8000 **Oral Abstract Session**

Upfront autologous stem cell transplantation (ASCT) versus carfilzomib-cyclophosphamide-dexamethasone (KCd) consolidation with K maintenance in transplant-eligible, newly diagnosed (NDTE) multiple myeloma (MM).

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Background: Upfront ASCT for NDTE MM remains under evaluation with high MRD rates following novel induction and consolidation (cons) strategies. Current phase 3 trials support ASCT, however these employ lenalidomide maintenance which predominantly benefits standard risk (SR) patients (pts). The CARDAMON trial investigated the role of ASCT using K based induction and maintenance. **Methods:** NDTE pts received 4 x KCd induction (K 20/56 mg/m^2 biweekly, C 500 mg D 1,8,15, d 40mg weekly) before 1:1 randomisation to ASCT or 4 x KCd cons. All received 18 months K maintenance (56mg/m^2 D1,8,15). Flow cytometric MRD (10^{-5}) was assessed post induction, pre-maintenance and at 6 months maintenance. Primary endpoints were ≥VGPR post induction and 2-year PFS from randomisation. 210 randomised pts were needed to exclude a 10% non-inferiority margin with 15% 1-sided alpha, 80% power. **Results:** 281 pts were registered, median age 59y (33–74), 24% high risk [t(4;14), t(14;16), t(14;20) or del(17p)]. Post induction, ≥VGPR rate was 58.5%, ORR was 87% with similar responses for high risk vs SR. 52 pts did not proceed to PBSCH (6 MR, 16 PD, 19 toxicity, 4 deaths: 3 infection, 1 cardiac event, 7 other). 109 were randomised to ASCT, 109 to KCd cons. ≥VGPR rate was 78.5% after cons and 80.0% after ASCT (p = 0.8). Median KCd cons dose was 55.5 mg/m^2, 99 (90.8%) pts completed 4 cycles, 104 (95.4%) pts received ASCT. After 2.6 years follow-up, median PFS was not reached for ASCT vs 3.8 years for cons (HR: 0.82 (70% CI 0.65, 1.05, p = 0.4). Observed 2-year PFS for ASCT was 75.5% vs 70.7% for cons; calculated difference in 2-year PFS rate (cons vs ASCT) was -4.5% (70% CI -9.2%, +1.1%, non-inferior). High risk pts had inferior outcomes to SR overall regardless of randomisation (2-year PFS ASCT: 52% vs 82% (HR 4.09); cons 48% vs 77% (HR 2.83)). 2 year PFS did not differ according to randomisation: SR 82% (ASCT) vs 77% (cons) HR: 1.29 (0.71-2.35); high risk: 52% (ASCT) vs 48% (cons) HR: 1.06 (0.50-2.23). MRD negativity post induction was 24.3% and similar by genetic risk. MRD negative rates were higher post ASCT (53.1%) than cons (35.8%) (p = 0.02) independent of genetics: SR 49% (ASCT) vs 36% (cons); high risk: 57% (ASCT) vs 32% (cons). G3+ adverse events to induction were infections (18.7%), hypertension (11.2%), anaemia (10.4%), cardiac disorders (3.6%), vomiting (2.2%), fatigue (2.2%), diarrhoea (1.8%). **Conclusions:** In NDMM receiving KCd induction and K maintenance, KCd cons was non-inferior to ASCT. High risk pts had inferior outcomes, that were not influenced by ASCT or cons randomisation. Clinical trial information: NCT02315716. Research Sponsor: Amgen.

	ASCT			Consolidation		
Disease response (%)	All (107)	High risk (25)	Std Risk (76)	All (107)	High Risk (25)	Std Risk (75)
CR/sCR	14.3	16	13.1	24.3	24	24
VGPR	65.7	60	67.1	54.2	44	57.3
PR	16.2	20	15.8	11.2	8	12
No response	1.0	0	1.3	1.8	0	2.6
Withdrawn for toxicity or PD	2.9	4	2.6	8.4	24	4

8001 **Oral Abstract Session**

Depth of response and minimal residual disease status in ultra high-risk multiple myeloma and plasma cell leukemia treated with daratumumab, bortezomib, lenalidomide, cyclophosphamide and dexamethasone (Dara-CVRd): Results of the UK optimum/MUKnine trial.

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Background: Patients with ultra high-risk (UHiR) newly diagnosed multiple myeloma (NDMM) and patients with plasma cell leukemia (PCL) continue to have dismal outcomes and are underrepresented in clinical trials. Recently, improved responses with anti-CD38 monoclonal antibody combination therapy have been reported for NDMM patients. We report here outcomes for NDMM UHiR and PCL patients treated in the OPTIMUM/MUKnine (NCT03188172) trial with daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone (Dara-CVRd) induction, augmented high-dose melphalan (HDMEL) and ASCT. With final analysis follow-up surpassed in Feb 2021, we report here early protocol defined endpoints from induction to day 100 post ASCT. **Methods:** Between Sep 2017 and Jul 2019, 107 patients with UHiR NDMM by central trial genetic ($\geq$2 high risk lesions: t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p)) or gene expression SKY92 (SkylineDx) profiling, or with PCL (circulating plasmablasts $>$ 20%) were included in OPTIMUM across 39 UK hospitals. Patients received up to 6 cycles of Dara-CVRd induction, HDMEL and ASCT augmented with bortezomib, followed by Dara-VR(d) consolidation for 18 cycles and Dara-R maintenance. Primary trial endpoints are minimal residual disease (MRD) status post ASCT and progression-free survival. Secondary endpoints include response, safety and quality of life. Data is complete but subject to further data cleaning prior to conference. **Results:** Median follow-up for the 107 patients in the safety population was 22.2 months (95% CI: 20.6 – 23.9). Two patients died during induction due to infection. Bone marrow aspirates suitable for MRD assessment by flow cytometry (10^{-5} sensitivity) were available for 81% of patients at end of induction and 78% at D100 post ASCT. Responses in the intention to treat population at end of induction were 94% ORR with 22% CR, 58% VGPR, 15% PR, 1% PD, 5% timepoint not reached (TNR; withdrew, became ineligible or died) and at D100 post ASCT 83% ORR with 47% CR, 32% VGPR, 5% PR, 7% PD, 10% TNR. MRD status was 41% MRDneg, 40% MRDpos and 19% not evaluable post induction and 64% MRDneg, 14% MRDpos and 22% not evaluable at D100 post ASCT. Responses at D100 post ASCT were lower in PCL with 22% CR, 22% VGPR, 22% PR, 22% PD, 12% TNR. Most frequent grade 3/4 AEs during induction were neutropenia (21%), thrombocytopenia (12%) and infection (12%). Grade 3 neuropathy rate was 3.7%. **Conclusions:** This is to our knowledge the first report on a trial for UHiR NDMM and PCL investigating Dara-CVRd induction and augmented ASCT. Response rates were high in this difficult-to-treat patient population, with toxicity comparable to other induction regimens. However, some early progressions highlight the need for innovative approaches to UHiR NDMM. Clinical trial information: NCT03188172. Research Sponsor: Myeloma UK and research support by Celgene and Janssen.

8002 **Oral Abstract Session**

Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by lenalidomide (R) or carfilzomib-lenalidomide (KR) maintenance: Efficacy in high-risk patients.

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Background: Cytogenetic abnormalities (CA) are one of the most powerful prognostic factors in multiple myeloma (MM). In the FORTE study, carfilzomib-lenalidomide-dexamethasone induction/consolidation with ASCT (KRd_ASCT) significantly improved progression-free survival (PFS) vs KRd without ASCT (KRd12, HR 0.64) or carfilzomib-cyclophosphamide-dexamethasone (KCd) plus ASCT (KCd_ASCT, HR 0.53). KR maintenance significantly improved PFS vs R (HR 0.63). **Methods:** MM patients (pts) were randomized to KRd_ASCT vs KCd_ASCT vs KRd12 and, thereafter, to KR vs R maintenance. Subgroup analyses according to FISH evaluated the impact of each single high-risk (HiR) CA [del17p, t(4;14), t(14;16), del1p and 1q gain (3 copies) or amp1q ($\geq$4 copies)] and that of combined CA, defining HiR by the presence of $\geq$1 HiR CA and double-hit (DH) by the presence of $\geq$2 HiR CA. Pts negative for all the HiR CA were considered at standard risk (SR). The primary objective was the impact of treatment on PFS according to pt risk. **Results:** 396 out of 474 enrolled pts were included in the analysis with complete FISH data: 243 HiR, 105 DH and 153 SR. Among HiR pts, 60 had del17p, 65 t(4;14), 20 t(14;16), 44 del1p, 126 1q gain and 49 amp1q. SR pts benefited from intensification with KRd_ASCT vs KRd12 (HR 0.47, p = 0.05) and KCd_ASCT (HR 0.38, p = 0.01), with a 4-year PFS of 80%, 67% and 57%, respectively. In HiR pts, KRd_ASCT improved PFS vs KRd12 (HR 0.6, p = 0.04) and KCd_ASCT (HR 0.57, p = 0.01), with a 4-year PFS of 62%, 45% and 45%, respectively. The advantage with KRd_ASCT vs KRd12 (HR 0.53, p = 0.07) and KCd_ASCT (HR 0.49; p = 0.03) was also observed in DH pts (4-year PFS 55%, 31% and 33%, respectively). Analyses by single CA were limited by the small number of pts in each subgroup, but a trend towards a PFS benefit from KRd_ASCT vs KRd12 was seen in pts with del17p (HR 0.61, p = 0.3), t(4;14) (HR 0.59, p = 0.2) and 1q gain (HR 0.45, p = 0.02). In pts with del1p, KRd_ASCT (HR 0.24, p = 0.06) and KRd12 (HR 0.33, p = 0.09) showed superiority over KCd_ASCT, while amp1q pts had the worst outcome regardless of treatment (KRd_ASCT vs KCd_ASCT, HR 1.16, p = 0.73; KRd12 vs KCd_ASCT, HR 1.34, p = 0.45). KR improved PFS vs R in SR (3-year PFS 90% vs 73%, HR 0.42, p = 0.06), HiR (3-year PFS 69% vs 56%, HR 0.6, p = 0.04) and DH pts (3-year PFS 67% vs 42%, HR 0.53, p = 0.1). Despite the small subgroups, a beneficial trend with KR vs R was observed in pts with del17p (HR 0.59, p = 0.37), t(4;14) (HR 0.59, p = 0.3), 1q gain (HR 0.54, p = 0.07) and del1p (HR 0.23, p = 0.08), while amp1q pts showed the worst outcome and no benefit from KR vs R (HR 0.83, p = 0.7). **Conclusions:** KRd_ASCT and KR maintenance are highly effective in SR and also in HiR and DH pts, with impressive 4-year PFS from diagnosis (KRd_ASCT: HiR 62%, DH 55%) and 3-year PFS from maintenance (KR: HiR 69%, DH 67%), thus supporting their use in HiR pts, who represent an unmet medical need. Clinical trial information: NCT02203643. Research Sponsor: Amgen; Bristol-Myers Squibb (Celgene).

8003 **Oral Abstract Session**

Subcutaneous daratumumab + bortezomib, cyclophosphamide, and dexamethasone (VCd) in patients with newly diagnosed light chain (AL) amyloidosis: Updated results from the phase 3 ANDROMEDA study.

