory disease (1REF). These patients have unacceptably poor outcomes. Underlying drivers of 1REF remain unclear. We hypothesized that circulating tumour DNA (ctDNA) profiling would identify the genetic drivers of 1REF. **Methods:** We analyzed plasma ctDNA, bone marrow (BM) MM cells from 89 patients, comprising 33 1REF and 56 contemporaneous 1L-responsive (RES) patients. ctDNA was available for all patients; BM was available for 63% (18 1REF and 38 RES). Ultra-deep targeted sequencing used a 21-gene panel enriched for MM drivers. High-confidence pathogenic variants were defined as variant allele frequency $\geq 1\%$ with ≥ 15 supporting reads. Genomic enrichment analyses used Fisher's exact test. Survival outcomes (progression-free survival, PFS and overall survival, OS) were available for 27 1REF patients and analyzed using Kaplan-Meier methods. **Results:** Interrogation of BM showed more mutations in 1REF versus RES (67% vs 34%; $p=0.04$) with *RAS/RAF* predominating (67% vs 26%; $p=0.007$). Mutation patterns in 1REF versus (vs) RES comprised predominantly *KRAS* (44% vs 21%), followed by *NRAS* (22% vs 8%). *BRAF* was detected exclusively in 1REF (17% vs 0%) and *TP53* showed no difference (6% vs 8%). ctDNA profiling revealed pathogenic variants in 18% of patients, enriched in 1REF vs RES (30% vs 11%; $p=0.02$), with *RAS/RAF* pathway mutations predominating (24% vs 2%; $p=0.001$), in line with BM observations. However, ctDNA *RAS/RAF* mutation patterns differed strikingly from BM. In 1REF vs RES, these comprised mainly *NRAS* (12% vs 0%; $p=0.01$) and *BRAF* (9% vs 0%; $p=0.04$), detected exclusively in 1REF, and *KRAS* (6% vs 2%). *TP53* did not co-occur with *RAS/RAF* and were comparable across both cohorts (6% vs 5%). Mutation-survival associations in 1REF patients also revealed differences between BM and ctDNA. BM mutations lacked prognostic value while ctDNA mutations predicted survival, suggesting ctDNA captures treatment-resistant systemic disease. Patients with any ctDNA mutations had significantly shorter PFS and OS compared to those without (PFS: 8.5 months vs not reached [NR], $p=0.0005$; OS: 12.0 months vs NR, $p=0.004$). Patients with *NRAS* mutations showed consistently poor outcomes, while the impact of *BRAF* varied. The worst outcome was seen in an ultra-high-risk subset (15%, 4/27) with *TP53* or *NRAS*, with all patients demonstrating an early fatal outcome (PFS 5.3 and OS 5.6 months; both $p<0.0001$). **Conclusions:** ctDNA *TP53* or *NRAS* identify a high-risk subset of 1REF patients with exceptionally poor outcomes, demonstrating that liquid biopsy, not BM evaluation, captures treatment-resistant systemic biology. These findings establish ctDNA as superior for risk stratification in 1REF MM and highlight an urgent need for alternative therapies in these patients. Research Sponsor: None.

A machine learning (ML)–based six-gene signature for risk stratification and therapeutic target identification in multiple myeloma.

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Background: Multiple myeloma (MM) accounts for 10–15% of hematologic malignancies with significant heterogeneity. Current risk stratification relies on clinical variables (ISS, sex, race, age, cytogenetics) but has limited prognostic accuracy (C-index ~0.63). TP53mt MM has worse outcomes, present in only 5% of newly diagnosed patients and increase to 25% at progression.

Methods: We performed differential gene expression (DGE) and gene set enrichment analysis (GSEA) between TP53mt (36) and TP53wt (717) MM from (MMRF CoMMpass). Intersection of DGE and GSEA identified 46 genes, which along with clinical variables were modeled using Cox regression and 4 ML algorithms: LASSO, CoxBoost, XGBoost and Random Forest. Models were trained on 70% and tested on 30% of data, with external validation on GSE24080 (n=559). The final 6–gene signature was functionally evaluated in drug sensitivity data from 16 MM cell lines (DepMap). Performance was assessed using concordance index (C-index) and hazard ratios (HR). **Results:** CoxBoost model 6–gene signature (UBE2C, STMN1, TK1, DSCC1, PTTG1, CENPF) outperformed all other models. Combined with clinical variables, it achieved C-index 0.742 in discovery (95% CI: 0.708–0.776) versus 0.629 for clinical variables alone (+18.0% improvement, $p < 0.001$). Minimal overfitting was observed (training: 0.748, test: 0.742, gap: 0.006). In multivariable Cox analysis, the CoxBoost risk score remained highly significant (HR 1.95, 95% CI: 1.51–2.52, $p < 0.001$) independent of ISS stage (HR 2.89, $p < 0.001$) and age (HR 1.39 per decade, $p < 0.001$). External validation on GSE24080 showed improved performance (C-index 0.683, +6.8% over clinical variables). The signature showed 50% gene overlap with LASSO (3/6 genes) and outperformed UAMS-70 (C-index 0.742 vs 0.631). Drug sensitivity analysis identified three compounds (MACIMORELIN, MW-150, BROFAROMINE) with selective activity against high-risk MM cells ($p < 0.001$), validated across 16 cell lines. **Conclusions:** TP53 and its downstream pathways are central to MM progression. CoxBoost modeling produced a 6–gene signature that improved MM risk stratification over clinical variables, identifies therapeutic vulnerabilities, and is computationally efficient model suitable for clinical deployment, warranting prospective validation in MM treatment stratification. Research Sponsor: None.

Performance of clinical-only and clinic-genomic machine learning models.

Model	Train C-Index	Test C-Index	Overfitting	Improvement vs Clinical	%Improvement
Clinical	0.69	0.72	-0.03	0	0
Random Forest	0.57	0.59	-0.02	-0.13	-18.56
LASSO	0.70	0.68	0.02	-0.04	-5.89
XGBoost	0.81	0.65	0.16	-0.06	-8.95
CoxBoost	0.75	0.74	0.01	0.02	3.31

SATMM: A systems genetic network analysis–based risk stratification tool validated across the disease trajectory of relapsed/refractory multiple myeloma.

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Background: Precision medicine in multiple myeloma (MM) requires risk stratification tools that account for the patient-specific impact of cytogenetic abnormalities on disease progression. We developed SATMM (SYGNAL Analytics Tests for MM) based on each patient's chromosomal abnormality subtype using the previously developed mmSYGNAL network. While originally validated in newly diagnosed (ND) cohorts, this study provides updated validation of SATMM in the relapsed/refractory (RR) setting. **Methods:** SATMM performance was evaluated in a new RR cohort from the Moffitt Cancer Center, stratified into Early RR (ERR; 1–3 prior events, n=258) and Late RR (LRR; > 3 prior events, n=251). Predictive accuracy was assessed via ROC analysis (AUC) and Kaplan–Meier (KM) survival curves to determine Median Progression-Free Survival (mPFS) and Cox Hazard Ratios (HR). SATMM was benchmarked against the established GEP70 and SKY92 gene panels. **Results:** As detailed in the accompanying table, SATMM demonstrated robust and superior predictive performance compared to existing panels throughout the RR disease trajectory: Prognostic Accuracy: SATMM achieved superior overall accuracy in both ERR (0.61) and LRR (0.55) groups compared to GEP70 (0.52 and 0.37) and SKY92 (0.54 and 0.43). Early-Stage Performance: In the ERR group, SATMM provided the most significant clinical separation with a Δ mPFS of 10.7 months (KM $p=1.60e-05$), outperforming GEP70 (8.9 months, KM $p=0.00053$) and SKY92 (4.4 months, non-significant). Late-Stage Performance: In the heavily pre-treated LRR group, SATMM maintained significant stratification (KM $p=0.0068$, HR $p=0.0078$) with an AUC of 0.62, GEP70 showed lesser performance (KM $p=0.021$, HR $p=0.021$) while SKY92 failed to provide accurate risk prognosis (AUC=0.43). High-Risk Patient Detection: SATMM identified a larger proportion of high-risk patients (ERR n=93 sen = 0.47; LRR n=117, sen = 0.51) with higher sensitivity (sen) compared to GEP70 (ERR n=25, sen = 0.13; LRR n=46, sen = 0.20) and SKY92 (ERR n=59, sen = 0.27; LRR n=111, sen = 0.41). **Conclusions:** SATMM is a patient-specific prognostic test that effectively stratifies risk based on the unique patient genomic profile compared to current gene panels. These data confirm that SATMM not only accurately predicts progression in ND patients but maintains its high performance across the entire disease trajectory, offering superior accuracy and sensitivity for high-risk detection for RR patients. Research Sponsor: Andy Hill Care Foundation.

Method	Disease status	AUC	Δ Median PFS	KM pvalue	High risk n	Cox HR	Cox HR pvalue	Accuracy	Sensitivity
SATMM	ERR	0.65	10.7	1.6E-05	93	0.512	1.3E-04	0.609	0.47
GEP70	ERR	0.64	8.9	0.00053	25	0.412	7.9E-04	0.523	0.129
SKY92	ERR	0.58	4.4	0.37	59	0.825	0.324	0.539	0.273
SATMM	LRR	0.62	3	0.0068	117	0.679	0.0078	0.546	0.508
GEP70	LRR	0.6	3.8	0.021	46	0.661	0.0212	0.367	0.204
SKY92	LRR	0.43	0.74	0.6	111	1.11	0.494	0.426	0.414

A common gene expression signature across multiple myeloma disease stages to identify high-risk of disease progression.

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Background: An accurate and timely identification of high-risk (HR) disease is crucial to maximize therapeutic opportunities nowadays available for multiple myeloma patients. **Methods:** In this study, 105 consecutive patients with smoldering (SMM = 33), newly diagnosed (NDMM = 42) and relapse/refractory (RRMM = 30) myeloma were enrolled. Bone marrow samples were processed by SKY92 assay (Skyline Dx) to detect HR gene expression (GE) signature and cytogenetics according with manufacturer guidelines. Statistics were performed using GraphPad Prism 8 and R (v4.4.2). Two-sided statistical tests were used, with significance of $P < 0.05$ and Benjamini-Hochberg method for false discovery rate (FDR) correction. **Results:** Based on SKY92 quality requirements, this test was feasible in the 81.1% of SMM, 92.8% of NDMM and 80.0% of RRMM cases, showing an increased detection of HR SKY92 signature frequency from SMM (18%) toward NDMM (43.5%) and RRMM (67%, $P = 0.0018$). By comparing SKY92 virtual FISH with available standard FISH data we observed a high performance of $t(4;14)$, $t(14;16/20)$ and $gain1q$ detection with an accuracy [95%(CI)] of 97.9 (93.9-100), 85.2 (71.8-98.6) and 87.2 (77.7-96.8) respectively, decreasing to 66.7 (49.8-83.5) for $del17p$ suggesting that this chromosomal aberrancy can be less likely recapitulated by GE-based projections. NDMM HR SKY92 patients showed a worst overall survival compared to patients with SKY92 standard risk (SR, $P = 0.0079$), a trend maintained in RRMM with a nearly significant statistics due to the cohort sample size ($P = 0.093$). These results suggested that HR patients could share a transcriptional trademark across disease stages. This hypothesis was tested by comparing SKY92 HR NDMM and RRMM versus SR GE data with the following observations: (i) relative risk-related clusterization by a principal component analysis (PCA) and (ii) modulation of canonical pathways frequently altered in cancer by a gene set enrichment analysis (GSEA). To test the predictivity of GE-based approaches in the asymptomatic phase of myeloma we projected GE data of SMM on the PCA bi-dimensional space previously generated with NDMM and RRMM data and we observed a partial overlap of samples based on SKY92 risk profiles across MM stages. Interestingly, a GSEA comparing SKY92 HR vs SR SMM outlined deregulated gene pathways associated with inflammation and aggressive disease. Consistently, available follow up data show a progression rate of 60% for HR SKY92 SMM compared with 0% of the SR group ($P = 0.173$). **Conclusions:** Our findings support the use of GE-based tools for MM patient's risk profiling and HR-related cytogenetic detection if FISH is not available. Furthermore, it provides evidence that HR patients share transcriptional traits across asymptomatic and symptomatic phases consistent with recent findings underlying common genomic features shared by a portion of SMM with MM. Research Sponsor: None.

Comparative analysis of subcutaneous Isa VRd (ISASOCUT) and intravenous Isa VRd (IMROZ) in transplant-ineligible newly diagnosed multiple myeloma across age groups.

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Background: Intravenous (IV) isatuximab (Isa) plus bortezomib, lenalidomide, and dexamethasone (VRd) significantly improved PFS in patients (pts) with transplant-ineligible newly diagnosed multiple myeloma (Ti NDMM) in the IMROZ randomized Phase (Ph) 3 study (NCT03319667). Efficacy and safety of subcutaneous (SC) Isa VRd, using an innovative on-body injector (OBI), has been demonstrated previously, including in Ti NDMM pts in the ISASOCUT Ph2 study (NCT05889221). Bortezomib was administered twice weekly (BIW) in IMROZ vs weekly in ISASOCUT. Here, safety and efficacy of Isa OBI VRd (ISASOCUT) and Isa IV VRd (IMROZ) are evaluated at 8 months (mos) follow-up. **Methods:** This analysis included 74 pts from ISASOCUT (Isa OBI VRd) and 265 from IMROZ (Isa IV VRd). Isa OBI VRd pts received Isa 1400 mg (weekly cycle [C]1, then every 2 weeks [Q2W] up to C12, and Q4W thereafter); each cycle lasted 28 days. SC bortezomib (1.3 mg/m²) was given BIW in C1 and weekly thereafter. Isa IV VRd pts received Isa 10 mg/kg weekly in C1, then Q2W, followed by Q4W from C18 onwards. SC bortezomib (1.3 mg/m²) was given BIW from C1-4. C1-4 lasted 42 days, with the remainder lasting 28 days each. This comparative analysis evaluated safety and efficacy at 8 mos follow-up by baseline age group (<75 yrs, ≥75 yrs). **Results:** Baseline demographic and disease characteristics were similar between Isa OBI VRd and Isa IV VRd pts. Incidence of serious TEAEs were similar between groups (35.1% and 42.2% for Isa OBI VRd and Isa IV VRd, respectively) and across age groups. The rate of systemic infusion reaction was lower with Isa OBI VRd vs Isa IV VRd (4 [5%] vs 60 [22.8%]). Grade (G) ≥3 neutropenic complications occurred in 2.7% Isa SC OBI pts and 3.8% Isa IV pts and were similar across age groups (<75 yrs, 2% vs 4.1%; ≥75 yrs, 4% vs 2.9%). Study discontinuation due to TEAEs occurred in 2.7% Isa SC OBI pts and 8.7% Isa IV pts, with lower rates in Isa SC OBI (<75 yrs, 0% vs 8.2%; ≥75 yrs, 8% vs 10.3%). Across both age groups, a lower incidence of G2 peripheral neuropathy (PN) was observed with Isa OBI VRd (weekly V) vs Isa IV VRd (BIW V) (<75 yrs, 20.4% vs 28.7%; ≥75 yrs, 20% vs 35.3%) as well as G≥3 PN (<75 yrs, 2% vs 9.2%; ≥75 yrs, 0% vs 7.4%). Isa OBI VRd (weekly V) was associated with less bortezomib dose reduction due to nervous system disorders (Isa OBI VRd [weekly V] vs Isa IV VRd [BIW V]: <75 yrs, 14.3% vs 37.4%; ≥75 yrs, 28.0% vs 35.3%). ≥VGPR rates for Isa OBI VRd and Isa IV VRd were 87.8% and 83.2%, respectively (RR: 1.055; 95% CI: 0.934-1.192), in pts aged <75 yrs and 80.0% and 82.6%, respectively (RR: 0.968; 95% CI: 0.774-1.211), in pts aged ≥75 yrs. **Conclusions:** In this comparative analysis, Isa OBI VRd with weekly bortezomib (ISASOCUT) is more tolerable for pts regarding PN than the BIW schedule (IMROZ). Both groups maintained similar ≥VGPR rates across age groups. These findings support the efficacy and safety of the Isa SC OBI with weekly bortezomib. Clinical trial information: NCT05889221 and NCT03319667. Research Sponsor: Sanofi.

ISABELA: A phase 2 study of isatuximab, belantamab mafodotin, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma.

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Background: Combination therapies form the backbone of multiple myeloma (MM) care, and therapies targeting BCMA are now a cornerstone of treatment. We evaluated ISABELA, a phase 2 study that combines an established regimen of isatuximab (isa), pomalidomide (pom), and dexamethasone (dex) with the recently approved anti-BCMA antibody drug conjugate belantamab mafodotin (belamaf) in relapsed/refractory (RR) MM. **Methods:** ISABELA is an investigator-initiated study (NCT05922501) enrolling up to 50 patients (pts) with RRMM who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor. We gave belamaf 1.9 mg/kg iv q8 weeks; isa 10 mg/kg iv weekly for cycle 1 and then days 1 and 15 for cycle 2 onward; pom 4 mg on days 1–21, and dex 40 mg weekly divided over two days. Each cycle was 28 days. Treatment was until progression or unacceptable toxicity. **Results:** At data cutoff, the trial had enrolled 17 pts with a median follow-up of 9.6 months. Median age was 72 (range 55–91); 65% were male. ISS at study entry: I (59%), II (24%), III (18%). Median number of prior regimens was 2 (range 1–12). All pts were refractory to their last line of therapy and were previously treated with lenalidomide and a proteasome inhibitor. Prior therapies included pom (59%), bortezomib (82%), carfilzomib (41%), ixazomib (35%), CD38 antibody (59%) [daratumumab, 59%; isa 12%], and auto SCT (24%). Prior exposure to newer therapies included drugs that target BCMA (24%) [teclistamab 6%, elranatamab 18%, CAR T-cells 12%]; GPRC5D (12%) [talquetamab]; and cereblon (29%) [mezigdomide, 29%; cemsidomide, 12%]. Soft tissue plasmacytomas were present in 18%. The overall response rate (ORR) was 86% (12/14, not evaluable (NE) 3), $\geq$ VGPR 43%, CR 7%, and 16-month PFS was 73% (95% CI 0.5–1). In CD38-antibody-naïve patients, ORR was 84% (5/6, NE 1) and 16-month PFS was 67% (95% CI 0.38–1). In triple-class exposed (BCMA naïve) pts, ORR was 75% (3/4, NE 2), and 12-month-PFS was 86% (95% CI 0.63–1). In quad-class exposed pts (including BCMA) (N=4), ORR was 100% and 12-month PFS was 75% (95% CI 0.43–1). Grade 3–4 hematologic adverse events (AEs) included neutropenia (53%), thrombocytopenia (29%), and anemia (12%). Common non-hematologic AEs (all; grade 3–4) included blurred vision (65%; 6%); fatigue (65%; 0%); hypertension (59%; 6%); diarrhea (53%; 0%); and AST/ALT increase (47%; 6%). Infections occurred in 35% with no grade $\geq$ 3 events. Ocular AEs by keratopathy visual acuity scale included grade 1 (14%), grade 2 (29%), grade 3 (36%). No patients discontinued treatment for AEs or ocular toxicity. **Conclusions:** This is the first report in RRMM for the combination of belamaf with a CD38 monoclonal antibody. The ISABELA regimen shows promising preliminary activity in RRMM with an ORR of 86% and 16-month PFS of 73%, including quad-class-exposed pts treated with anti-BCMA therapy, with manageable, reversible AEs. Clinical trial information: NCT05922501. Research Sponsor: GSK; Sanofi.