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Background: Systemic AL amyloidosis is a plasma cell disease characterized by the deposition of insoluble amyloid fibrils causing organ dysfunction and death. Primary results from the ANDROMEDA study showed that addition of subcutaneous (SC) daratumumab (DARA) to the standard of care combination of bortezomib, cyclophosphamide, and dexamethasone (VCd) was superior to VCd alone, with higher rates of hematologic complete response (CR) and an acceptable safety profile. DARA-VCd was approved for newly diagnosed AL amyloidosis in January 2021. Here we present an update of the primary ANDROMEDA study results with longer follow-up. **Methods:** ANDROMEDA is a randomized, open-label, active-controlled phase 3 study. Adult patients (pts) with newly diagnosed AL amyloidosis were randomized 1:1 to DARA-VCd or VCd and were treated for 6 28-day Cycles (Cyc). Bortezomib (1.3 mg/m^2), cyclophosphamide (300 mg/m^2 maximum weekly dose 500 mg), and dexamethasone (40 mg) were given weekly. DARA SC was given weekly (Cyc 1–2) and every 2 weeks (wk) (Cyc 3–6). After Cyc 6, pts in the DARA-VCd group received DARA SC alone every 4 wk for up to 24 Cyc from first dose. Disease status was evaluated every 4 wk in Cyc 1–6 and every 8 wk after Cyc 7. The primary endpoint was overall hematologic CR rate in the intent-to-treat population. Secondary endpoints were major organ deterioration progression-free survival (PFS), organ response rate, time to hematologic response, survival, and safety. **Results:** Of 388 randomized pts, 195 were randomized to DARA-VCd and 193 to VCd. As of November 2020, the median treatment duration was 18.5 months (mo) for DARA-VCd and 5.3 mo for VCd; 78 pts (40%) in the DARA-VCd group were still on treatment. The overall hematologic CR rate continued to be higher with DARA-VCd than VCd (59% vs 19%; odds ratio [OR] 5.9; 95% CI 3.7–9.4; $P<$ 0.0001). More pts achieved a very good partial response or better ($\geq$VGPR) with DARA-VCd than VCd (79% vs 50%; OR 3.7; 95% CI 2.4–5.9; $P<$ 0.0001). Among responders, median time from randomization to $\geq$VGPR was shorter for DARA-VCd than VCd (0.56 vs 0.82 mo). Cardiac response rates were higher with DARA-VCd than VCd at 6 mo (42% vs 22%) and at 12 mo (57% vs 28%); renal response rates were 54% vs 27% at 6 mo and 57% vs 27% at 12 mo. A total of 71 deaths occurred (DARA-VCd, n = 31; VCd, n = 40). From Cyc 7 onward in the DARA-VCd group, no grade 3/4 treatment-emergent adverse events occurred in $\geq$5% of pts. There were no systemic administration-related reactions with DARA-VCd after Cyc 6. Analysis of major organ deterioration PFS will be updated after ~200 events have occurred. **Conclusions:** Updated results from the ANDROMEDA study reinforce the clinical superiority of DARA-VCd over VCd in pts with newly diagnosed AL amyloidosis. Based on its recent approval, DARA-VCd represents a new standard of care in AL amyloidosis. Clinical trial information: NCT03201965. Research Sponsor: Janssen Research & Development, LLC.

8004 **Oral Abstract Session**

Daratumumab (DARA) maintenance or observation (OBS) after treatment with bortezomib, thalidomide and dexamethasone (VTd) with or without DARA and autologous stem cell transplant (ASCT) in patients (pts) with newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 2.

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Background: D-VTd plus ASCT was approved for transplant-eligible (TE) NDMM based on part 1 of CASSIOPEIA. We report a prespecified interim analysis of CASSIOPEIA part 2: DARA maintenance vs OBS in pts with ≥partial response (PR) in part 1, regardless of induction/consolidation (ind/cons) treatment. **Methods:** CASSIOPEIA is a 2-part, randomized, open-label, phase 3 study in TE NDMM. Pts received 4 cycles ind and 2 cycles cons with D-VTd or VTd. 886 pts who achieved ≥PR were rerandomized to DARA 16 mg/kg IV Q8W for up to 2 yr (n = 442) or OBS (n = 444) until progressive disease per IMWG. Pts were stratified by ind (D-VTd vs VTd) and depth of response (minimum residual disease [MRD] status and post cons response ≥PR). Primary endpoint was progression-free survival (PFS) after second randomization. This interim analysis assessed efficacy and safety after 281 PFS events. A preplanned hierarchical procedure tested key secondary endpoints: time to progression (TTP), ≥complete response (CR), MRD negativity rates by NGS and overall survival (OS). **Results:** At median follow-up of 35.4 mo, median PFS was not reached (NR) with DARA and 46.7 mo with OBS (HR 0.53; 95% CI 0.42–0.68; P <0.0001). PFS advantage for DARA was consistent across most subgroups. However, a prespecified analysis showed significant interaction with ind/cons treatment arm (P< 0.0001). PFS HR for DARA vs OBS was 0.32 (95% CI 0.23–0.46) in the VTd arm and 1.02 (0.71–1.47) in the D-VTd arm. Median TTP was NR for DARA vs 46.7 mo for OBS (HR 0.49; 95% CI 0.38–0.62; P <0.0001). More pts in the DARA vs OBS arm achieved ≥CR (72.9% vs 60.8%; OR 2.17; 95% CI 1.54–3.07; P <0.0001). MRD negativity (in ≥CR pts at 10^{-5}) was 58.6% with DARA vs 47.1% with OBS (OR 1.80; 95% CI 1.33–2.43; P= 0.0001). Median OS was NR in either arm. Most common (≥2.5%) grade 3/4 adverse events (AEs) with DARA vs OBS were pneumonia (2.5% vs 1.4%), lymphopenia (3.6% vs 1.8%), and hypertension (3.0% vs 1.6%). Serious AEs occurred in 22.7% (DARA) vs 18.9% (OBS) of pts; the most common (≥2.5%) was pneumonia (2.5% vs 1.6%). 13 (3.0%) pts discontinued DARA due to an AE. The rate of infusion-related reactions was 54.5% (DARA-nave pts) and 2.2% (prior DARA pts); 90% were grade 1/2.Second primary malignancies occurred in 5.5% (DARA) vs 2.7% (OBS) of pts. **Conclusions:** CASSIOPEIA part 2 demonstrated a clinical benefit of DARA maintenance in TE NDMM pts, with significantly longer PFS for DARA vs OBS. With current follow-up, maintenance PFS benefit appeared only in pts treated with VTd as ind/cons. Pts who received D-VTd ind/cons with or without DARA maintenance achieved similar PFS; longer follow-up is needed for PFS2 and OS. DARA significantly increased deeper response and MRD negativity rates vs OBS, and was well tolerated with no new safety signals. Clinical trial information: NCT02541383. Research Sponsor: Janssen Research & Development, LLC.

8005 **Oral Abstract Session**

Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1.

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Background: CARTITUDE-1 (NCT03548207) is a phase 1b/2 study evaluating ciltacabtagene autoleucel (cilta-cel; JNJ-68284528), a CAR T-cell therapy with two BCMA–targeting single-domain antibodies, in patients (pts) with R/R MM. Here, we report updated results in pts with a longer duration (median 12.4 months) of follow-up. **Methods:** Eligible pts had MM and received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and had received a PI, IMiD, and anti-CD38 antibody. After apheresis, bridging therapy was permitted. Pts received a single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg; range $0.5\text{-}1.0\times10^6$) 5–7 days (d) after lymphodepletion (300 mg/m^2 cyclophosphamide, 30 mg/m^2 fludarabine daily for 3 d). The primary objectives were to characterize cilta-cel safety, confirm the recommended phase 2 dose (RP2D; phase 1b), and evaluate efficacy (phase 2). Cytokine release syndrome (CRS) was graded by Lee *et al* (Blood 2014) and neurotoxicity by CTCAE, v5.0 (in phase 1b). CRS and ICANS were graded by ASTCT criteria (in phase 2). Here, Lee *et al* and CTCAE v5.0 were mapped to ASTCT for CRS and ICANS, respectively. **Results:** As of Sept 1, 2020, 97 pts with a median of 6 prior lines received cilta-cel. Overall response rate per independent review committee (primary endpoint) was 97% (95% CI, 91–99), with 67% achieving stringent complete response (sCR). Median time to first response was 1 month (range, 1–9), and median time to CR or better was 2 months (range, 1–15). Responses deepened over time, and median duration of response was not reached. Of 57 pts evaluable for minimal residual disease (MRD) assessment, 93% were MRD-negative at 10^{-5}. The 12-month progression-free survival (PFS) and overall survival rates (95% CI) were 77% (66–84) and 89% (80–94), respectively; median PFS was not reached. Grade 3/4 hematologic AEs ≥20% included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). CRS occurred in 95% of pts (4% grade 3/4), with median time to onset of 7 d (range, 1–12), and median duration of 4 d (range, 1–14, excluding 1 pt with 97-d duration). CRS resolved in all but one with grade 5 CRS/haemophagocytic lymphohistiocytosis. CAR T-cell neurotoxicity occurred in 21% of pts (grade ≥3, 10%). Fourteen deaths occurred during the study after cilta-cel infusion: none within the first 30 days, 2 within 100 days; and 12 more than 100 days post infusion, of which 5 were due to disease progression, and 4 due to treatment-related AEs. **Conclusions:** A single infusion of cilta-cel yielded early, deep, and durable responses in heavily pretreated pts with MM, with a manageable safety profile at the RP2D. Cilta-cel is under further investigation in other MM populations in earlier lines of therapy and in outpatient settings. Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8006 **Oral Abstract Session**

Efficacy and safety of elranatamab (PF-06863135), a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MM).

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Background: Elranatamab (PF-06863135) is a humanized bispecific monoclonal antibody (IgG2a) that targets BCMA, a member of the tumor necrosis factor receptor superfamily expressed in MM, and CD3 on T cells. We reported results for intravenous (IV) dosing (Raje et al. Blood. 2019;134(S1):1869) and now update for subcutaneous (SC) dosing from the ongoing Phase 1 study (MagnetisMM-1). **Methods:** Patients (pts) received elranatamab at 80, 130, 215, 360, 600, and 1000μg/kg SC weekly. A modified toxicity probability interval method was used for escalation, with monitoring for dose-limiting toxicity (DLT) to end of the first cycle. Treatment-emergent adverse events (TEAEs) were graded by Common Terminology Criteria for Adverse Events (v4.03), and cytokine release syndrome (CRS) by American Society for Transplantation and Cellular Therapy criteria (Lee et al. Biol Blood Marrow Transplant. 2019;25:625). Response was assessed by International Myeloma Working Group criteria. Pharmacokinetics, cytokine profiling, and T cell immunophenotyping were performed. **Results:** 30 pts had received elranatamab as of 4-Aug-2020 at 80 (n = 6), 130 (n = 4), 215 (n = 4), 360 (n = 4), 600 (n = 6), or 1000 (n = 6) μg/kg SC weekly. Pts had a median of 8 prior treatments; 87% had triple refractory disease, 97% had prior anti-CD38 therapy, and 23% had prior BCMA-directed antibody drug conjugate or chimeric antigen receptor T cell therapy. The most common all causality TEAEs included lymphopenia (n = 24, 80%; 20% G3, 60% G4), CRS (n = 22, 73%; none $>$ G2), anemia (n = 17, 57%; 43% G3, 3% G4), injection site reaction (n = 16, 53%; none $>$ G2), thrombocytopenia (n = 16, 53%; 23% G3, 17% G4), and neutropenia (n = 12, 40%; 17% G3, 17% G4). Both CRS and immune effector cell-associated neurotoxicity syndrome (n = 6, 20%) were limited to $\leq$G2 with median durations of 2 and 1.5 days, respectively. No DLT was observed. Exposure increased with dose, and T_{max} ranged from 3–7 days. Cytokine increases occurred with the first dose, and increased T-cell proliferation was observed in peripheral blood. The overall response rate (ORR) for doses $\geq$215μg/kg was 75% (n = 15/20) including partial response (PR; n = 6), very good PR (VGPR; n = 3), complete response (CR; n = 1), and stringent CR (sCR; n = 5). Median time to response was 22 days, and 3 of 4 pts (75%) with prior BCMA-directed therapy achieved response (VGPR, n = 2 and sCR, n = 1). Updated data, including duration of response, will be presented. **Conclusions:** Elranatamab demonstrated a manageable safety profile, and SC doses $\geq$215μg/kg achieved ORR of 75% with CR/sCR rate of 30%. These results demonstrate the safety and efficacy of SC elranatamab in this relapsed/refractory population and support ongoing development of elranatamab for pts with MM, both as monotherapy and in combination with standard or novel therapies. Clinical trial information: NCT03269136. Research Sponsor: Pfizer.

8007 **Oral Abstract Session**

Updated phase 1 results of teclistamab, a B-cell maturation antigen (BCMA) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM).