Safety and reliability of isatuximab subcutaneous on-body injector: Results across the phase 3 IRAKLIA, phase 2 IZALCO and phase 1b TCD15484 trials.

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Background: Subcutaneous (SC) drug delivery options have become more widely available in multiple myeloma (MM). SC delivery of isatuximab (Isa), an anti-CD38 monoclonal antibody, has been investigated across clinical trials via a novel hands-free on-body injector (OBI). Isa SC OBI features a small, retractable needle, establishing the first device-enabled delivery of an oncologic treatment. The Phase 3 IRAKLIA, Phase 2 IZALCO, and Phase 1b (TCD15484) trials consistently demonstrated similar efficacy and safety of Isa SC OBI vs Isa IV in relapsed/refractory MM (RRMM) patients (pts). Here, we present a cross-trial analysis exploring safety and reliability of Isa SC OBI in RRMM pts. **Methods:** Pts with RRMM in IRAKLIA (N=263) and the Phase 1b expansion cohort (N=22) received 1400 mg Isa SC OBI plus pomalidomide and dexamethasone (d). In IZALCO, RRMM pts (N=64) received 1400 mg Isa SC OBI + carfilzomib (K)-d. Pts were monitored for 4 hrs (IRAKLIA) or 1-2 hrs (IZALCO) following first administration and for 1 hr for the following cycle (C) 1 administrations to assess local tolerability. Pre-infusion medications included montelukast (C1), steroids, acetaminophen and H1 antihistamines. Pts without systemic infusion-related reactions (IRRs) after 4 consecutive administrations of Isa SC OBI had subsequent pre-medication reassessed at investigator's discretion. Safety and device performance explored in this cross-trial analysis of company sponsored studies were assessed in the Isa SC OBI cohorts by the duration of injection, IRRs, local injection-site reactions (ISRs), and injection/device success, which were defined similarly across all trials. **Results:** The median duration of Isa SC OBI injection was 13 mins in IRAKLIA, 12 mins in IZALCO, and 10 mins in the Phase 1b trial (6426 total injections, N=349 pts). IRRs across trials occurred in 6/6426 (0.09%) injections and 4/349 (1.15%) pts. IRRs were mostly grade 1 (G; 3/6426, 0.05%) with 1 G3 (0.02%); none leading to discontinuation. In IRAKLIA, 80/263 (30.4%) pts did not require premedication (931/5145 injections, 18.1%); no IRRs occurred in this group. Across trials, ISRs occurred in 21/349 (6.02%) pts resulting in 35 (0.54%) ISR events. Most ISRs were G1 (33, 0.51%), the remaining were G2 (2, 0.03%) and generally occurred on the day of injection. 99.9% (6421/6426) of injections in 98.6% (344/349) pts were successful (completed without interruption) across all trials. **Conclusions:** These findings support overall low, self-limiting rates of IRRs and ISRs across trials, with >6000 (99.9%) Isa SC OBI injections successfully delivered. Isa SC OBI shows reproducible safety and reliability in IRAKLIA, IZALCO and Phase 1b trials, supporting it as a novel administration option for MM pts and its potential for future exploration in at-home administration. Clinical trial information: NCT04045795, NCT05405166, and NCT05704049. Research Sponsor: Sanofi.

Updated results from the phase 2 IZALCO study: Efficacy and safety of isatuximab subcutaneous plus carfilzomib and dexamethasone in relapsed/refractory multiple myeloma.

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Background: In combination with conventional doublet and triplet therapy, isatuximab (Isa) provides significant benefit to patients (pts) across the multiple myeloma (MM) spectrum. Subcutaneous (SC) administration of Isa could be a more convenient option for pts and caregivers. The Phase (Ph)3 IRAKLIA trial in relapsed/refractory MM (RRMM) pts demonstrated non-inferiority in efficacy and pharmacokinetics of Isa SC delivered via a wearable on-body injector (OBI) in combination with pomalidomide and dexamethasone (Pd) vs Isa IV Pd. The Ph2 IZALCO study (NCT05704049) also showed efficacy and safety of Isa SC plus carfilzomib and dexamethasone (Kd), either by manual or OBI injections, in RRMM pts. Following exposure to both methods, pts showed higher preference for OBI vs manual SC injection. Here we present updated efficacy and safety results from IZALCO. **Methods:** Isa SC 1400 mg was given weekly in Cycle (C)1 then biweekly. In Part 1, pts received Isa injected SC manually. In Part 2, pts were randomized to Isa administered SC via OBI (Isa SC OBI; C1–C3) followed by manual SC injection (C4–C6), or to manual SC injection (C1–C3) followed by Isa SC OBI (C4–C6). Starting at C7, pts could choose either treatment method. All pts were treated with carfilzomib (20 mg/m² on Day [D]1–2 then 56 mg/m² on D8–9, 15–16 at C1, then D1–2, 8–9, and 15–16) and dexamethasone (20 mg on D1–2, 8–9, 15–16, and 22–23). **Results:** A total of 74 RRMM pts were enrolled (8 in Part 1; 66 in the randomized cohort, Part 2). At the data cut-off of November 10, 2025, 59 pts remained on study. At study entry, pts had median age of 65 (44–85) years, median weight of 75.9 (40.0–129.0) kg, and median of 1 prior line of therapy (1–5), and 56.8% had ISS stage I. The median duration of Isa SC OBI administration was 12 mins and manual SC injection was 6 mins. None of the Isa SC injections, manual or OBI, were interrupted. Median time to best response was 5.3 months (mos) (95% CI: 3.25–6.24). At median follow-up of 21.9 mos, median PFS was not reached (NR) (95% CI: 16.23–NR). PFS at 18 mos was 61.5% (95% CI: 48.7–72.0). OS at 18 mos was 80.8% (95% CI: 69.8–88.2); median OS was not reached (95% CI: NR–NR). Overall, grade (G) ≥3 TEAEs occurred in 66.2%, and serious TEAEs in 51.4% pts. Infusion reaction (IR) on C1D1 occurred in 2 pts (2.7%) with manual SC injections; no IRs occurred with OBI. Six (8.1%) pts had 13 injection-site reactions (ISR), all G1, in 24/25 (0.54%) manual or OBI injections. Only 1 ISR was deemed related to OBI. Pt satisfaction with injection method remained consistently high with Isa SC OBI up to C25D15. **Conclusions:** Updated results of the IZALCO study continue to show the efficacy and safety of Isa SC plus Kd delivered either by manual injection or Isa SC OBI, while demonstrating high pt satisfaction and preference for Isa SC OBI. These findings are consistent with those reported in the Ph3 IKEMA study (Isa IV plus Kd). Clinical trial information: NCT05704049. Research Sponsor: Sanofi.

Durable clinical benefit with B-cell maturation antigen (BCMA)–directed therapy, belantamab mafodotin plus pomalidomide and dexamethasone (BPd) in relapsed/refractory multiple myeloma (RRMM): DREAMM-8 long-term responder (LTR) analysis.

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Background: BCMA–directed therapies have changed the RRMM treatment landscape. In the phase 3, open-label, randomized DREAMM-8 trial (NCT04484623), BPd demonstrated significant progression-free survival (PFS) benefit compared with pomalidomide, bortezomib, and dexamethasone (PvD) in patients (pts) with RRMM who received ≥ 1 prior line of therapy (LOT). This post hoc analysis examined the characteristics of and outcomes in pts achieving sustained clinical benefit with BPd. **Methods:** DREAMM-8 is an ongoing, phase 3, open label study evaluating BPd and PvD in pts with RRMM with ≥ 1 prior LOT, including lenalidomide. Pts were randomized 1:1 and treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. The primary endpoint was PFS; secondary endpoints included minimal residual disease (MRD) negativity (10^{-5}), PFS2, response rates, and safety. LTRs were pts with PFS ≥ 30 months (data cutoff: July 7, 2025; median follow up 36 months in both arms). **Results:** Of the 302 pts in DREAMM-8 (BPd, n=155; PvD, n=147), 81 were LTRs. The BPd arm had more than twice the proportion of LTRs (n=59 [38%]) as the PvD arm (n=22 [15%]). Baseline characteristics between treatment arms were generally well balanced. In LTRs, median PFS potentially favored BPd (not reached [NR]; 95% CI, NR–NR) vs PvD (NR; 95% CI, 42.7 months–NR), with a hazard ratio (HR) of 0.72 (95% CI, 0.20–2.53). BPd LTRs continued to demonstrate potential benefits after the first subsequent therapy, with median PFS2 (95% CI) of NR (NR–NR) in the BPd LTR arm and NR (44.2 months–NR) in the PvD LTR arm (HR, 0.33; 95% CI, 0.07–1.69). LTRs treated with BPd vs PvD had deeper responses: 76% vs 59% had complete response or better ($\geq$ CR), 56% vs 32% had MRD negativity plus $\geq$ CR overall (73% vs 54% of pts with $\geq$ CR), and 39% vs 18% had sustained MRD negativity for ≥ 12 months, respectively. A higher proportion of pts with high-risk cytogenetics (ie, ≥ 1 of t[4;14], t[14;16], or del[17p13]) treated with BPd vs PvD achieved long-term response (27% vs 11%). The safety profile in LTRs was generally consistent with that previously reported. **Conclusions:** More than one-third of pts treated with BPd achieved LTR status, representing a 2.5-fold higher rate than with PvD, with similar rates in pts with high-risk cytogenetics; median PFS with BPd remains unreached. These findings suggest that this broadly accessible BCMA-targeted regimen delivers potential durable clinical benefit, characterized by deep and sustained disease-free survival. Clinical trial information: NCT04484623. Research Sponsor: Sponsored by GSK. Editorial support provided by Nucleus Global, an Inizio company and funded by GSK (study ID 207499). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from Biowa.

PFS2 outcomes by prior therapy from DREAMM-8: A phase 3 study assessing belantamab mafodotin (belamaf), pomalidomide, and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).

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Background: B-cell maturation antigen (BCMA)-directed therapies have transformed the treatment landscape in RRMM. Belamaf, a BCMA-targeting antibody-drug conjugate, in combination with Pd significantly improved progression-free survival (PFS) vs PVd (hazard ratio [HR], 0.52; 95% CI, 0.37-0.73; $P < 0.001$) in pts with RRMM in DREAMM-8 (median follow-up, 22 mo). This PFS benefit was maintained with extended follow-up (HR, 0.49; 95% CI, 0.36-0.67; median follow-up 36 mo); median PFS2 also favored BPd vs PVd (47.1 vs 21.7 mo, respectively; HR, 0.52; 95% CI, 0.38-0.70), indicating sustained clinical benefit over time. We report PFS2 outcomes from DREAMM-8 in subgroups based on prior therapy to further understand the long-term impact of BPd and inform treatment sequencing. **Methods:** DREAMM-8 (NCT04484623) is a phase 3, randomized, open-label study evaluating BPd vs PVd in pts with RRMM with ≥ 1 prior line of therapy including lenalidomide (LEN). Pts could not have received prior BCMA-targeted therapy. PFS2 was defined as time from randomization to disease progression after initiation of subsequent anti-myeloma therapy or death. PFS2 was assessed based on prior-treatment subgroups. **Results:** In the BPd arm (DCO: Jul 7, 2025; median follow-up, 36 mo), PFS2 benefit was maintained in all subgroups, including pts who were LEN refractory and anti-CD38 exposed/refractory. In LEN-refractory pts, BPd treatment led to almost a 3-fold median PFS2 improvement vs PVd (41.7 vs 15.0 mo). A total of 56/155 pts (36%) in the BPd arm and 93/147 (63%) in the PVd arm received any first subsequent therapy (FST) at data cutoff. Across both arms, 36% of pts received steroids, 28% received anti-CD38 therapies ($>50\%$ of pts with any subsequent therapy in each arm), and 23% received proteasome inhibitors as FST. A total of 21 pts (7%) received novel therapies (BPd, $n=6$ [4%]; PVd, $n=15$ [10%]) as FST, including BCMA-targeted bispecific antibodies (bsAbs), non-BCMA bsAbs, CELMoDs, venetoclax, and belamaf. Improved median PFS2 was observed in patients who had novel therapies as FST ($n=21$) vs non-novel agents ($n=128$) (26.0 vs 20.1 mo; HR, 0.61; 95% CI, 0.34-1.09). **Conclusions:** BCMA-directed therapy, BPd, resulted in improved PFS2 outcomes vs PVd, demonstrating sustained clinical benefit beyond initial belamaf therapy. This benefit was seen regardless of prior treatment, with LEN-refractory pts experiencing almost a 3-fold PFS2 benefit, and despite a higher proportion of pts receiving novel therapies as FST in the PVd arm. PFS2 benefit with high use of subsequent anti-CD38 agents supports sequencing of belamaf combinations early in the treatment paradigm prior to anti-CD38 agents. Research Sponsor: Sponsored by GSK. Editorial support provided by Nucleus Global, an Inizio company and funded by GSK (study ID 207499). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from Biowa.

Real-world one-year comparative outcomes of quadruplet and triplet induction regimens in older, transplant-ineligible multiple myeloma patients.

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Background: Older patients with newly diagnosed multiple myeloma (MM) frequently experience early treatment discontinuation due to toxicity, comorbidities, and frailty. Although randomized trials support anti-CD38-based induction regimens, real-world comparative data evaluating early clinical outcomes in older, transplant-ineligible patients remain limited.

Methods: We conducted a retrospective, multi-institutional cohort study using TriNetX, including adults aged ≥ 70 years with newly diagnosed MM after 2019 who initiated treatment within two months of diagnosis and did not undergo autologous stem cell transplantation. We performed two matched comparative analyses: Dara-RVd versus RVd and Dara-RVd versus Dara-Rd. We first assessed the proportion of patients initiating second-line therapy at 12 and 24 months. Analyses were then restricted to patients who remained on first-line therapy for at least one year to evaluate early clinical outcomes, including all-cause mortality and healthcare utilization (emergency department [ED] visits, ICU admissions, and bacterial infection or sepsis). Matching included demographics, comorbidities, presence of extramedullary plasmacytoma, and baseline laboratory values (LDH, albumin, $\beta 2$ microglobulin, creatinine, and hemoglobin), BMI and recent hospitalization. Hazard ratio (HR) and risk ratio (RR) with 95% confidence intervals (CI) were reported. **Results:** Compared with RVd, Dara-RVd showed similar second-line initiation within 12 months (13% vs 14%; $p=0.857$) and 24 months (14% vs 19%; $p=0.086$). Among 768 matched patients per group who remained on first-line therapy at one year (mean age 75 years), Dara-RVd was associated with lower 1-year all-cause mortality (12% vs 17%; HR 0.70; 95% CI 0.55–0.90) and reduced healthcare utilization, including ≥ 1 ED visit (30% vs 36%; RR 0.85; 95% CI 0.73–0.98) and ICU admission (8% vs 12%; RR 0.70; 95% CI 0.52–0.95), while infection rates were similar. Compared with Dara-Rd, Dara-RVd showed comparable second-line initiation within 12 months (13% vs 10%; $p=0.126$) and 24 months (15% vs 11%; $p=0.218$). Among 511 matched patients per group who remained on first-line therapy at one year (mean age 76 years), no significant differences were observed in 1-year all-cause mortality or healthcare utilization outcomes. **Conclusions:** In older, transplant-ineligible patients with newly diagnosed MM who remained on therapy at one year, Dara-RVd was associated with improved early survival and lower healthcare utilization compared with RVd, while outcomes were comparable to Dara-Rd. Despite the retrospective design and potential unmeasured confounding, these findings support daratumumab-based regimens in older patients. Prospective studies incorporating frailty and early treatment discontinuation are needed to better define optimal induction strategies. Research Sponsor: None.

Comparative efficacy of belantamab mafodotin plus bortezomib and dexamethasone (BvD) vs standard of care in patients with relapsed/refractory multiple myeloma (RRMM).

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Background: BvD is approved in the United States as a third-line or later (3L+) option for patients with RRMM based on the DREAMM-7 study of BvD vs daratumumab (D) plus bortezomib (V) and dexamethasone (d; DVd). This study aimed to compare the relative efficacy of BvD vs pomalidomide (P) plus Vd (PvD), elotuzumab plus Pd (EPd), isatuximab plus Pd (IsaPd), and idecabtagene vicleucel (ide-cel) in adults with 3L+ RRMM who received a proteasome inhibitor and an immunomodulatory drug. In the absence of head-to-head trials, indirect treatment comparisons (ITCs) can inform on the relative efficacy of regimens. **Methods:** ITCs of progression-free survival (PFS) and overall survival (OS) were conducted using the eligible study populations (only patients with ≥ 2 prior lines of therapy [LOT]) from the DREAMM-7 (BvD), DREAMM-8 (PvD), ELOQUENT-3 (EPd), ICARIA-MM (IsaPd), and KarMMA-3 (ide-cel) trials. Individual pt data (IPD) were available for patients treated with BvD and PvD, while only published summary data were available for patients treated with EPd, IsaPd, and ide-cel. In base-case analyses, study populations were weighted (using inverse probability of treatment weighting to compare to PvD and matching adjusted indirect comparison for the other treatments) to match in terms of age, prior exposure to bortezomib, prior exposure to lenalidomide, refractoriness to lenalidomide, number of prior LOT, and cytogenetic risk. Weighting was done separately for each comparator treatment. Weighted Cox regression was then performed to compare outcomes of patients treated with BvD to each respective comparator treatment. **Results:** In the base-case models, weighting yielded very good balance for all matched covariates (standardized mean difference < 0.25 for each covariate across each comparison, and < 0.10 in all cases except for age, prior bortezomib, and > 4 prior LOT in the PvD comparison). Hazard ratios for BvD vs EPd, IsaPd, and ide-cel for PFS and OS significantly favored BvD (Table). For BvD vs PvD, PFS significantly favored BvD and OS numerically favored BvD. **Conclusions:** In DREAMM-7, direct comparison of BvD vs DVd showed PFS and OS improvements with BvD. This indirect comparison of patients in the 3L+ setting further showed that BvD improved PFS and OS vs PvD, EPd, IsaPd, and ide-cel. Research Sponsor: GSK.