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Background: BCMA-targeted immunotherapies offer considerable promise for relapsed/refractory MM. Teclistamab (JNJ-64007957) is a BCMA × CD3 bispecific IgG4 antibody that redirects CD3+ T cells to BCMA-expressing MM cells. We present updated results of patients (pts) treated at the recommended phase 2 dose (RP2D) in the first-in-human phase 1 study of teclistamab. **Methods:** Eligible pts had MM and were relapsed, refractory or intolerant to established therapies. Primary objectives were to identify the RP2D (part 1) and characterize safety and tolerability of teclistamab at the RP2D (part 2)**.** Teclistamab was given intravenously (IV; range 0.3–19.2 μg/kg [biweekly]; range 19.2–720 μg/kg [weekly]) or subcutaneously (SC; range 80.0–3000 μg/kg weekly) in different cohorts, with step-up dosing used for ≥38.4 μg/kg doses. Adverse events (AEs) were graded by CTCAE v4.03 (cytokine release syndrome [CRS] by Lee et al 2014). Response was assessed per IMWG criteria. **Results:** As of Feb 4, 2021, 156 pts received teclistamab (IV n = 84; SC n = 72). The RP2D, identified as weekly SC 1500 μg/kg teclistamab with 60.0 and 300 μg/kg step-up doses, was given to 40 pts (median follow-up 4.3 mo [range 1.1–10.4+]). Pts dosed at the RP2D (median age, 62.5 y [range, 39–84]; 65% male) had received a median of 5 prior lines of therapy (range 2–11; 100% triple-class exposed; 65% penta-drug exposed; 83% triple-class refractory; 35% penta-drug refractory; 85% refractory to their last line of therapy). There were no dose-limiting toxicities at the RP2D in part 1. The most common AEs at the RP2D were CRS (70%; grade 3/4 0) and neutropenia (60%; grade 3/4 40%); grade 1 neurotoxicity was reported in 1 (3%) pt. Median time to CRS onset was later with SC vs IV dosing (day after SC injection vs day of IV infusion). The overall response rate in response-evaluable pts treated at the RP2D (n = 40) was 65%; 58% achieved a very good partial response or better and 30% achieved a complete response (CR) or better; median time to first confirmed response was 1.0 mo (range 0.2–3.1). At the RP2D, median duration of response was not reached; 23 of 26 responders (88%), after median follow-up of 5.3 mo (range 1.2–10.4+), were alive and continuing on treatment with responses deepening over time. Of 14 evaluable pts across all cohorts, 9 with CR were minimal residual disease–negative at 10^{-6}. At the RP2D, teclistamab exposure was sustained across the dosing interval and exceeded target levels, and consistent T cell activation was observed. **Conclusions:** Teclistamab at the RP2D (weekly 1500 μg/kg SC) was well-tolerated and showed encouraging efficacy with durable, deepening responses, supporting further investigation as monotherapy and in combination with other agents. With the extended exposure profile at the RP2D and delayed and low-grade CRS observed with SC administration, alternative SC dosing strategies are being explored. Clinical trial information: NCT03145181. Research Sponsor: Janssen Research & Development, LLC.

8008 **Oral Abstract Session**

Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM).

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Background: New immunotherapy targets in MM are needed as patients (pts) continue to relapse. The orphan receptor GPRC5D is expressed on malignant plasma cells in MM. Talquetamab (JNJ-64407564) is a bispecific IgG4 antibody that redirects T cell killing to MM cells by binding to the novel target, GPRC5D, and CD3. We present updated results of talquetamab at the recommended phase 2 dose (RP2D) from a phase 1 trial in relapsed/refractory MM. **Methods:** Eligible pts with MM who had relapsed or refractory disease or were intolerant to standard therapies received talquetamab intravenously (IV; range 0.5–180 μg/kg) or subcutaneously (SC; range 5.0–800 μg/kg) weekly or biweekly. Primary objectives were identification of the RP2D (part 1) and talquetamab safety and tolerability at the RP2D (part 2). Adverse events (AEs) were graded by CTCAE v4.03 (cytokine release syndrome [CRS] per Lee 2014). Response was assessed per IMWG criteria. **Results:** As of Feb 8, 2021, 174 pts received talquetamab, 102 by IV and 72 by SC; in parts 1 and 2, 28 pts were treated at the RP2D, identified as weekly SC 405 μg/kg, with 10.0 and 60.0 μg/kg step-up doses. Pts treated at the RP2D had a median age of 61.5 y (range 46–80) and a median of 5.5 prior lines of therapy (range 2–14; 100%/79% triple-class/penta-drug exposed; 71%/18% triple-class/penta-drug refractory; 86% refractory to last line of therapy; 21% with prior B-cell maturation antigen–directed therapy). No dose-limiting toxicities occurred at the RP2D in part 1. Most common AEs at the RP2D were CRS (79%; grade 3 4%; median time to onset: day after SC injection), neutropenia (64%; grade 3/4 54%), anemia (57%; grade 3/4 29%) and dysgeusia (57%; all grade 1/2); infections were reported in 32% of pts (grade 3/4 4%) and neurotoxicity in 7% (grade 3/4 0). In all, 75% of pts dosed at the RP2D had skin-related AEs (grade 3/4 0), including 18% with nail disorders. The overall response rate at the RP2D in response-evaluable pts (n = 24) was 63%, with 50% reaching very good partial response or better; 9/17 (53%) evaluable triple-class refractory pts and 3/3 (100%) penta-drug refractory pts had a response. Median time to first confirmed response at the RP2D was 1.0 mo (range 0.2–3.8); responses were durable and deepened over time (median follow-up 6.2 mo [range 2.7–9.7+] for responders at the RP2D). At the RP2D, exposure was maintained over the maximum EC_{90} target level from an ex vivo cytotoxicity assay, and consistent T cell activation was seen. **Conclusions:** At the RP2D of weekly 405 μg/kg SC, talquetamab showed a high clinical response rate and was well-tolerated in pts with relapsed/refractory MM; based on pharmacokinetic data, other SC dosing strategies are being explored. The promising efficacy, safety profile and convenience of SC dosing support monotherapy development and combination approaches with this novel agent. Clinical trial information: NCT03399799. Research Sponsor: Janssen Research & Developent, LLC.

8009 **Poster Discussion Session**

MASS-FIX versus standard methods to predict for PFS and OS among multiple myeloma patients participating on the STAMINA trial.

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Background: Measuring response among patients with multiple myeloma is essential for the care of patients. Deeper responses have been associated with better progression free survival (PFS) and overall survival (OS). Serum (SIFE) and urine immunofixation are the currently used markers for biochemical documentation of CR after which marrow is tested for plasma cell clearance. Next generation flow cytometry and sequencing are used to document the presence of minimal residual disease (MRD). Mass spectrometry of blood by MALDI (Mass-Fix) is a new simple, inexpensive, sensitive, and specific means of detecting monoclonal immunoglobulins. To better test the hypothesis that Mass-Fix is superior to existing methodologies to predict for survival outcomes—especially SIFE– samples from the STAMINA trial (NCT01109004), a trial comparing 3 transplant approaches among patients who have already received induction, were employed. **Methods:** Five-hundred and seventy-five patients were included. Samples from enrollment post-induction (post-I) and 1-year post enrollment (1YR) were tested when available. Four response parameters were assessed univariately: Mass-Fix, SIFE, complete response, and MRD by next generation flow cytometry. Mass spectrometry spectra were evaluated in a blinded fashion. Complete response was according to the 2006 International Myeloma Working Group criteria. Multivariate Cox proportional hazard models using stepwise regression were developed to explore the independent effect of the different response parameters on PFS and OS and interactions with other risk factors. **Results:** Of the 4 response measures, only MRD and Mass-Fix predicted for PFS and OS at multiple testing points on multivariate analyses (Table). Of the 4 post-I measurements, only MRD predicted for PFS; however, Mass-Fix was the only post-I measurement to predict for OS. Of all the 1-year measures, both 1YR Mass-Fix and 1YR MRD positivity predicted for inferior PFS and OS. In models including MRD and Mass-Fix, SIFE and CR were not prognostic for PFS or OS. **Conclusions:** Mass-Fix is a powerful means to track monoclonal proteins. The full utility of Mass-Fix was not exploited given the absence of a diagnostic sample and the fact that only serum (and not urine) was tested. Despite these limitations, it performed well at pre-induction and at 1 year. Mass-Fix provides a convenient and non-invasive means of predicting for myeloma outcomes. Clinical trial information: NCT01109004. Research Sponsor: This manuscript was prepared using BMT CTN 0702 Research Materials obtained from the NHLBI. This project was also supported by Grant Number P30 CA015083 and CA186781 from the National Cancer Institute and by the Predolin Foundation. Support for the clinic.

Multivariate PFS and OS.

Post-induction sample	PFS RR (95%CI)	P	OS RR (95%CI)	P
MRD positive	1.50 (1.07, 2.08)	0.017	-	-
Mass-Fix positive	-	NS	1.64 (1.05, 2.57)	0.03
<CR	-	NS	-	-
SIFE positive	-	NS	-	-
1-year sample				
MRD positive	3.01 (1.93, 4.70)	<0.0001	2.77 (1.50, 5.12)	0.0012
Mass-Fix positive	1.62 (1.11, 2.35)	0.012	1.93 (1.04, 3.56)	0.036
<CR	-	NS	NS	NS
SIFE positive	-	NS	NS	NS

RR, risk ratio; NS, not significant.

Analysis of minimal residual disease in bone marrow by NGF and in peripheral blood by mass spectrometry in newly diagnosed multiple myeloma patients enrolled in the GEM2012MENOS65 clinical trial.

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Background: Analysis of minimal residual disease (MRD) in the bone marrow (BM) of patients with multiple myeloma (MM) is accepted by the IMWG to evaluate treatment efficacy and is a well-established prognostic factor. However, there is an unmet need to explore the clinical value of MRD in peripheral blood (PB). **Methods:** Newly diagnosed MM patients enrolled in the GEM2012MENOS65 trial received six induction (Ind) cycles of bortezomib, lenalidomide, and dexamethasone (VRD) followed by autologous stem cell transplantation (ASCT) and 2 further cycles of consolidation (Cons) with VRD. MRD was analyzed in BM using Next Generation Flow (NGF) and in serum by Mass Spectrometry (MS) using IgG/A/M, κ, λ, free κ and free λ specific beads, both after Ind, at day 100 after ASCT, and after Cons. Sequential samples from the first 184 patients were analyzed. **Results:** Results of both methods were in agreement (NGF+/MS+ and NGF-/MS-) in 83% of cases post-Ind (152/184), 80% post-ASCT (139/174) and 76% post-Cons (128/169). Stratifying by the log range of MRD by NGF, discordances (NGF+/MS- and NGF-/MS+) seemed to increase at the lower MRD ranges, being 22%, 21% and 19% from $\geq 10^{-5}$ to $<10^{-4}$ and 21%, 21%, 23% at $\geq$x10^{-6}(post-Ind, ASCT and Cons, respectively). Analysis of discordances showed that they could be partly explained by the higher percentages of cases found to be positive by MS as compared by NGF at part of the time-points analyzed and at each log range of MRD. From $\geq 10^{-5}$ to $<10^{-4}$, MRD was detected by NGF in 36%, 28%, 20% of cases post-Ind, ASCT and Cons, respectively *vs* MS in 37%, 29%, 21% of them; at $\geq$x10^{-6}, NGF was positive in 11%, 14%, 19% of cases *vs* MS in 23%, 19% and 16% of them. Considering NGF as a reference, the negative predictive value (NPV) of MS per MRD range ($\geq 10^{-5}$ to $<10^{-4}$ and $\geq$x10^{-6}, respectively) was: post-Ind: 83% (p<0,0001), 94% (p=0,034); post-ASCT 86% (p<0,0001), 90% (p=0,022); post-Cons 89% (p<0,0001), 85% (p=0,0469). Despite these discordances, the prognostic value of each technique in terms of undetectable MRD and progression-free survival (PFS) was consistent at all time-points (Table) and further, discordant cases (NGF+/MS- and NGF-/MS+) did not display a significantly different PFS as compared to NGF-/MS- cases. **Conclusions:** The results of MRD assessed by NGF in BM and by MS in PB show a significant concordance and are associated with a similar prognostic value analyzed in terms of PFS. Given its high NPV, MRD in peripheral blood by MS provides a gateway for BM aspiration/biopsy and MRD assessment by NGF. Research Sponsor: PETHEMA-GEM.

	Post-Ind		Post-ASCT		Post-Consol		
Groups	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	% PFS after 2 years
MS + vs MS -	0.02	3.2 (1.3-8,3)	0.06	2.5 (1.0- 6.5)	0.005	5.5 (1.7-17.2)	70 vs. 95
NGF + vs NGF -	0.02	3.3 (1.3-9.1)	0.02	3.3 (1.2-8.9)	0.002	6.2 (1.9-19.6)	72 vs. 97
MS+ NGF+ vs MS- NGF-	0.02	3.4 (1.2-9.3)	0.03	3.3 (1.1-9.5)	0.001	9.4 (2.5-35.8)	63 vs. 96

8011 **Poster Discussion Session**

Interim analysis of a phase 2 minimal residual disease (MRD)-adaptive trial of elotuzumab, carfilzomib, lenalidomide, and dexamethasone (Elo-KRd) for newly diagnosed multiple myeloma (MM).