Comparison (sample size/effective sample size value)	BvD vs PvD (86 and 68/35)		BvD vs EPd (103/42 and 60)		BvD vs IsaPd (85/52 and 154)		BvD vs Ide-cel(96/50 and 254)	
	PFS	OS	PFS	OS	PFS	OS	PFS	OS
Outcome								
Hazard ratio	0.517	0.604	0.337	0.405	0.538	0.348	0.468	0.509
95% confidence interval	0.275, 0.331,	0.173, 0.209,	0.346, 0.195,	0.287, 0.274,	0.972 1.103	0.654 0.787	0.836 0.623	0.762 0.945
p-value	0.041	0.101	0.001	0.008	0.006	<0.001	0.002	0.033

Age and frailty analyses of transplant-ineligible (TIE) patients (pts) with newly diagnosed multiple myeloma (NDMM) in the phase 3 MAIA and CEPHEUS trials of daratumumab + lenalidomide-dexamethasone (Rd) and bortezomib-Rd (VRd).

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Background: MAIA and CEPHEUS trials demonstrated that daratumumab (Dara) with standard of care (SOC) VRd or Rd significantly improved clinical outcomes versus SOC in TIE NDMM. Here we describe efficacy and safety in TIE pts from both trials by age and baseline (BL) frailty using the latest data cuts. **Methods:** Pts were randomized 1:1 to DRd (n=368) or Rd (n=369) in MAIA and 1:1 to DVRd (n=144) or VRd (n=145) in CEPHEUS. Progression-free survival (PFS), complete response or better ($\geq$ CR), overall MRD negativity (neg) at 10^{-5} with $\geq$ CR, sustained MRD neg with $\geq$ CR (confirmed MRD neg $\geq 12 \pm 1$ months [mo] apart without MRD positivity in between), and safety were assessed by age (<70, 70–<75, or ≥ 75 years [y]) and BL frailty (assessed by IFM simplified frailty score: 0–1, non-frail; ≥ 2 , frail). **Results:** Median follow-up was 64.5 mo in MAIA and 76.0 mo in CEPHEUS. In MAIA, 155 (21%) pts were <70 y, 261 (35%) 70–<75 y, and 321 (44%) ≥ 75 y; 341 (46%) pts were frail, 88.0 % of whom were ≥ 70 y. In CEPHEUS TIE pts, 70 (24%) pts were <70 y, 133 (46%) 70–<75 y, and 86 (30%) ≥ 75 y; 83 (29%) pts were frail, 86% of whom were ≥ 70 y. DRd or DVRd improved PFS, MRD neg rates, sustained MRD neg rates, and $\geq$ CR rates vs Rd or VRd arms across age and frailty subgroups in both trials (Table). Safety was consistent with established individual drug profiles, and adverse event rates were generally comparable across treatment arms and subgroups within both trials. Additional data on patient-specific factors relevant to these subgroups will be presented. **Conclusions:** Dara-based regimens improved efficacy outcomes across subgroups in MAIA and CEPHEUS trials, reinforcing Dara-based regimens as SOC in TIE NDMM regardless of age or frailty. These data offer clinically relevant insights to help guide treatment selection for TIE pts. Clinical trial information: NCT03652064; NCT02252172. Research Sponsor: Johnson & Johnson.

Age/ Frailty status	PFS, hazard ratio (95% CI)		$\geq$ CR rate, %		MRD neg with $\geq$ CR (10^{-5}) rate, %		Sustained MRD neg with $\geq$ CR (10^{-5}) rate, %	
	MAIA*	CEPHEUS**	MAIA*	CEPHEUS**	MAIA*	CEPHEUS**	MAIA*	CEPHEUS**
<70 y	0.35 (0.21–0.56)	0.60 (0.31–1.18)	56.4 vs 31.2	85.7 vs 68.6	35.9 vs 11.7	74.3 vs 42.9	25.6 vs 3.9	62.9 vs 28.6
70–<75 y	0.64 (0.45–0.89)	0.60 (0.37–0.99)	56.2 vs 31.3	77.9 vs 69.2	36.2 vs 12.2	55.9 vs 47.7	20.8 vs 5.3	45.6 vs 38.5
≥ 75 y	0.59 (0.44–0.79)	0.46 (0.22–0.94)	44.4 vs 28.6	80.5 vs 44.4	26.9 vs 9.9	58.5 vs 26.7	13.8 vs 3.1	43.9 vs 15.6
Frail	0.64 (0.48–0.85)	0.62 (0.32–1.18)	44.8 vs 33.1	72.9 vs 54.3	25.6 vs 13.0	56.3 vs 34.3	15.7 vs 4.1	39.6 vs 17.1
Non-frail	0.48 (0.36–0.64)	0.51 (0.34–0.78)	56.6 vs 27.5	84.4 vs 63.6	37.8 vs 9.5	63.5 vs 41.8	21.4 vs 4.0	54.2 vs 32.7

*MAIA: DRd vs Rd; **CEPHEUS: DVRd vs VRd.

Minimal residual disease dynamics in newly diagnosed multiple myeloma and impact on progression-free survival: A cohort study.

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Background: Minimal residual disease (MRD) is a sensitive tool for evaluating treatment response in multiple myeloma (MM) and is a surrogate marker of progression-free survival (PFS) and overall survival (OS). Consecutive MRD evaluations offer important information regarding the depth and the duration of response to treatment and can be used to guide the patients' management. **Methods:** This single center, retrospective study included patients with newly diagnosed MM (NDMM), who were evaluated with at least 3 consecutive MRD tests. Four subgroups of patients were identified: sustained MRD positive (sMRDpos), sustained MRD negative (sMRDneg), converted to MRD negative (conMRDneg) and converted to MRD positive (conMRDpos). The aim of the study was to compare PFS between groups. **Results:** Overall, 335 NDMM patients were included in the analysis. The median age at diagnosis was 59 years (range 35-89), and the median number of assessments was 5 (range 3-14). Regarding risk stratification, 56 (16.7%) were ISS-3, and 52 (15.5%) were labeled as high-risk per the novel IMS/IMWG HRMM criteria. The median number of MRD evaluations in each patient was 5 (range 3-13). One third received quadruplet regimen. The median follow-up of the cohort was 6.1 years. Patient distribution according to MRD status was as follows: 191 (57%) sustained negativity, 40 (12%) sustained positivity, 53 (15.8%) converted to negative, whereas 51 (15.2%) converted to positive. Median PFS and OS were not achieved in any of the MRD subgroups. Sustained MRD negativity was associated with superior PFS compared to all the other subgroups (HR=0.21, 95% CI: 0.10 – 0.42, $p<0.001$). Sustained MRD positivity was associated with significantly inferior PFS compared to sMRDneg (HR=4.84; 95% CI: 1.91 – 12.30, $p<0.001$) and conMRDpos had also inferior PFS compared to the sMRDneg (HR= 6.04, 95% CI: 2.74 – 13.31, $p<0.001$). Furthermore, the presence of at least one MRD positive, at any time-point, was associated with inferior PFS compared to the sMRDneg (HR= 4.29, 95% CI: 2.05 – 8.99, $p<0.001$). Among the sustained MRD negative patients, high risk cytogenetics yielded a trend towards worse PFS (HR= 1.42, 95% CI: 0.30 – 6.69, $p=0.659$), possibly suggesting that sMRDneg overrides high risk cytogenetics. Finally, among the 165 patients who sustained MRD negativity, the median number of MRD tests were 5 (range 3-14). Among these patients with more than 5 tests had superior PFS, compared to less than 5, with a HR= 0.04, 95% CI: 0.01 – 0.33, $p=0.003$ signaling no further need of additional consecutive MRD testing in such patients. **Conclusions:** In patients with NDMM in the real-world setting, sustained MRD negativity is associated with prolonged PFS, even in HR patients, whereas the presence of even one MRD positive result impacted PFS. Research Sponsor: None.

Exploratory associations between incretin-based therapies and plasma cell disorders in patients with type 2 diabetes: A real-world study.

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Background: Incretin-based therapies, including dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), are widely used in the management of type 2 diabetes mellitus (T2DM). Experimental and clinical data suggest that metabolic and immune pathways may influence plasma cell dyscrasia development, yet the relationship between incretin-based therapies and monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma (MM) remains unclear. In this study, we aimed to evaluate the association between incretin-based therapy exposure and the risk of MGUS and MM. **Methods:** A multicenter, retrospective cohort study was conducted using the TriNetX Global Collaborative Network, a federated electronic health record database, between January 1, 2015, and December 31, 2025. Adult patients with T2DM were categorized into six exposure cohorts. Individuals treated with GLP-1RAs with a minimum of one year of therapy were compared with patients initiating sodium-glucose cotransporter-2 inhibitors (SGLT2i), sulfonylureas (SU), and thiazolidinediones (TZDs). The same cohort design was applied to DPP-4i users. A 1:1 propensity score matching (PSM) model was applied to minimize confounding by balancing baseline demographics, clinical comorbidities, laboratory parameters, and concurrent medication use. Individuals with a prior cancer diagnosis were excluded. The primary endpoint was progression to MM, and the secondary endpoint was the development of MGUS. Statistical analyses were performed within the TriNetX platform. **Results:** After 1:1 PSM, GLP-1RA therapy was associated with a significantly lower risk of both MGUS and MM compared with SU (n = 141,225 per group; MGUS RR 0.59, 95% CI 0.50–0.69; MM RR 0.84, 95% CI 0.77–0.92) and SGLT2i (n = 57,919 per group; MGUS RR 0.75, 95% CI 0.65–0.86; MM RR 0.62, 95% CI 0.49–0.79). No significant differences in MGUS or MM risk were observed when GLP-1RAs were compared with TZDs. In contrast, DPP-4i use was associated with an increased risk of MM compared with TZDs (n = 29,462 per group; RR 1.93, 95% CI 1.40–2.66) and SGLT2i (n = 68,481 per group; RR 1.44, 95% CI 1.19–1.74). No significant associations were observed for MGUS across comparators, and no significant differences in MGUS or MM risk were seen between DPP-4i and SU (Table 1). **Conclusions:** In patients with T2DM, GLP-1RA exposure were associated with differential rates of MGUS and MM diagnosis across antihyperglycemic drug classes. GLP-1RA was associated with a lower rates of MGUS and MM compared with SU and SGLT2i, whereas DPP-4i use was associated with higher MM rates when compared with SGLT2i and TZDs. While these findings are clinically promising, prospective studies are needed to confirm causality and clarify underlying mechanisms. Research Sponsor: None.

Incretin-based therapies and all-cause mortality and progression to multiple myeloma in patients with MGUS and type 2 diabetes: A real-world cohort study.

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Background: Monoclonal gammopathy of undetermined significance (MGUS) progresses to multiple myeloma (MM) at an estimated rate of approximately 1–2% per year. Emerging evidence suggests metabolic dysfunction, including type 2 diabetes mellitus (T2DM) may influence the trajectory of progression to MM. Incretin based therapies have immunomodulatory and metabolic effects that could modify outcomes in patients with plasma cell dyscrasias. We conducted this study to evaluate the association between incretin-based therapies and the risk of progression to MM and all-cause mortality among patients with MGUS and T2DM.

Methods: A multicenter, retrospective cohort study was conducted using the TriNetX Global Collaborative Network, a federated electronic health record database, from January 1, 2015, to December 31, 2025. Adult patients with T2DM and MGUS who had at least one year of treatment exposure to incretin-based therapies both before and after MGUS diagnosis were included. Patients were categorized into six exposure cohorts. Outcomes among glucagon-like peptide-1 receptor agonist (GLP-1RA) and dipeptidyl peptidase-4 inhibitor (DPP-4i) users were compared with matched cohorts receiving sulfonylureas (SU), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and thiazolidinediones (TZDs). Individuals with a prior cancer diagnosis were excluded. A 1:1 propensity score matching (PSM) approach was applied to balance demographics, comorbidities, laboratory parameters, and concurrent medication use. The primary outcome was all-cause mortality, and the secondary outcome was progression to MM. All statistical analyses were performed within the TriNetX platform. **Results:** After 1:1 PSM, GLP-1RA use was associated with lower all-cause mortality compared with SU ($n = 393$ per group; RR 0.35, 95% CI 0.25–0.49). No significant differences were observed in all-cause mortality or progression to MM when GLP-1RAs were compared with SGLT2i or TZDs. In contrast, DPP-4i use was associated with significantly higher all-cause mortality compared with SGLT2i ($n = 315$ per group; RR 2.53, 95% CI 1.77–3.62) and TZDs ($n = 120$ per group; RR 2.37, 95% CI 1.27–4.44). DPP-4i exposure was not significantly associated with progression to MM across any comparator group. **Conclusions:** Among patients with T2DM and MGUS, GLP-1RA use was associated with significantly lower all-cause mortality compared with SU, whereas DPP-4i use was associated with increased mortality compared with SGLT2i and TZDs, with no significant effect on progression to MM. These findings suggest a clinically meaningful survival differences across antihyperglycemic therapies and should be validated in future prospective studies. Research Sponsor: None.

Early intravenous immunoglobulin use in multiple myeloma patients treated with talquetamab: Effect on risk of infections and mortality.

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Background: Bispecific T-cell-engaging (BiTE) antibodies have transformed the treatment of relapsed or refractory multiple myeloma (MM) but are associated with high rates of infectious complications. Talquetamab, a GPRC5D-directed BiTE, induces immune dysfunction but has been shown to be associated with less infection risk than anti-BCMA BiTEs. Although there is evidence supporting prophylactic intravenous immunoglobulin (IVIG) use for pts receiving anti-BCMA BiTEs, there is limited data assessing the benefit of early IVIG use in patients treated with talquetamab. **Methods:** A retrospective multicenter cohort study using the TriNetX Research Network to evaluate outcomes among adults with MM treated with talquetamab. Patients who received IVIG within 4 weeks of talquetamab initiation were compared to those who did not receive IVIG within 4 weeks. Propensity score matching was performed which included comorbidities, demographics, prior therapies (PIs, ImiDs, anti-CD38 abs, other BiTEs, belantamab, SCTx and CAR T), lab markers of disease severity, IgG levels, EM disease and plasma cell leukemia. Primary outcomes were 1-year all-cause mortality and infection incidence. Secondary outcomes included infection subtypes and ICU admission. Multivariable Cox proportional hazards models were used to identify independent associations. **Results:** Among 834 pts treated with talquetamab, 305 received IVIG within 4 wks of initiation. After propensity score matching, 271 patients remained in each cohort with balanced baseline characteristics. Early IVIG use was associated with lower 1-year mortality (14.8% vs. 26.7%; OR, 0.48; 95% CI, 0.31–0.74) and fewer infections of any type (41.7% vs. 55.0%; OR, 0.59; 95% CI, 0.42–0.82). Reductions were most pronounced for respiratory and bloodstream infections. In multivariable analysis, early IVIG remained independently associated with lower hazard of mortality (HR, 0.52; 95% CI, 0.37–0.73). In addition, a sub-analysis comparing early IVIG with no IVIG exposure within 1 year found similar findings. **Conclusions:** Early IVIG administration following talquetamab initiation was associated with reduced infection risk and improved survival in a large real-world cohort. These findings support consideration of early IVIG as part of routine supportive care for patients receiving talquetamab. Research Sponsor: None.

Outcome (after propensity matching)	IVIG within 4 weeks (n=271)	No IVIG within 4 weeks (n=271)	OR	95% CI	P-value
1-year mortality	40 (14.8)	72 (26.7)	0.48	0.31–0.74	0.0008
Any infection	113 (41.7)	149 (55.0)	0.59	0.42–0.82	0.002
Respiratory infections	37 (13.6)	55 (20.3)	0.62	0.39–0.98	0.04
Bloodstream infections	39 (14.4)	61 (22.5)	0.58	0.37–0.90	0.016
Opportunistic infections	13 (4.8)	10 (3.6)	1.31	0.57–3.05	>0.2
Skin & Soft Tissue infections	12 (4.4)	10 (3.6)	1.21	0.51–2.85	>0.2
Urinary tract infections	12 (4.4)	13 (4.8)	0.92	0.41–2.05	>0.2

Comparative safety and efficacy of DKRd versus DVRd regimens in multiple myeloma: A systematic review and meta-analysis.

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Background: The addition of anti-CD38 monoclonal antibodies to proteasome inhibitor-based triplet regimens, such as bortezomib-lenalidomide-dexamethasone (VRd) and carfilzomib-lenalidomide-dexamethasone (KRd), has improved depth of response, minimal residual disease (MRD) negativity, and survival in newly diagnosed multiple myeloma (NDMM). Comparative data on the efficacy and safety of daratumumab-KRd (DKRd) versus daratumumab-VRd (DVRd) are limited. We performed a systematic review and meta-analysis to evaluate these regimens in patients with NDMM. **Methods:** Following PRISMA guidelines, we searched PubMed, Scopus, Web of Science, and Embase from inception to November 2025 for clinical trials and observational studies of patients with NDMM treated with DVRd or DKRd. Outcomes included progression-free survival (PFS), overall survival (OS), MRD negativity, tumor response, and safety. Two independent reviewers screened studies and extracted data from each included article. Meta-analyses were done using R version 4.3.0. Heterogeneity was assessed using Cochrane's Q-test and I². **Results:** Sixteen studies involving 2114 patients were included. Two-year OS was comparable between regimens (DKRd: 94.12%; DVRd 94.17%; $p=0.979$) while two-year PFS favored DVRd (92.76% vs 85.04%; $p<0.001$). At 10–5 sensitivity, post-induction MRD negativity was higher with DKRd (57.10% vs 28.60%; $p=0.004$). DVRd achieved superior post-induction (98.94% vs 94.62%; $p<0.001$) and best overall responses (98.96% vs 95.10%; $p=0.019$). Safety outcomes generally favored DKRd, with fewer serious adverse events (32.79% vs 60.51%; $p<0.001$) and grade ≥ 3 adverse events (77.78% vs 90.34%; $p<0.001$). Grade ≥ 3 neutropenia (50.78% vs 30.90%; $p<0.001$) and thrombocytopenia (25.51% versus 9.62%; $p=0.005$) were more common with DVRd. Treatment discontinuation rates favored DKRd (1.94% versus 8.23%; $p=0.015$). Mortality remained low in both arms (1.41% versus 3.00%; $p=0.403$). **Conclusions:** In NDMM, DKRd achieved deeper early MRD responses and better tolerability, whereas DVRd provided superior two-year PFS and overall response rates. Treatment selection should balance efficacy against toxicity. Research Sponsor: None.

Plasma exchange in myeloma-associated acute kidney injury: A multicenter propensity-matched cohort study.