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Background: The addition of a monoclonal antibody to triplet induction regimens in patients (pts) with MM with intent for autologous stem cell transplant (ASCT) has resulted in higher overall and deep response rates. In this study we are investigating the impact of the addition of Elo to KRd on complete response (CR) and/or MRD-negative rates in newly diagnosed MM regardless of transplant eligibility. **Methods:** Pts were enrolled from four MM Research Consortium sites into this phase 2 study. All patients receive 12 cycles of Elo-KRd in 28-day cycles: Elo per standard dosing, K 20/56/70 mg/m^2 days 1, 8 and 15, R 25 mg days 1-21, and dexamethasone 40 mg days 1, 8, 15, 22. ASCT eligible candidates can undergo stem cell collection after cycle 4 and then resume treatment; pts who elect to proceed to ASCT are censored for response at that time. Pts MRD(-) ($<10^{-5}$) by NGS after cycles 8 (C8) and 12 (C12) proceed to Elo-Rd until progression. Patients who convert from MRD(+) to MRD(-) between C8 and C12 receive an additional 6 cycles of Elo-KRd (total 18 cycles) followed by Elo-Rd, and pts MRD(+) after C12 receive an additional 12 cycles of Elo-KRd (total 24) followed by Elo-Rd. The primary endpoint of the study is sCR and/or MRD(-) rate after C8 E-KRd. MRD status was determined by ClonoSEQ next generation sequencing (NGS, $<10^{-5}$) [Adaptive Biotechnologies]. An improvement in the sCR and/or MRD(-) rate by NGS from a historical 30% to 50% at the end of C8 will be considered promising. **Results:** 44 pts are enrolled, 39 of whom are evaluable for response (cutoff Jan 10 2021). Median age is 62 years (range 43-81, 23% age $>$70) and 23 (52%) have high-risk cytogenetic abnormalities (HRCA) including 13 (30%) with $>$2 high-risk abnormalities (6 pts unknown cytogenetics). 34/39 (87%) have MRD trackable by clonoSEQ. The rate of sCR and/or MRD(-) by NGS at the end of C8 is 19/33 (58%), meeting the statistical threshold for establishing efficacy (2 pts censored for elective ASCT before C8 and 4 pts receiving therapy but have not reached C8). With a median follow-up of 24 months, estimated 2-year progression free survival is 87% (100% for standard risk, 79% for HRCA) and estimated 2-year overall survival is 89% (82% for HRCA). No pt who was MRD(-) by NGS after C8 has progressed, including 6 pts with HRCA. Serious adverse events occurred in 30 pts (68%). 89% experienced treatment emergent AEs, the most common ($>$10%) of which was pneumonia (14%). One pt had grade 5 myocardial infarction. **Conclusions:** Elo-KRd demonstrates tolerability consistent with known toxicities of these agents and met the primary endpoint of sCR and/or MRD(-) of $>$50% after 8 cycles. With longer follow-up, the study results may validate that an MRD-adaptive design for de-escalation of therapy in MM can generate deep responses while reducing treatment exposure. Clinical trial information: NCT02969837. Research Sponsor: Bristol Myers Squibb.

8012 **Poster Discussion Session**

Prospective comparison of whole body MRI and FDG PET/CT for detection of multiple myeloma and correlation with markers of disease burden: Results of the iTIMM trial.

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Background: Early and sensitive detection of bone marrow disease and stratified patient management according to clinical risk can confer survival advantages in multiple myeloma (MM). Whole body MRI (WB MRI) and Fluorodeoxyglucose (FDG) PET/CT are included in international guidelines for imaging in patients with a suspected diagnosis of MM. However prospective studies comparing detection of MM by contemporary WB MRI as per recent MY-RADS consensus against FDG PET/CT are lacking. We report here protocol-defined endpoints from the prospective iTIMM (NCT02403102) study, comparing WB MRI and PET/CT, their relationship with serum and bone marrow estimates of disease burden, as well as molecular tumor characteristics. **Methods:** Patients with newly diagnosed MM or at first relapse planned to receive chemotherapy and autologous stem cell transplantation were enrolled in iTIMM. Matched baseline WB MRI and FDG PET/CT were performed and baseline clinical data including tumor genetics collected. Scans were double reported for presence of focal and diffuse disease by expert MRI and PET/CT radiologists, blinded to each other's assessment. Paired methods were used to compare burden and patterns of disease on WB MRI compared to FDG PET/CT at baseline. Primary and secondary trial endpoints include relationship between post-treatment WB MRI response and progression-free survival, for which follow-up is ongoing. Exploratory endpoints include comparison of baseline WB MRI and PET/CT and their correlation with laboratory parameters, for which data is complete and reported here. **Results:** From May 2015 to March 2018, sixty patients (35 male; mean age 60 years) underwent baseline WB MRI as per MY-RADS consensus and FDG PET/CT. At least one focal lesion was detected in 50/60 patients (83.3%) by WB MRI and in 36/60 patients (60%) by PET/CT. WB MRI was more sensitive ($P < 0.05$) across anatomical regions except for ribs and cervical spine. Four patients in our study showed two or more focal lesions $\geq$5 mm only on WB MRI but not PET/CT. All lesions detected by WB MRI but not PET/CT resolved in follow-up scans after treatment, excluding false positives. In 49/60 (81.7%) patients, diffuse disease was detected by WB MRI, compared to 10/60 (16.7%) by PET-CT; WB MRI was more sensitive across all anatomical areas ($P < 0.05$). Plasma cell infiltration and paraprotein levels were significantly higher for patients with diffuse disease on WB MRI, but not on PET/CT. All genetically high-risk tumours, defined by t(4;14), t(14;16), del(1p), gain(1q) or del(17p), showed diffuse infiltration on WB MRI. **Conclusions:** WB MRI increases detection of focal and diffuse disease compared with FDG PET/CT, including improved detection of focal lesions meeting criteria for active disease as per International Myeloma Working Group diagnostic criteria, proposing it as a gold standard for tumor imaging in MM. Clinical trial information: NCT02403102. Research Sponsor: Cancer Research UK and NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research.

8013 **Poster Discussion Session**

CARTITUDE-2: Efficacy and safety of ciltacabtagene autoleucel (cilta-cel), a BCMA-directed CAR T-cell therapy, in patients with progressive multiple myeloma (MM) after one to three prior lines of therapy.

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Background: Cilta-cel is a CAR T-cell therapy expressing two BCMA-targeting, single-domain antibodies designed to confer avidity. The multicohort, phase 2 CARTITUDE-2 study (NCT04133636) is evaluating cilta-cel safety and efficacy in various clinical settings for patients (pts) with MM and exploring suitability of outpatient administration. Here, we present initial results from Cohort A. **Methods:** Cohort A pts had progressive MM after 1–3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), were lenalidomide refractory, and had no prior exposure to BCMA-targeting agents. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg) was given 5–7 days (d) after start of lymphodepletion (daily cyclophosphamide [300 mg/m^2] and fludarabine [30 mg/m^2] for 3 d). The primary objective was minimal residual disease (MRD) 10^{-5} negativity. Secondary outcomes were response rates (IMWG) and safety (per CTCAE; CRS and ICANS by ASTCT). **Results:** As of Feb 2021 data cutoff (median follow-up: 5.8 months [mo]; range: 2.5–9.8 mos), 20 pts (65% male; median age 60 years [38–75]) received cilta-cel; 1 pt was treated in an outpatient setting. Pts received a median of 2 prior LOT (1–3); 12 pts received <3 prior lines and 8 received 3 prior LOT. All pts were exposed to PI, IMiD, and dexamethasone, 95% to alkylating agents, and 65% to daratumumab. The majority (95%) were refractory to the last LOT; 40% were triple refractory. Overall response rate was 95% (95% CI: 75–100), 75% (95% CI: 51–91) achieved stringent CR/CR, and 85% (95% CI: 62–97) achieved $\geq$VGPR. Median time to first response was 1.0 mo (0.7–3.3); median time to best response was 1.9 mo (0.9–5.1). Median duration of response was not reached. All pts (n = 4) with MRD-evaluable samples at 10^{-5} at data cutoff were MRD-negative. Hematologic AEs $\geq$20% were neutropenia (95%; gr 3/4: 90%), thrombocytopenia (80%; gr 3/4: 35%), anemia (65%; gr 3/4: 40%), lymphopenia (60%; gr 3/4: 55%), and leukopenia (55%; all gr 3/4). CRS occurred in 85% of pts; 10% were gr 3/4. Median time to CRS onset was 7 d (5–9), with a median duration of 3.5 d (2–11). CAR T-cell neurotoxicity occurred in 20% of pts (all gr 1/2). Three pts had ICANS (1 gr 1; 2 gr 2); median time to onset was 8 d (7–11) and median duration was 2 d (1–2). One pt had gr 2 facial paralysis; time to onset was 29 d with a duration of 51 d. One death occurred due to COVID-19 (assessed as treatment (tx)-related by investigator). Safety profile was manageable in the pt treated in an outpatient setting. **Conclusions:** A single cilta-cel infusion at the recommended phase 2 dose led to early and deep responses with a manageable safety profile in pts with MM who had 1–3 prior LOT. Updated efficacy and safety findings will inform suitability of outpatient tx in this and other cohorts of CARTITUDE-2 as well as the CARTITUDE-4 study. Clinical trial information: NCT04133636. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8014 **Poster Discussion Session**

Long-term follow-up results of a multicenter first-in-human study of the dual BCMA/CD19 Targeted FasT CAR-T GC012F for patients with relapsed/refractory multiple myeloma.

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Background: The dual CAR-T GC012F developed on the novel FasT CAR-T platform targeting B cell maturation antigen (BCMA), and CD19 was designed to improve depth of response and overall efficacy for CAR-T as therapy for Multiple Myeloma. Here, we present updated data for study (NCT04236011; NCT04182581) including additional pts treated. **Methods:** From October 2019 to July 2020, 19 heavily pretreated Relapsed/Refractory Multiple Myeloma (RRMM) pts (age 27-71) with a median of 5 prior lines (range 2-9) received a single infusion of GC012F. 94.7% (18/19) were high risk (HR- defined by mSMART), 5 pts had extramedullary disease, 1 pts presented with plasma cell leukemia, and 15/19 were refractory to last therapy. 4/19 pts had received prior anti- CD38, 18/19 pts prior IMiD. 18/19 pts were refractory to PI, 17 pts to IMiD, 3 pts being primary refractory. After lymphodepletion over 2-3 days (30 mg/m^2/d, 300mg/ m^2/d Flu/Cy) CAR-T cells were administered as single infusion at 3 dose levels: 1x10^5/kg (DL1) n=1, 2x10^5/kg (DL2) n=9 and 3x10^5/kg (DL3) n=9. **Results:** As of Jan 12, 2021 cut-off, 19 pts were evaluated for response. Overall response rate (ORR) was 94.7% - all responses VGPR or better (94.7% - 16/18 sCR, 2/18 VGPR) with all pts MRD- by flow cytometry (10^{-4}-10^{-6}) - earliest response d 28 post infusion. 100% of pts achieved a reduction of paraprotein, 18/19 a 100% reduction. Best response was MRD- sCR in 16/19 patients (84.2%). In DL3 (n=9) 4 additional pts were response evaluable for 6 mth follow-up: 100% (9/9) of pts achieved MRD-sCR as best response, 87.5% (7/8) of response evaluable pts maintained MRD-sCR at landmark analysis of 6 mths. At data cut off, the median time to follow up was 13.8 mths (6.1-16.4) – median duration of response not yet reached. Cytokine Release Syndrome (CRS) and ICANs were graded by ASBMT criteria: grade 1-2 n=16 (84.2%), grade 3 n=2 (10.5%). Median duration of CRS was 4 d (1-8 d). No grade 4/5 CRS or ICANS were observed. 2 deaths occurred on study and were assessed as not related to therapy – one reported previously; one patient was diagnosed with pseudomonas pneumonia on Day 52, refused life-saving treatment and passed. CAR-T median Tmax was 10 d (range 8-14d), median peak copy number (Cmax) was 127548 (16,011-374,346) copies /ug DNA with long duration of persistence of up to 60 weeks at time of data cut off. Patients continue to be monitored for safety and efficacy. **Conclusions:** BCMA-CD19 dual FasT CAR-T GC012F showed early, deep and durable responses with a high ORR (94.7% - VGPR and better) including a high MRD- sCR rate (DL3=100%, n=9) in high risk RRMM pts including those refractory to anti-CD38, PI and IMIDs with a favorable safety profile consistent with previous findings. BCMA-CD19 dual FasT CAR-T GC012F may present a new treatment approach for patients with RRMM including those with high-risk features refractory to standard of care. Clinical trial information: NCT04236011; NCT04182581. Research Sponsor: Gracellbio.