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Background: Acute kidney injury (AKI) in newly diagnosed multiple myeloma (MM) is frequently driven by light chain cast nephropathy and associated with dialysis dependence and early mortality. Plasmapheresis or plasma exchange (either one referred to here as PLEX) have been used to accelerate free light chain (FLC) removal, despite inconsistent evidence of clinical benefit. Whether PLEX improves renal or survival outcomes in the modern treatment era remains uncertain. **Methods:** A retrospective multicenter cohort study using the TriNetX Research Network identified newly diagnosed MM pts from 2014–2024 presenting with AKI (an ICD-10 code for acute renal failure or $\text{Cr} > / = 3.0 \text{ mg/dL}$ and a 6 mo prior $\text{Cr} < 1.5$) and laboratory evidence of light chain cast nephropathy (defined as a free light chain concentration $> 1,500 \text{ mg/L}$). Pts were included if they received PLEX within 7d of diagnosis, and were compared to those who did not receive PLEX. Pts were excluded if they had pre-existing end stage renal disease. Propensity score matching included demographics, comorbidities, myeloma therapies and laboratory values (Cr, calcium, albumin, hgb). **Results:** Among 5,454 eligible pts, 251 (4.6%) received PLEX (81% were plasma exchange and 19% were plasmapheresis). After propensity score matching, 248 pts were included in each group with well-balanced baseline characteristics (ex: ave Cr 4.1 and 4.2 in the PLEX vs no PLEX groups, respectively; 38% received PIs in each group). PLEX was not associated with reduced dialysis dependence at 90 days (16.1% vs 18.1%; odds ratio [OR] 0.87, 95% confidence interval [CI] 0.54–1.39) or 180 days (18.5% vs 20.2%; OR 0.90, 95% CI 0.58–1.41). Mortality at 90 (17.7% vs 15%) and 180 days (23.4% vs 23.9%) and ICU admission rates (20% vs 21%) were similar between groups. Dialysis-free survival over 180 days did not differ. Findings were consistent across all prespecified sensitivity analyses, including pts receiving early PI-based therapy and those with extreme free light chain burden ($\text{FLC} > 5000 \text{ mg/L}$, 28% of total cases), with no differences in dialysis dependence or survival. Patients treated with PLEX were numerically more likely to achieve creatinine $< 2.0 \text{ mg/dL}$ at both 90 days (83.9% vs 77.4%; OR 1.81, 95% CI 0.97–2.38; $p = 0.07$) and 180 days (86.3% vs 79.8%; OR 1.59, 95% CI 0.98–2.56; $p = 0.06$), but these differences did not reach statistical significance, except for those with $\text{FLC} > 5000$ (at 90d: 77% vs 63%, $p = 0.02$; and at 180d: 83% vs 66%, $p = 0.006$). **Conclusions:** In this large, contemporary, real-world retrospective cohort, PLEX was not associated with significantly improved renal recovery, dialysis-free survival, or mortality among patients with newly diagnosed myeloma-associated AKI due to light chain nephropathy. These results support current guidelines emphasizing rapid initiation of effective anti-myeloma therapy rather than routine extracorporeal light chain removal. Research Sponsor: None.

Trends in frontline treatment patterns for multiple myeloma among US veterans, 1999–2025.

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Background: Frontline treatment for multiple myeloma (MM) has evolved substantially, transitioning from alkylating therapy to newer therapeutic classes, including immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. Despite these advances, real-world treatment patterns remain heterogeneous, and MM therapies carry substantial toxicity and costs. Using nationwide Veterans Health Administration (VHA) data, an integrated health system with longitudinal follow-up, we characterized frontline treatment patterns for MM among US Veterans from 1999 to 2025. **Methods:** We identified Veterans diagnosed with MM in the VHA from 1999 to 2025. Diagnoses were confirmed using a published and validated natural language processing (NLP) algorithm, with the index date defined as the first MM-specific treatment, excluding dexamethasone alone. Patients receiving no MM-specific therapy or dexamethasone alone were excluded. Frontline treatments were defined as treatments initiated within 30 days of the index date. Treatments were captured using VA inpatient and outpatient pharmacy files, inpatient and outpatient procedure records for injectable agents, Fee Basis and Community Care data, and CMS Medicare Part D claims. Because the VHA does not require insurance approval, a 30-day window was used to define frontline treatment. Hematopoietic stem cell transplant was excluded to focus on trends in frontline treatments. MM-specific treatments were defined using a clinician-reviewed list of medications and relevant Current Procedural Terminology (CPT) codes. **Results:** We identified 4,738 Veterans with MM from 1999 to 2025. Median age was 72.1 years (IQR 65.1–78.1), and 96.7% were men. Non-Hispanic Black accounted for 20.1%, non-Hispanic White 55.6%, Hispanic 3.0%, and other races 1.5%. Median BMI was 27.6 (IQR 24.3–31.8), and 63.3% lived in urban areas. Melphalan predominated in 1999 (85.3%) but steadily declined. Cyclophosphamide use increased from 10.5% in 1999 to a peak of 29.2% in 2015, followed by a decline to 10.4% in 2024. Thalidomide use peaked in 2005 (61.8%) and declined to near zero by 2017. Lenalidomide use increased after 2006, reaching 78.1% in 2024. Bortezomib increased from 1.2% in 2004, peaking at 49.4% in 2015 and remaining common, whereas carfilzomib and ixazomib were infrequently used (< 6%). Monoclonal antibody use expanded after 2019 with daratumumab, reaching 45.5% in 2024. **Conclusions:** Using national VHA data from 1999 to 2025, we describe real-world frontline MM treatment patterns among US Veterans, illustrating temporal shifts in therapeutic class use, including increasing adoption of monoclonal antibodies within an integrated, longitudinal health system. Research Sponsor: None.

QUINTESSENTIAL-2: A phase 3 study of arlocabtagene autoleucel versus standard of care in adult patients with relapsed and refractory multiple myeloma (RRMM) exposed to lenalidomide.

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Background: Despite advances in multiple myeloma (MM) treatment, most patients (pts) will relapse, highlighting the need for new drug classes in RRMM. Further, with the extensive use of lenalidomide (LEN), an immunomodulatory drug (IMiD), in frontline and maintenance therapies, LEN-refractoriness has become increasingly common and 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 cell immune populations and limited expression on other tissues. Arlocabtagene autoleucel (arlo-cel) is a GPRC5D-directed autologous CAR T cell therapy that has demonstrated safety and efficacy in pts with RRMM in a first-in-human phase 1 study. ORR was 94% and 91% in pts with 1–3 and ≥ 3 prior LOT (pLOT), respectively, after a single arlo-cel infusion (150×10^6 CAR T-cells); ORR was 92% in pts with ≥ 3 pLOT following a 75×10^6 CAR T cell infusion. These phase 1 study outcomes support further clinical development of arlo-cel. **Methods:** QUINTESSENTIAL-2 (NCT06615479) is a randomized, open-label, multicenter, phase 3 confirmatory study comparing the efficacy and safety of arlo-cel vs SOC in adults with RRMM and prior LEN. Key inclusion criteria were age ≥ 18 years, confirmed diagnosis of MM per IMWG criteria, 1–3 pLOT (may include a proteasome inhibitor, IMiD, anti-CD38 antibody, and BCMA-targeted therapy), be exposed to LEN (≥ 2 consecutive cycles, unless PD was the best response to LEN-containing treatment or if there was LEN intolerance or unacceptable toxicity), have measurable disease, and ECOG PS of 0 or 1. Pts who received prior GPRC5D-targeted therapy are excluded. Eligible pts will be randomized 1:1 across 2 arms. Arm A includes leukapheresis within 3–4 days of randomization, mandatory bridging therapy ≤ 6 days of randomization with DPd (daratumumab, pomalidomide, dexamethasone) or Kd (carfilzomib, dexamethasone) per investigator choice and lymphodepleting chemotherapy prior to a single arlo-cel infusion. Arm B includes SOC of DPd or Kd per investigator choice, dosed per labeling, until PD. Primary endpoints are PFS and minimal residual disease (MRD) negativity in CR. Key secondary endpoints include OS and ORR. Other endpoints include safety, MRD-negative status, CR rate, time to response, duration of response, pharmacokinetics, and pt-reported outcomes. Pts will be followed for ≤ 5 years after the last pt is randomized, and with a long-term follow-up study (≤ 15 years post-infusion) for pts receiving arlo-cel. Anticipated enrollment is 440 pts at ~ 125 sites globally. The first pt was enrolled in March 2025. ©American Society of Hematology (2025). Reused with permission. Clinical trial information: NCT06615479. Research Sponsor: Bristol Myers Squibb.

MOMENTUM: A phase 2, open-label, single-arm, multicenter study to evaluate the efficacy of cemsidomide + dexamethasone in subjects with relapsed/refractory multiple myeloma (RRMM).

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Background: Cemsidomide is a novel, highly potent, cereblon-based, IKZF1/3 MonoDAC degrader, having a similar mechanism of action as BMS's IMiD or CELMoD degraders for MM. Cemsidomide displays catalytic activity enabling rapid and deep target degradation with high binding affinity to overcome resistance due to low cereblon levels. Cemsidomide binds to cereblon to facilitate the recruitment and ubiquitination of IKZF1/3 leading to the proteasomal degradation of both proteins. IKZF1/3 degradation induces multiple myeloma cell death, activation of fully differentiated T-cells which prevents T-cell exhaustion and promotes secretion of key immune stimulating cytokines. In a Phase 1 study, cemsidomide, given orally QD over 14 days with a 14 day "off" period (14/14) in combination with weekly dexamethasone in a heavily pre-treated patient population (7 median prior lines), was well tolerated and demonstrated durable anti-myeloma activity at increasing dose levels. A 53% ORR was observed at the highest dose of 100 µg QD 14/14, with a 36% ORR observed across all dose levels (Dhakal IMS 2025). **Methods:** MOMENTUM (NCT07284758) is a Phase 2 multi-center, open-label, single-arm, global study to further evaluate the anti-myeloma activity as well as safety, tolerability, and PK/PD of cemsidomide. The study will enroll ~100 patients. The patient population eligible for this study include those who have received at least 3 prior antimyeloma regimens, which must have included an IKZF1/3 degrader other than cemsidomide, a proteasome inhibitor, an anti-CD38 antibody, and a TCE or CAR-T therapy (unless not indicated). Prior TCE or CAR-T therapy may be one or more targets including but not limited to: BCMA, GPRC5D, FcRH5, and CD38. Patients must have an ECOG score of ≤2, and adequate organ function prior to dosing. Patients will receive cemsidomide 100 µg QD 14/14 and dexamethasone in a 28-day cycle until progressive disease, AE requiring treatment discontinuation, or withdrawal of consent. The primary endpoint of this study is ORR per IMWG response Criteria (IMS 2025) assessed by an Independent Review Committee (IRC). Secondary endpoints include assessment of DOR, PFS, and OS. Exploratory objectives include antimyeloma activity assessed by investigator, degradation of IKF1/3, quantification of protein expression, and patient QoL assessments. Exposure-response relationships between cemsidomide and relevant markers of safety and efficacy will also be analyzed. A safety review committee and an IRC will be established to oversee safety and efficacy throughout the trial. The study is open to enrollment as of December 2025. Clinical trial information: NCT07284758. Research Sponsor: C4 Therapeutics.