8015 **Poster Discussion Session**

Phase 1 Study of CART-ddBCMA, a CAR-T therapy utilizing a novel synthetic binding domain, for the treatment of subjects with relapsed and refractory multiple myeloma.

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Background: CART-ddBCMA is an autologous CAR-T cell therapy encoding a novel non-scFv synthetic binding domain targeting BCMA with a 4-1BB costimulatory motif and CD3-zeta T-cell activation domain. The novel binding domain is based on a computationally-derived triple-helix protein scaffold that is small (73 amino acids), stable, engineered to reduce immunogenicity, and can be modified to bind alternative targets. **Methods:** ARC-101 (NCT04155749), ARM 1 (CART-ddBCMA) is a Phase 1, multicenter, open-label, dose escalation trial enrolling subjects who have received $\geq$3 prior regimens, including proteasome inhibitor(s), immuno-modulatory agent(s), and anti-CD38 antibody, or are triple-refractory. Subjects undergo lymphodepletion with fludarabine and cyclophosphamide, then receive CART-ddBCMA as a single infusion. Planned dose levels are 100, 300, and up to 900 x 10^6 CAR+ T cells. The primary endpoint is incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Secondary endpoints include clinical response per IMWG criteria, MRD, DOR, PFS, OS, and CAR-T cell kinetics. **Results:** As of 29 Jan 2021, 10 subjects received CART-ddBCMA, 9 subjects were evaluable, and 1 subject was pending assessment. Median age was 66 years [min:max 54 to 75]. 6 subjects received 100 x 10^6 CAR+ T cells, and 4 subjects received 300 x 10^6 CAR+ T cells. Median CAR+ expression was 74.5% (min:max 61-87%) of total T cells. Of the evaluable subjects, median follow-up after cell infusion was 208 days (min:max 45 to 355+ days), 9/9 subjects were penta-refractory, 1 subject was also refractory to BCMA-directed ADC. 8/9 had high-risk cytogenetics (1 subject's sample not evaluable), and 6/9 subjects had extramedullary disease. No DLTs were reported. Per ASTCT Consensus Grading (Lee et al, 2019), 8 subjects developed G1/2 CRS, 1 subject in the higher dose cohort developed G3 CRS that rapidly resolved with tocilizumab. 1 subject developed G2 ICANS which rapidly resolved with intervention. 7 subjects received tocilizumab; 3 received dexamethasone. ORR was 100% (9/9) per IMWG criteria including 4 sCR, 1 VGPR, and 4 PR. 1 subject with PR relapsed and was retreated. All other subjects have ongoing responses; observations included sFLC normalization and elimination of detectable bone marrow disease by Month 1. Ongoing responses for subjects not yet achieving CR continue to deepen. 7 subjects were evaluable by MRD of which 5 are MRD-negative, and 2 are pending results. CAR-T cell expansion, as measured by vector transgene copies per microgram genomic DNA was observed in all patients. **Conclusions:** Early efficacy results are encouraging, with 9/9 (100%) ORR and manageable toxicities. 8/9 responses are ongoing and responses continue to deepen. These data are encouraging in high-risk subjects with penta-refractory myeloma. Subjects continue to be enrolled and treated. Clinical trial information: NCT04155749. Research Sponsor: Arcellx.

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in relapsed and refractory multiple myeloma: Updated KarMMa results.

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Background: Patients (pts) with RRMM previously exposed to immunomodulatory agents, proteasome inhibitors (PIs), and CD38 antibodies (mAbs) have poor outcomes with subsequent treatments. Ide-cel, a BCMA-directed CAR T cell therapy, showed frequent, deep, and durable responses in heavily pretreated pts with RRMM in the pivotal KarMMa trial (Munshi NC, et al. *J Clin Oncol* 2020;38[suppl 15]. Abstract 8503). Here, we present updated data. **Methods:** Pts with $\geq$ 3 prior regimens (including immunomodulatory agent, PI, and CD38 mAb) and refractory to their last regimen per IMWG criteria were eligible (NCT03361748). Pts received 150450 $\times$ 10^6 CAR+ T cells (target dose range) after 3 days of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2). Endpoints included overall response rate (ORR; primary) and complete response (CR) rate (key secondary). Additional secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** KarMMa enrolled 140 pts, and 128 received ide-cel. Pts had a median age of 61 years and a median of 6 (range, 3-16) prior regimens; 84% were triple-class refractory, and 26% were penta-class refractory (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab). Most pts (88%) had bridging therapy. Median follow-up was 15.4 mo (data cutoff, 7 Apr 2020). ORR was 73% and median PFS was 8.8 mo in all treated pts; both increased with higher dose (Table). At the highest target dose (450 $\times$ 10^6 CAR+ T cells), the ORR was 81%, the CR rate was 39%, and the median PFS increased to 12.2 months with longer follow-up. Responses were observed in all subgroups including difficult-to-treat subsets (eg, extramedullary disease [ORR, 70%], high tumor burden [71%], and R-ISS stage III disease [48%]). OS continues to mature and the median has not been reached; the 15-month event-free rate for OS was 71%. Cytopenias (97%) and cytokine release syndrome (CRS; 84%) were the most common any-grade toxicities. CRS was mostly grade 1/2; 5 pts (4%) had grade 3, 1 had grade 4 (at 300 $\times$ 10^6), and 1 had grade 5 (at 300 $\times$ 10^6). Investigator-identified neurotoxicity was reported in 23 pts (18%); 4 pts (3%) had grade 3 and 0 had grade $\geq$ 4. Tocilizumab was used in 67 and 3 pts with CRS and neurotoxicity, respectively. **Conclusions:** Updated results from the KarMMa trial continue to demonstrate deep, durable responses with ide-cel in heavily pretreated pts with RRMM. Efficacy and safety reflect prior reports and support a favorable clinical benefit-risk profile for ide-cel across the target dose range. Clinical trial information: NCT03361748. Research Sponsor: Celgene, a Bristol-Myers Squibb Company and bluebird bio.

Dose, $\times$ 10^6 CAR+ T cells	150 (n = 4)	300 (n = 70)	450 (n = 54)	Total (N = 128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	42 (33)
Median DOR, mo*	†	9.9	11.3	10.7
Median PFS,mo*	†	5.8	12.2	8.8

sCR, stringent CR. *Kaplan-Meier estimate. †Not reported due to small n.

8017 **Poster Discussion Session**

Updates from ICARIA-MM, a phase 3 study of isatuximab (Isa) plus pomalidomide and low-dose dexamethasone (Pd) versus Pd in relapsed and refractory multiple myeloma (RRMM).

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Background: Isa is an approved monoclonal antibody that binds to a specific epitope on the CD38 receptor**.** The Phase 3 ICARIA-MM study (NCT02990338) demonstrated significantly improved progression-free survival (PFS) with Isa-Pd vs Pd (P= 0.001) and a manageable safety profile (Attal M, et al. *Lancet* 2019;394:2096-2107). Here we report updated ICARIA results. **Methods:** Pts with RRMM (N = 307) who have received ≥2 prior therapies, including lenalidomide (Len) and a proteasome inhibitor (PI), were randomized to Isa-Pd (n = 154) or Pd (n = 153). Isa was administered intravenously at 10 mg/kg weekly for 4 weeks, and every other week thereafter. This preplanned second interim analysis assessed longer term outcomes, including time to next treatment (TTNT), overall survival (OS), time from randomization to disease progression on first subsequent therapy or death (PFS2), and safety. **Results:** Pts had a median of 3 prior lines of therapy (IQR 2–4; table). As of Oct 1, 2020 (median follow-up, 35.3 months [mo]), 27 Isa-Pd pts (18%) vs 12 Pd pts (8%) were still on treatment; 60% vs 72% had proceeded to subsequent therapy. Median TTNT was 15.5 mo with Isa-Pd vs 8.9 mo with Pd (hazard ratio [HR] 0.56; 95% confidence interval [CI] 0.42–0.74; P< 0.0001); 24% vs 58% of pts with subsequent therapy received daratumumab (dara). Overall response rate (ORR) in subsequent treatment with dara monotherapy was higher after Pd (38%) than Isa-Pd (14%), but was similar (32% vs 31%) with dara combination therapy (table). Median PFS2 in the intent-to-treat population was 17.5 mo with Isa-Pd vs 12.9 mo with Pd (HR 0.76; 95% CI 0.58–0.99; P= 0.0202). Median OS was 24.6 mo with Isa-Pd vs 17.7 mo with Pd (HR 0.76; 95% CI 0.58–1.01; one-sided P= 0.0280). Median treatment duration was 47.6 weeks (range 1.3–171.6) with Isa-Pd vs 24.0 weeks (range 1.0–168.6) with Pd. Serious treatment-emergent adverse event (TEAEs) were seen in 73% of Isa-Pd pts vs 60% of Pd pts. Most frequent non-hematologic TEAEs (any grade) with Isa-Pd were infusion reaction (38%), upper respiratory tract infection (34%), and diarrhea (30%). Grade 3–4 neutropenia (85% vs 71%) and thrombocytopenia (34% vs 25%) were more frequent with Isa-Pd than with Pd. **Conclusions:** Isa-Pd demonstrates a significant improvement in TTNT and PFS2 compared with Pd. A strong trend in OS benefit was also seen in the Isa-Pd arm, with approximately 7 mo improvement in median OS. The overall safety profile remains unchanged from prior analyses. Funding: Sanofi. Clinical trial information: NCT02990338. Research Sponsor: Sanofi.

Prior treatments, n (%)	Isa-Pd (n = 154)	Pd (n = 153)
Len	154 (100)	153 (100)
PI	154 (100)	153 (100)
Len-refractory	144 (94)	140 (92)
PI-refractory	118 (77)	115 (75)
ORR on subsequent dara combination treatments, n/N* (%)		
ALL	4/13 (31)	7/22 (32)
+Immunomodulator	2/5 (40)	2/7 (29)
+Alkylator	0/4 (0)	1/5 (20)
+PI	2/5 (40)	4/12 (33)

*N = number of patients with best overall response assessment.

8018 **Poster Discussion Session**

Oral selinexor, pomalidomide, and dexamethasone (XPd) at recommended phase 2 dose in relapsed refractory multiple myeloma (MM).

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Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL is approved with low-dose dexamethasone (dex) ± bortezomib (BOR) for patients (pts) with previously treated MM. In the Phase 3 BOSTON study, once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS) and overall response rate (ORR) with marked reduction of peripheral neuropathy as compared to standard twice weekly BOR/dex (Vd), despite XVd utilizing 40% less BOR and 25% less dex than Vd. Pomalidomide (POM) plus dex (Pd) has an ORR of 31% and median PFS (mPFS) of 4 months in MM pts refractory to BOR and lenalidomide (LEN). We hypothesized that the addition of once weekly SEL to Pd (XPd) would be an active, all-oral combination with an acceptable safety profile in pts with LEN refractory and BOR treated MM. **Methods:** In the SPd arm of the multi-arm Phase 1b/2 STOMP study, SEL was evaluated at 60, 80, or 100 mg QW or 60 or 80 mg twice weekly in combination with Pd. Study objectives were to determine the maximum tolerated dose and recommended Phase 2 dose (RP2D), and assess the safety and activity of the SPd regimen including in pts receiving the RP2D. **Results:** As of 4 Jan 2021, 65 pts (33 male) were enrolled with median age of 64 years (range 37-85 years) and median of 3 (range 1-10) prior lines of therapy. Previously treated/refractory rates were LEN 100%/85%, BOR 92%/49%, carfilzomib 43%/37%, POM 31%/29%, and daratumumab (dara) 26%/26%. RP2D was SEL 60 mg QW, POM 4 mg (days 1-21), dex 40 mg QW. Common hematologic, treatment-related adverse events (TRAEs) included (all grades, grades ≥3) neutropenia (63%, 55%), anemia (58%, 32%), and thrombocytopenia (54%, 31%). Non-hematologic TRAEs included nausea (62%, 2%), fatigue (55%, 11%), and decreased appetite (45%, 2%). Among POM nave or nonrefractory MM pts (N = 44), ORR was 57% (1 sCR, 1 CR, 8 VGPR, 15 PR); mPFS was 12.2 months. In pts treated with RP2D (N = 20), ORR was 65% (1 sCR, 5 VGPR, 7 PR); mPFS was not reached with a median follow-up time of 3.9 months. In POM-refractory pts and those with prior dara, ORR was 44% (7/16) and 60% (9/15), respectively. **Conclusions:** SEL, once weekly, can be safely combined with Pd in pts with heavily pretreated MM. No new safety signals were identified. The all-oral combination of XPd is highly active with an ORR of 65% at RP2D (compared to expected ORR ≤30% for Pd) and produces durable responses with a mPFS of 12.2 months overall. These data support a planned Phase 3 study with an all-oral combination of XPd vs Pd in pts who have been previously treated with LEN, a PI, and an anti-CD38 mAb. Clinical trial information: NCT02343042. Research Sponsor: Karyopharm Therapeutics.

8019 **Poster Discussion Session**

Survival among older patients with previously treated multiple myeloma treated with selinexor, bortezomib, and dexamethasone (XVd) in the BOSTON study.

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Background: Multiple myeloma (MM) typically affects older populations, which are more vulnerable to toxicity with anti-MM treatments. These patients (pts) have significant morbidity and mortality, resulting in a need for dose modifications or alternative suboptimal treatment options. Significant improvements were observed in the BOSTON study with XVd vs Vd in median progression-free survival (PFS), overall response rate (ORR), and rates of peripheral neuropathy (PN); median overall survival (OS) trended in favor of XVd. **Methods:** The phase 3 randomized BOSTON trial (NCT03110562) is a controlled, open-label study of once weekly XVd vs. twice weekly standard Vd in pts with MM and 1-3 prior treatment regimens. We performed post-hoc analyses to compare survival benefits in pts $\geq$65 vs $<$ 65 years of age. **Results:** The BOSTON study enrolled a total of 402 pts between June 2017 and February 2019 that were randomized into XVd or Vd arms. The numbers of pts treated with XVd or Vd who were $\geq$65 were 109/132 and 86/75 who were $<$ 65, respectively. Baseline characteristics were similar by age although pts $\geq$65 years were less likely to have received ASCT than those $<$ 65 years (48.4% vs. 25.3%). Median PFS was prolonged with XVd compared with Vd, across both age groups: $\geq$65 (HR, 0.55 [95% CI, 0.37-0.83] P = 0.002) and $<$ 65, (HR, 0. 74 [95% CI, 0.49-1.11], P = 0.07). Vd was associated with a lower ORR (64.4%) than treatment with XVd (76.1%) (OR, 1.77 [95% CI, 1.00-3.11], P = 0.024) in pts $\geq$65, while the ORR in those $<$ 65 was 76.7% with XVd and 58.7% (OR, 2.33 [95% CI, 1.18-4.59], P = 0.007) with Vd. As of Jan 2021, the median OS for the overall population was not reached for both arms (HR = 0.86; p = 0.193), with 61 and 75 deaths in the XVd and Vd arms, respectively. Median OS was not reached in pts $\geq$65 with XVd and was 28.6 months with Vd (HR = 0.60; 95% CI, 0.38-0.94; p = 0.012), while there was no difference in the OS for pts $<$ 65 (HR = 1.52; 95% CI, 0.86-2.68; p = 0.926). Pts $\geq$65 had a lower incidence of death with XVd as compared to Vd (29 vs 56) and there were 32 deaths with XVd and 19 with Vd in pts $<$ 65. Grade $\geq$3 treatment-emergent adverse events were not observed more often in older compared to younger pts. Amongst pts $\geq$65, PN of any grade was lower with XVd (32.1%) compared to Vd (46.5%); (OR 0.57 [95% CI 0.34-0.97], p = 0.017), including a lower incidence of grade $\geq$3 PN (XVd 4.6% vs. Vd 11.6%). Pts $<$ 65 followed a similar trend of PN AEs of any grade: XVd, 32.6%; Vd, 48.0% (OR 0.42 [95% CI 0.21-0.82], p = 0.006). **Conclusions:** In an older patient population with a poor prognosis, XVd was associated with a significant survival benefit, improved PFS and OR with reduced PN, and requires relatively short and infrequent clinic visits. XVd may be a simple, effective regimen for pts $\geq$65 years of age. Clinical trial information: NCT03110562. Research Sponsor: None.

8020 **Poster Discussion Session**

Oral ixazomib-dexamethasone versus oral pomalidomide-dexamethasone for lenalidomide-refractory, proteasome inhibitor-exposed multiple myeloma (MM) patients: A global, multicenter, randomized, open-label, phase 2 trial.

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Background: MM patients (pts) often receive several lines of therapy with multiple drug combinations and, as lenalidomide (R)-containing regimens are commonly used as first-line therapy, R-free options for subsequent lines are necessary. Additionally, as pts age and become less tolerant to treatment, more convenient regimens, such as all-oral options, with less toxicity are needed. Dexamethasone (dex)-based doublets are effective and tolerable in this setting. **Methods:** Proteasome inhibitor (PI)-exposed and/or intolerant and R-refractory pts who had ≥2 prior therapies (N = 122) were randomized 3:2 to receive: ixazomib (ixa) 4 mg (5.5 mg from cycle 2 if tolerated) on day (d) 1, 8, 15, and dex 20 mg (≥75 years [yrs], 10 mg) on d 1, 2, 8, 9, 15, 16, 22, 23; or pomalidomide (pom) 4 mg on d 1–21, and dex 40 mg (≥75 yrs, 20 mg) on d 1, 8, 15, 22, in 28-d cycles until progressive disease (PD) or unacceptable toxicity. Pts were stratified by age (< 65 vs ≥65 yrs), International Staging System (ISS) disease stage at study entry (I/II vs III), and prior lines of therapy (2 vs ≥3). The study was powered to test the primary endpoint of progression-free survival (PFS). **Results:** In the ixa-dex (n = 73) vs pom-dex (n = 49) arms, median age was 72 vs 68 yrs (36% vs 18% ≥75 yrs), 25% vs 22% of pts had ISS stage III MM, and 52% vs 53% had received ≥3 prior therapies (per stratification). At data cutoff (5/31/2020), 19% vs 20% of pts were ongoing on treatment with ixa-dex vs pom-dex; primary reasons for discontinuation were PD (47% vs 57%) and adverse events (AEs; 23% vs 12%). With median follow-up of 15.3 vs 17.3 months (mos), median PFS (mPFS) was 7.1 vs 4.8 mos with ixa-dex vs pom-dex (hazard ratio [HR] 0.847; 95% confidence interval [CI] 0.535–1.341; p = 0.477); the Table shows mPFS by prior lines, and secondary endpoints. Pts received a median of 6 cycles with both ixa-dex (range 1–25) and pom-dex (range 1–27); 64% of ixa-dex pts were able to escalate to a 5.5 mg dose of ixa. 69% vs 81% of ixa-dex vs pom-dex pts had grade (G) ≥3 AEs, 51% vs 53% had serious AEs, 39% vs 36% had an AE leading to drug discontinuation, 44% vs 32% had an AE leading to dose reduction, and 13% vs 13% died on study. Health-related quality of life (HRQoL; EORTC QLQ-C30/MY20, and EQ-5D-5L) was maintained, and similar between arms. **Conclusions:** Ixa-dex prolonged PFS vs pom-dex in these heavily pretreated, PI-exposed and/or intolerant, R-refractory pts, but the difference was not statistically significant. Ixa-dex was well tolerated, with lower G≥3 AE rates vs pom-dex, and comparable HRQoL. Clinical trial information: NCT03170882. Research Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

8021 **Poster Session**

High-dose lenalidomide and melphalan as conditioning for autologous stem cell transplantation in relapsed or refractory multiple myeloma.

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Background: Autologous stem cell transplantation (ASCT) remains a standard of care of eligible patients with multiple myeloma, despite the many novel therapies introduced over the past decade. High dose melphalan (HDM) is the only approved regimen to date. Lenalidomide (LEN) is an oral immunomodulatory drug which has become the backbone of myeloma therapy from induction through salvage and maintenance. Early studies noted a dose response relationship, and found myelosuppression to be the dose limiting toxicity. We previously reported on our phase 1 study of high dose lenalidomide (HDLEN) with HDM in conditioning for ASCT, where no DLT was noted up to 350mg PO daily of LEN. Here we report the phase 2 data of patients undergoing ASCT with combination conditioning regimen. **Methods:** 50 patients with relapsed/refractory multiple myeloma (RRMM) underwent ASCT using HDLEN+HDM conditioning. HDLEN was dosed at 350mg PO daily from day -5 to day -1 and HDM was dosed 100mg/m2 on days -2 and -1. TPatients were heavily pre-treated: 32% had prior HDM-ASCT, 96% had received prior lenalidomide, and 42% prior pomalidomide; 40% prior anti-CD38 mAB. Of note, 68% entered the study with progressive disease at time of enrollment. **Results:** Overall response rate was 96%, with 80% being ≥VGPR. Median progression free survival (PFS) was noted at 14.3 months, while overall survival (OS) was 68.2 months. PFS was similar when patients were stratified by prior ASCT, depth of response at enrollment, or presence of high risk FISH. Toxicities were mostly hematologic (100% neutropenia and thrombocytopenia, 90% anemia), GI (88% diarrhea, 72% nausea, 42% vomiting) and metabolic (30-96% derangement in electrolytes), and similar to historical controls receiving HDM alone. Second malignancies were noted in 2 patients. **Conclusions:** HDLEN/HDM is a well tolerated and effective conditioning regimen for ASCT in patients with RRMM. This regimen merits further investigation as ASCT is likely to remain an integral part of the treatment of RRMM patients, yet few advancements have been made to this modality. HDLEN may be particularly useful in patients with high risk disease and those progressing after multiple lines of therapy. HDLEN added little toxicity to HDM and SPMs were not more frequent than expected per SEER database for patients in this age range. Clinical trial information: NCT01054196. Research Sponsor: Celgene.

Best response, n (%)	N = 50
Stable Disease	2 (4)
Partial Response	8 (16)
Very Good Partial Response	22 (44)
Unconfirmed Complete Response	1 (2)
Complete Response	8 (16)
Stringent Complete Response	9 (18)
Overall Response Rate	48 (96)

8022 **Poster Session**

Improved outcomes with maintenance therapy after salvage autologous hematopoietic cell transplantation (AHCT) in multiple myeloma: A CIBMTR study.

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Background: Maintenance therapy in multiple myeloma (MM) after first autologous hematopoietic cell transplantation (AHCT1) is considered standard of care. Data regarding maintenance therapy after a salvage AHCT (AHCT2) in the setting of relapsed MM are scarce. Therefore, we used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to examine the use of maintenance therapy after AHCT2 in MM patients and its effect on post-transplant patient outcomes. **Methods:** We included US adult MM patients who underwent AHCT2 after melphalan conditioning regimen from 2010-2018, and excluded patients who underwent tandem transplants. Outcomes of interest included non-relapse mortality (NRM), relapse/progression (REL), progression-free and overall survival (PFS, OS). Cox proportional hazards models were developed to study the main effect (maintenance use) with other covariates of interest including age, sex, race, performance status, HCT-comorbidity index, MM subtype, stage, creatinine, cytogenetic, conditioning melphalan dose, disease status at transplant, and time from AHCT1 to AHCT2. **Results:** Of 522 patients, 342 received maintenance therapy and 180 did not after AHCT2. Baseline characteristics were similar between the two groups. Median follow up was 58 months in the maintenance group and 61.5 months in the no-maintenance group. Common maintenance regimens included immunomodulatory drugs (IMID)-lenalidomide (N = 145, 42%) or pomalidomide (N = 46, 13%) and proteasome inhibitor, bortezomib (N = 45, 13%). Univariate analysis showed superior outcomes at 5 years in maintenance compared to the no-maintenance group: NRM 2 (0.7-3.9)% vs 9.9 (5.9-14.9)%, $p < 0.001$, REL 70.2 (64.4-75.8)% vs 80.3 (73.6-86.3)%, p 0.003, PFS 27.8% (22.4-33.5) vs. 9.8% (5.5-15.2), $p < 0.001$, and OS 54% (47.5-60.5) vs 30.9% (23.2-39.2) $p < 0.001$, respectively. IMID-containing maintenance regimens were associated with an improved 5-year PFS and OS compared to other maintenance regimens. Use of maintenance therapy retained its association with improved outcomes in multivariate analysis, including NRM: hazard ratio (HR) 0.19 (0.08-0.44), p 0.0001, REL: HR 0.58 (0.47-0.72), $p < 0.0001$, PFS HR 0.52 (0.43-0.64), $p < 0.0001$, and OS HR 0.46 (0.36-0.60), $p < 0.0001$. We conducted additional analyses to investigate a possible selection bias in the maintenance group including landmark analysis at 100-days and 6-months post-AHCT2 as well as a subgroup analysis of patients who received melphalan 200mg/m^2 as conditioning for AHCT2 (as a surrogate for fitness)- all these analyses also showed improved outcomes in the maintenance group. Second cancers were reported in 17 (5%) patients in the maintenance group and 6 (3%) patients and no-maintenance group (p 0.39). **Conclusions:** Maintenance therapy after AHCT2 is associated with superior outcomes in MM patients. Research Sponsor: U.S. National Institutes of Health.