A phase 1/2 study of mRNA-2808 in participants with relapsed or refractory multiple myeloma.

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Background: Multiple myeloma (MM) remains mostly incurable despite therapeutic advances and relapsed or refractory multiple myeloma (RRMM) remains a significant unmet need. mRNA-2808 is an intravenously (IV) administered mRNA-encoded, multiplexed T-cell engager (TCE) that delivers *in vivo* translation of three distinct TCEs targeting BCMA, GPRC5D, and FcRH5. This multiplexed approach aims to enhance immune-mediated cytotoxicity, overcome tumor heterogeneity and target-mediated resistance. Previous preclinical studies of mRNA-2808 have demonstrated efficient *in vivo* translation of TCEs, potent activity against both primary MM cells *ex vivo* and murine tumor xenografts *in vivo*, and target-cell depletion in non-human primates. Taken together, this supports the clinical evaluation of mRNA-2808. **Methods:** This ongoing, first-in-human, open-label, multicenter Phase 1/2 study evaluates the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of mRNA-2808 administered to participants with RRMM. Key eligibility criteria include RRMM with prior exposure to a proteasome inhibitor, an IMiD, and an anti-CD38 monoclonal antibody and are either triple-class refractory or have progressed on or within 60 days of their last line of therapy, have measurable disease including bone marrow plasma cells >30% or plasmacytoma ≥2cm in size, and ECOG PS 0–2. Prior exposure to BCMA, GPRC5D, or FcRH5 targeted therapies is allowed. The study comprises two parts: Part 1 (dose escalation) to determine the recommended Phase 2 dose(s) (RP2D) and Part 2 (dose expansion) to further assess safety and efficacy of selected RP2D(s). The dose-escalation in Part 1 will proceed in 2 phases: Accelerated Titration Phase (single participant per dose level (DL)) and Standard Titration Phase (at least 3 participants per DL). The Accelerated Titration Phase will continue until a dose limiting toxicity (DLT) or a clinically significant AE of ≥Grade 2 is observed. If a ≥Grade 2 CRS and/or ≥Grade 2 neurotoxicity including ICANS occurs, step-up dosing will be implemented. During the Standard Titration Phase, dosing decisions will be guided by a Bayesian Optimal Interval design based on the observed DLT rate from the current cohort and recommendations from the Safety Review Committee. During Cycle 1 (28-day cycles), mRNA-2808 will be administered IV weekly, and during Cycles 2–12 every 2 weeks. Treatment with mRNA-2808 will continue for up to 12 cycles. Participants who achieve at least a partial response by the end of Cycle 5 may transition to a 4-week dosing schedule at the Investigator's discretion. Additional exploratory endpoints will evaluate surrogates of efficacy, mechanism of action, and characterize exposure. Dose Levels 1 and 2 have been completed without DLT and dose escalation is ongoing (NCT07116616). Clinical trial information: NCT07116616. Research Sponsor: Moderna, Inc.

Initial phase 1b/2 study results of purinostat mesylate (PM) in combination with pomalidomide (POM) and low dexamethasone (DEX) in patients with RRMM.

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Background: MM remains an incurable disease and resistance mechanisms are emerging. PM is a high selective HDAC I/Ib inhibitor. In phase I study, PM monotherapy had shown good tolerability and efficacy in relapsed/refractory (RR) hematologic malignancies including MM. A phase 1b/2 study is being conducted to further assess the efficacy and safety of PM combined with POM and low DEX (80mg/cycle) in RRMM. **Methods:** The ongoing phase 1b/2 study includes dose escalation followed by dose expansion. Eligible RRMM had received ≥ 1 prior line of therapy (LOT) including ≥ 1 PI and ≥ 1 IMiD. Cohort A (21D cycle) and Cohort B (28D cycle) of the PM combination regimens are assessed using 3+3 escalation design. Pts in Cohort A receive PM at levels of 4, 6, 8.4, 11.2 and 15mg/m² IV on D1,4,8,11; POM 4mg QD on D1-14; DEX 20mg on D1,4,8,11. Pts in Cohort B receive PM at same dose range to Cohort A, on D1,4,15,18; POM 4mg QD on D1-21; DEX 20mg on D1,4,15,18. Pts continue to receive PM until disease progression or unacceptable toxicity. Primary outcomes are DLT and ORR. Secondary outcomes include PFS et al. **Results:** As of Dec 23, 2025, 27 Pts were recruited including 6 in Cohort A and 21 in Cohort B. The dose had been escalated to 6mg/m² and 11.2mg/m² in Cohort A and B. Cohort A: Median age was 61.5 years, 66.7% male, 16.7% had prior ASCT. 2 (33.3%) Pts had high risk cytogenetics, including 1q21 duplication (n=1), t (4;14) (n=1) and 1p32 deletion (n=1). 6 Pts were evaluable with median 1 (1-3) prior LOT. The ORR was 50% with 1 sCR and 2 PR along with 1 MR. With a median F/U of 138 days, the median PFS was 151 days (95% CI, 21-NR). Median DOR was NR. The most common $\geq$ G3 TEAEs were neutropenia (83.3%), lymphocytopenia (83.3%) and thrombocytopenia (100%). No DLT was reported. Cohort B: Median age was 61.0 years, 57.1% male, 19.1% had prior ASCT and 19.1% had extramedullary disease (EMD). 7 (33.3%) Pts had high risk characteristics, including 1q21 duplication (n=7), t (4;14) (n=2) and early relapse after ASCT (n=3). Median prior LOT is 2 (1-5). Among 16 evaluable Pts, the ORR was 37.5% with 1 sCR, 1 CR, 3 VGPR and 1 PR; additional 4 Pts achieved MR. In 7 Pts given the dose of 8.4mg/m², the ORR was 42.9% with 3 VGPR; 3 more Pts achieved MR. With median F/U of 104 days, the median PFS and DOR were NR. The most common $\geq$ G3 TEAEs were neutropenia (81.0%), lymphocytopenia (61.9%) and thrombocytopenia (38.1%). 1 DLT (G4 neutropenia) was reported. Moreover, in 4 Pts with EMD, 2 achieved objective response. In 4 Pts with super high risk (Double or Triple Hit/early relapse), 1 achieved sCR and 1 achieved VGPR. 1 Pt with prior 5-line therapy including BCMA-ADC had shown VGPR after treatment. **Conclusion:** PM as a highly selective HDACi in combination with POM and low DEX shown encouraging efficacy and safety in RRMM. Complicated cases with EMD, super high-risk characteristics or heavily pretreatment can benefit from the PM triplet therapy. Clinical trial information: NCT06484829. Research Sponsor: None.

A phase 1b/2 study of mirdametinib in combination with sirolimus for patients with RAS-mutated relapsed/refractory multiple myeloma.

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Background: Relapsed and refractory multiple myeloma (RRMM) remains a significant therapeutic challenge, particularly among patients with genomic alterations in the RAS pathway (KRAS/NRAS mutations). These mutations occur in 60–70% of RRMM and are associated with aggressive disease and poor outcomes. Preclinical evidence suggests that dual inhibition of MEK and mTOR is required to effectively suppress oncogenic signaling in RAS dependent MM. This study evaluates the combination of the MEK inhibitor mirdametinib and the mTOR inhibitor sirolimus in patients with RAS-mutated RRMM. **Methods:** This is an open-label, single center, Phase 1b/2 study in adults with RRMM who are penta-class exposed and have no remaining standard therapeutic options. Patients must have RAS dependent MM as evidenced by a KRAS or NRAS mutation. Patients will be screened for these mutations at the NIH clinical center if unknown prior to referral. The phase 1b portion uses a standard 3+3 dose-escalation design to determine the recommended phase 2 dose (RP2D) of mirdametinib in combination with sirolimus. Phase 2 is a dose-expansion cohort using a Simon two-stage design to evaluate preliminary efficacy at the RP2D by overall response rate per the IMWG. Key eligibility criteria include adults aged ≥ 18 years with relapsed or refractory multiple myeloma per IMWG criteria, documented KRAS or NRAS mutation, prior exposure to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody, ECOG performance status 0–2, and adequate organ function. Correlative studies include serial assessment of MAPK and mTOR pathway inhibition and pharmacodynamic biomarkers in peripheral blood and bone marrow samples. The study is actively enrolling at the NIH Clinical Center (NCT06876142), with a planned total enrollment of 54 patients. Clinical trial information: NCT06876142. Research Sponsor: None.