8023 **Poster Session**

Phase 2 study of MGTA-145 + plerixafor for rapid and reliable hematopoietic stem cell (HSC) mobilization for autologous transplant in multiple myeloma.

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Background: MGTA-145 (GroβT), a CXCR2 agonist, has shown promising activity for HSC mobilization with plerixafor in pre-clinical models and healthy volunteers. **Methods:** This phase 2 single center study evaluates HSC mobilization with MGTA-145 + plerixafor and same day apheresis in patients with multiple myeloma. Patients received plerixafor 0.24 mg/kg (0.16 mg/kg if renal dysfunction) SQ, followed 2 hours later by MGTA-145 (0.03 mg/kg) IV over 3-10 minutes and apheresis within 30 minutes. Mobilization was repeated for a second day if day 1 yield was $< 6 \times 10^6$ CD34+ cells/kg. This interim analysis reports on mobilization in 10 patients (of 25 planned), including safety cohort of first 6 patients completing transplant. Primary endpoint is collection of 2×10^6 CD34+ cells/kg. **Results:** Median age was 63 years (range: 46-68), 50% were female, 22% had ISS stage 3 & 50% had high-risk FISH. Induction therapy was VRD in 7 and daratumumab + VRD in 3 patients; median induction duration: 4 months (3-6) & median lenalidomide exposure: 6 cycles (4-6), with $>$ VGPR in 70%. Median total stem cell yield (CD34+ cells/kg x 10^6) was 7.1 (3-16.2), day 1 yield was 5.4 (1.1-16.2) & yield per apheresis session was 4 (1.1-16.2). 100% of patients met the primary endpoint of collecting sufficient HSCs in < 2 days of mobilization + apheresis to proceed to transplant (2×10^6 CD34+ cells/kg). Secondary endpoints of 4 and 6×10^6 CD34+ cells/kg in < 2 days were met in 90% & 80% patients. 30% patients underwent 1 apheresis, while 70% underwent 2 sessions. MGTA-145 was well tolerated. At least 1 adverse event (AE) was seen in 90% of patients, 20% had grade 2 AEs (anemia, hypokalemia) and 20% had grade 3 AEs (worsening of baseline grade 3 anemia; hypocalcemia); all resolved. Acute & transient bone pain was seen in 40% of patients (back-2, hip-1, sternum-1), all grade 1, all on day 1, & resolved without intervention after 6 minutes (3-10). All 6 patients in the safety cohort have completed transplant with melphalan 200 mg/m^2. Median of 4.1 (3.4-5.6) x 10^6 CD34+ cells/kg were infused. All patients have engrafted timely (DiPersio Blood 2009); median time to neutrophil engraftment: 12 days (11-13) & platelet engraftment: 17 days (16-19). Apheresis graft analysis is available in these 6 patients. Grafts with MGTA-145+plerixafor showed high enrichment for CD90+CD45RA- among CD34+ cells, a CD34 subset of long term engrafting HSCs (median: 31% of CD34+ cells, 27-52), higher than seen with G-CSF (6%, Goncalves TCT 2021). 67% of grafts were minimal residual disease negative with next generation flow cytometry. **Conclusions:** This is the first study to evaluate the novel regimen of MGTA-145 + plerixafor for same day stem cell mobilization & collection in myeloma/hematologic malignancies, with 100% efficacy in interim analysis and the first to demonstrate successful engraftment in patients with cells collected with this GCSF free regimen. Clinical trial information: NCT04552743. Research Sponsor: Magenta Therapeutics, U.S. National Institutes of Health, PI (Sidana) has a KL2 grant from NIH, although study per se was not sponsored via NIH funds.

8024 **Poster Session**

Effects of refractory status to lenalidomide on safety and efficacy of selinexor, bortezomib, and dexamethasone (XVd) versus bortezomib and dexamethasone (Vd) in patients with previously treated multiple myeloma.

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Background: Lenalidomide (LEN) is typically a frontline therapy for newly diagnosed MM. Patients (pts) with MM refractory to LEN are less likely to repond to other IMiDs and represent a signification area of unmet medical need. In the BOSTON study in the ITT population, XVd was associated with significant improvements in median progression-free survival (PFS), overall response rate (ORR), and rates of peripheral neuropathy, with trends in overall survival (OS) favoring XVd. **Methods:** The BOSTON trial (NCT03110562) is a Phase 3 randomized, controlled, open-label study of once weekly XVd vs twice weekly Vd in pts with MM and 1-3 prior therapies. We performed post-hoc analyses on two different subgroups to compare outcomes based on refractory status to LEN and immunomodulatory drug (IMiD) therapy. These post hoc analyses evaluated if PFS, overall response rate (ORR), time to next treatment (TTNT) and safety was influenced by prior treatment with LEN when comparing XVd with Vd. **Results:** Amongst the 402 pts in BOSTON, 160 had MM refractory to any IMiD (XVd = 74, Vd = 86). Of those, 106 were documented to be refractory to LEN (XVd = 53, Vd = 53) and 296 were not refractory to LEN (XVd = 142, Vd = 154). Baseline characteristics were generally well balanced between subgroups. In these subgroups based on refractory status to IMiD or LEN, median PFS was significantly longer in the XVd arm as compared to Vd (IMiD refractory, 13.9 vs. 8.4 months (mo), p = 0.005; LEN refractory, 10.2 vs. 7.1 mo, p = 0.012; not LEN refractory, 15.4 vs 9.6 mo, p = 0.014). Significant increases in TTNT were observed with XVd treatment in pts that were IMiD refractory (14.8 vs. 10.2 mo, p = 0.003), LEN refractory (13.0 vs. 7.6 mo, p = 0.015), and not refractory to LEN (19.1 vs 12.9 mo, p = 0.005). ORR was improved with XVd compared to Vd regardless of refractory status (IMiD refractory, 68.9% vs 55.8%, p = 0.045; LEN refractory, 67.9% vs. 47.2%, p = 0.016; and not refractory to LEN, 79.6% vs 67.5%, p = 0.010). The most common treatment-emergent AEs for the XVd/Vd arms for all subgroups were thrombocytopenia (66.2/30.6%; 71.7/40.4%; 55.6/22.4%), nausea (48.6/11.8%; 50.9/11.5%; 50.0/9.2%), and fatigue (40.5/20.0%; 45.3/21.2%; 40.8/17.1%) for IMiD, LEN, and not LEN refractory, respectively. Incidence of PN AEs of any grade were reduced compared to pts treated with Vd (IMiD refractory, 27% vs. 42.4%; LEN refractory, 30.2% vs 36.5%; not refractory, LEN 33.1% vs 50.7%). **Conclusions:** In pts with previously treated MM, PFS, ORR, and TTNT were significantly improved regardless of documented refractory status to any IMiD or to LEN-specifically. These analyses support the use of the XVd combination for pts with disease refractory to LEN and likely to any IMiD. Clinical trial information: NCT03110562. Research Sponsor: None.

8025 **Poster Session**

The clinical study of anti-BCMA CAR-T with single-domain antibody as antigen binding domain.

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Background: Relapsed/refractory (RR) multiple myeloma (MM), RRMM, remains as an incurable disease and has a 5-year survival rate of nearly 50%. To address the unmet medical need, an autologous CAR-T cell therapy was developed previously with a humanized single-domain antibody (sdAb) targeting BCMA as the antigen binding domain, 4-1BB and CD3ζ as cytoplasmic domain. **Methods:** An investigator-initiated clinical trial (IIT) was conducted in China to assess the safety and efficacy of the sdAb-based CAR-T. The trail was started in June 2018 and the last patient infused in June 2019. As of 1 February 2021, 34 were treated and followed up. The patients had received multiple lines of prior treatment (including bortezomib, lenalidomide, and others). Following a lymphodepleting regimen of cyclophosphamide (300-600 mg/m^2, d-5, -4) and fludarabine (25-30 mg/m^2, d-5 to d-3), patients were infused with 2.5-10.0 $\times$ 10^6 CAR$^+$ cells/kg body weight. CAR-T was infused immediately after preparation and quality control performed in all patients except one, who was infused a 10.0 $\times$ 10^6 CAR$^+$ cells/kg dose of frozen cells. Efficacy was assessed based on the IMWG criteria, toxicity was graded by CTCAE 4.02, and CRS grading was based on the grading system by CARTOX working group. **Results:** All 34 patients had the tumor burden of plasma cells in bone marrow, or M protein or free light chains (FLCs) in serum, 7 patients were accompanied with extramedullary diseases. The efficacy shows the best ORR is 88.2% (30/34), sCR rate is 55.9% (19/34). The mPFS was 12.1 months, several patients shows continuous sCR after 2 years. No obvious correlation between efficacy and dosage were found in three dose groups of 2.5$\times$10^6 CAR$^+$ cells/kg (6 pts), 5.0$\times$10^6 CAR$^+$ cells/kg (23 pts) or 10.0$\times$10^6 CAR$^+$ cells/kg (5 pts). The observed adverse events include thrombocytopenia ($\geq$grade 3, 38.2%), neutropenia ($\geq$grade 3, 44.1%), leukopenia ($\geq$grade 3, 32.4%), lymphopeniPa ($\geq$grade 3, 26.5%), and anemia ($\geq$grade 3, 20.6%). CRS was monitored occurring in 29 patients (any grade, 85.3%, $\geq$grade 3, 2.9%). **Conclusions:** Our result demonstrates that the CART employing one humanized sdAb targeting BCMA is safe and efficacious for clinical application. The phase I clinical trial has been initiated in China for searching the RP2D using the cryopreserved CAR-T cells. Clinical trial information: NCT03661554. Research Sponsor: Henan Medical Science and Technology Foundation (grant number 2018020484; SBGJ2018085); Henan Provincial Scientific and Technological Project (grant number 162300410095).

8026 **Poster Session**

Isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone in elderly patients with relapsed multiple myeloma: IKEMA subgroup analysis.

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Background: A prespecified interim efficacy analysis of the Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; *P*=0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD-) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile. This subgroup analysis of IKEMA examined efficacy and safety in pts aged <70 and ≥70 years. **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). The primary end point was PFS, as assessed by an independent response committee. We compared outcomes in pts <70 vs ≥70 years; division into different or additional age groups resulted in smaller sample sizes. **Results:** Of the 302 randomized pts, 71.5% were aged <70 years (Isa-Kd: 70.9%; Kd: 72.4%) and 28.5% were aged ≥70 years (Isa-Kd: 29.1%; Kd: 27.6%). Consistent with the significant improvement of PFS in the overall population, the addition of Isa to Kd resulted in improved PFS independently of age (Table). The CR, ≥very good partial response (VGPR), and MRD- rates were higher with Isa-Kd vs Kd. Within the Isa-Kd arm, CR rate and ≥VGPR rate were similar in elderly and younger pts. MRD- was observed in 32.3% of younger pts and 23.1% of elderly pts with Isa-Kd. In both arms, Grade ≥3 and serious treatment-emergent adverse events (TEAEs) were more frequently reported in elderly pts vs pts <70 years old (Table). For both age groups, the incidence of Grade ≥3 TEAEs was higher whereas the incidence of serious TEAEs was similar between Isa-Kd and Kd. In the elderly subgroup, 3 (5.9%) pts receiving Isa-Kd and 1 (2.9%) receiving Kd had fatal TEAEs (Isa-Kd, infection; Kd, general health deterioration due to progressive disease). The most common Grade ≥3 TEAEs in pts aged <70 and ≥70 years treated with Isa-Kd vs Kd were hypertension (18.3% vs 17.0% [<70 years] and 25.5% vs 26.5% [≥70 years]) and pneumonia (14.3% vs 9.1% [<70 years] and 21.6% vs 20.6% [≥70 years]). **Conclusions:** The addition of Isa to Kd improved PFS and quality of response in elderly pts, with a manageable safety profile, consistent with the benefit observed in the overall IKEMA study population. Isa-Kd provides a potential new treatment option for elderly pts with RMM. Funding: Sanofi. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	<70 Years		≥70 Years	
	Isa-Kd (n = 127)	Kd (n = 89)	Isa-Kd (n = 52)	Kd (n = 34)
PFS HR (95% CI)	0.609 (0.384–0.968)		0.364 (0.176–0.751)	
CR, %	40.2	29.2	38.5	23.5
≥VGPR, %	72.4	56.2	73.1	55.9
MRD-, %	32.3	13.5	23.1	11.8
Grade ≥3 TEAEs, %*	71.4	63.6	90.2	76.5
Serious TEAEs, %*	54.0	52.3	72.5	70.6
Fatal TEAEs, %*	2.4	3.4	5.9	2.9
TEAEs leading to definitive discontinuation, %*	7.1	10.2	11.8	23.5

*n = 126; n = 88; n = 51; n = 34.

8027 **Poster Session**

Effects of weekly selinexor, bortezomib, dexamethasone (XVd) versus standard twice weekly bortezomib and dexamethasone (Vd) on *RAS*-mutated previously treated multiple myeloma (MM).

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Background: Activating mutations of the RAS genes *NRAS*, *KRAS*, and *HRAS* (*RAS*^{mut}) occur in up to 50% of MM and portend poor survival and high recurrence rates. MM cells with *RAS*^{mut} are susceptible to inhibition of germinal center kinase (GCK), resulting in IKAROS degradation independent of cereblon (CRBN). Selinexor is a selective inhibitor of nuclear export (SINE) compound that can induce IKAROS degradation through CRBN-independent pathways to overcome immunomodulatory drug resistance. We explored the benefit of selinexor treatment for pts with *RAS*^{mut} MM. **Methods:** In the randomized BOSTON study, pts with MM after 1-3 therapies received weekly XVd or twice weekly Vd. In the single-arm STORM study pts with penta-treated, triple class refractory MM were treated with twice weekly Xd. Both treatment regimens are now FDA approved. Mutations were assessed post-hoc by exome sequencing of 119 and 52 pts from BOSTON and STORM, respectively. Pts were considered *RAS*^{mut} if their MM had *NRAS*, *KRAS* or *HRAS* mutations in codons 12, 13 or 61. **Results:** There were 54 pts (45%) with *RAS*^{mut} in BOSTON (XVd = 26, Vd = 28), and 17 (33%) in STORM. In BOSTON, pts with *RAS*^{mut} MM treated with XVd had significantly longer progression-free survival (PFS) than those treated with Vd (median [med] = 12.9 vs 6.7 months [mo], hazard ratio [HR] = 0.48 [95% CI 0.24-0.97], p = 0.039). For pts treated with Vd, those with *RAS*^{mut} had significantly shorter overall survival (OS) compared to *RAS*-wild-type (WT) (med = 16.8 mo vs not reached [NR], HR = 2.87 [95% CI 1.03-7.99], p = 0.035). PFS was not significantly different (med = 6.74 vs 9.82 mo, HR = 1.64 [95% CI 0.88-3.07], p = 0.122). Amongst pts on XVd, there was no difference in survival between *RAS*^{mut} and *RAS*^{WT} pts (PFS: med = 12.8 vs 12.9 mo, HR = 1.08 [95% CI 0.52-2.26], p = 0.83; OS: med = NR vs NR, HR = 0.94 [95% CI 0.36-2.45], p = 0.91). In STORM, pts with *RAS*^{mut} had shorter OS compared to *RAS*^{wt} pts (med = 6.1 vs NR, HR = 2.05 [95% CI 1.22-5.19], p = 0.010). Preliminary studies to explore the mechanisms of action related to *RAS*^{mut} MM sensitivity to XVd demonstrated that selinexor treatment in vitro leads to downregulation of GCK. **Conclusions:** Despite typically having the worst outcomes, pts with *RAS*^{mut} MM had a similar benefit from XVd as *RAS*^{WT} MM, showing that the XVd combination can overcome *RAS*^{mut}. Mechanistically, selinexor induced down regulation of GCK and enhanced killing of *RAS*^{mut} MM cells. With a manageable safety profile, the XVd regimen could provide a viable treatment option to improve survival of pts with MM with RAS mutations. Clinical trial information: NCT03110562. Research Sponsor: None.

	PFS		OS	
	p-value	HR (95% CI)	p-value	HR (95% CI)
BOSTON *RAS*^{mut} XVd vs Vd	0.039	0.48 (0.24-0.97)	0.22	0.57 (0.23, 1.41)
BOSTON XVd arm*RAS*^{mut} vs *RAS*^{WT}	0.83	1.08 (0.52, 2.26)	0.91	0.94 (0.36, 2.45)
BOSTON Vd arm*RAS*^{mut} vs *RAS*^{WT}	0.12	1.64 (0.88, 3.07)	0.035	2.87 (1.03, 7.99)
STORM (Xd)*RAS*^{mut} vs *RAS*^{WT}	0.28	1.58 (0.69, 3.63)	0.010	2.51 (1.22, 5.19)

8028 **Poster Session**

Incidence, mitigation, and management of neurologic adverse events in patients with multiple myeloma (MM) treated with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-2.

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Background: Cilta-cel (JNJ-68284528) is a chimeric antigen receptor T (CAR-T)-cell therapy with 2 BCMA-targeting, single-domain antibodies designed to confer high avidity binding. CARTITUDE-2 (NCT04133636) is a phase 2, multicohort, open-label study assessing the efficacy and safety of cilta-cel in patients (pts) with MM in various clinical settings. Here, we describe the mitigation and management strategies implemented to identify and reduce the risk for neurologic adverse events (AEs) in Cohort A pts (progressive MM after 1−3 prior lines of therapy). **Methods:** Eligible pts (≥18 years of age) had MM per IMWG criteria, measurable disease, ECOG ≤1, progressive disease after 1−3 prior lines of therapy (including a PI and IMiD) and were lenalidomide refractory (no prior BCMA-targeting agent). Cilta-cel (0.75×10^6 [range $0.5–1.0\times10^6$] CAR+ viable T cells/kg) was given as a single infusion 5–7 days after start of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 daily for 3 days). Monitoring and mitigation strategies for neurologic AEs include providing more effective bridging therapy to reduce tumor burden prior to lymphodepletion, frequent assessment of CAR-T-related ICANS using the ICE tool, regular handwriting assessments to detect micrographia, and neuroimaging (brain MRI) and EEG for pts with prior neurologic disease. Management strategies include evaluating infectious and paraneoplastic etiologies upon observation of ICANS ≥Grade (gr) 1, administration of tocilizumab (if concurrent CRS, all gr of ICANS) and/or dexamethasone (gr 2/3) or methylprednisolone (gr 4). ICANS and CRS were graded by ASTCT criteria; neurotoxicities not classified as ICANS were graded per CTCAE Version 5.0. **Results:** As of 15 Jan 2021 (median follow-up: 5.8 months [range: 2.5–9.8 months]), 20 pts in Cohort A received cilta-cel. Median age was 60 years (range: 38–75); 65% were male. Neurotoxicities occurred in 4 pts (20%). Three pts had ICANS (gr 1/2); median time to onset of symptoms was 8 days (range: 7–11) and median duration was 2 days (range: 1–2). Two of the 3 pts received supportive measures to treat ICANS, including levetiracetam and steroids; all 3 had concurrent CRS and all recovered. One pt developed isolated facial paralysis (gr 2) on Day 29 after cilta-cel infusion, and recovered 51 days after the onset of event following treatment with dexamethasone for 28 days. No movement or neurocognitive disorders were reported. **Conclusions:** Neurologic AEs were generally manageable in pts with MM following treatment with cilta-cel. With a median of 5.8 months of follow-up, there were no movement or neurocognitive disorders in pts from Cohort A. These results suggest that early detection and management of neurologic AEs can lead to better treatment outcomes. Clinical trial information: NCT04133636. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8029 **Poster Session**

Personalized, ctDNA analysis to detect minimal residual disease and identify patients at high risk of relapse with multiple myeloma.

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Background: Despite treatment with high-dose chemotherapy followed by autologous stem cell transplantation (AHCT), MM patients invariably relapse. MRD-negativity post-AHCT has emerged as the most important prognostic marker. Currently, MRD in MM is monitored via bone marrow aspirate sampling. Marrow MRD assays are limited by the spatial heterogeneity of marrow MM localization; extramedullary disease and sampling variability of marrow aspiration. Sensitive, non-invasive blood-based MRD assay is an unmet need. ctDNA as a noninvasive biomarker can be utilized to predict relapse in MM. Here we attempt to evaluate MRD using ctDNA in AHCT recipients with MM. **Methods:** In this retrospective, single-center study, we analyzed ctDNA MRD in blood samples collected from 28 patients with MM after upfront AHCT. A total of 80 plasma timepoints were available pre and post AHCT with a median follow-up of 92.4 months. Multiparameter flow cytometry (MFC) at 10-4 level was used to assess the MRD from the BM biopsy. Individual bone marrow aspirates or FFPE slides from the time of MM diagnosis and matched normal blood were whole-exome sequenced, and somatic mutations were identified. MRD assessment at 3 months post-AHCT was performed by ctDNA analysis using a personalized, tumor-informed (Signatera^{TM}, bespoke mPCR NGS assay). The prognostic value of ctDNA was evaluated by correlating MRD status with clinical outcomes. **Results:** Table provides the baseline disease characteristics. Median age was 67 [41-75] years and 16 [57.1%] were males. ctDNA was detectable in 70.8% (17/24) of pre-AHCT, 53.6% (15/28) of ~3 months post-AHCT, and 39.2% (11/28) of patients during the surveillance phase post-AHCT. Of the 15 ctDNA MRD positive patients, 93.3% (n=14) experienced relapse on follow-up (hazard ratio: 5.64; 95% CI: 1.8-17; p=0.0003). Patients negative for ctDNA at 3 months post-AHCT had significantly superior progression-free survival (PFS) compared to positive (median PFS, 84 months vs. 31 months; p=0.003) The positive predictive value (PPV) for relapse among patients positive for ctDNA at 3 months post-AHCT was 93.3%, and significantly higher than marrow MFC of 68.4%. **Conclusions:** Our study shows the feasibility that a tumor-informed assay on archival blood samples is predictive of relapse post-AHCT. Future prospective studies with real-time marrow NGS and ctDNA samples are needed to define the role of ctDNA in MM and its prognostic significance. Research Sponsor: None.

Baseline characteristics.

Characteristics	N=28 (%)
Isotype	
IgG kappa/lambda	20 (71)
IgA kappa/lambda	3 (11)
Light chain	5 (18)
ISS stage	
I	15 (54)
II	11 (39)
III	1 (3.5)
Unknown	1 (3.5)
High risk cytogenetics	4 (14)
Induction	
VRD	13 (46)
CyBorD	11 (39)
Others	4 915)
Post-Transplant response	
Complete/near complete response	14 (50)
Very good partial response	5 (18)
Partial response	9 (32)

8030 **Poster Session**

Cilta-cel versus conventional treatment in patients with relapse/refractory multiple myeloma.

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Background: CARTITUDE-1 is a single arm study of Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) anti-BCMA CAR-T cell therapy in US patients (pts) with relapsed multiple myeloma (RRMM) refractory to both IMiD and proteasome inhibitor (PI) or with at least 3 prior lines of therapy and previously exposed to anti-CD38 monoclonal antibody (MoAb). While recently reported efficacy results of cilta-cel were encouraging, it is unknown how they compare with similar pts receiving conventional (non CAR-T) treatment. **Methods:** We utilized a contemporary US-based dataset of pts with MM refractory to anti-CD38 MoAb (MAMMOTH) to identify pts who would meet eligibility for CARTITUDE-1 and who received conventional therapy. We analyzed the intent-to-treat population (ITT) in CARTITUDE-1, defined as pts who underwent apheresis (N=113) and a modified ITT population (mITT) defined as subset of pts who received cilta-cel at the RP2D (N=97). From the MAMMOTH dataset, we identified a population corresponding to CARTITUDE-1 ITT (N=190) and a mITT population, pts without death or progression within 47 days (median time between apheresis and cilta-cel infusion) from onset of therapy (N=122). We calculated propensity scores (PS) with demographics, N of prior therapies, cytogenetics and refractoriness to MM agents as covariates. An analyst blinded to outcomes performed nearest neighbor 1:1 PS matching. We analyzed overall response rate (ORR), progression-free (PFS) and overall survival (OS) for ITT and mITT in CARTITUDE-1 vs matching MAMMOTH cohorts. **Results:** Ninety-five ITT (75 received bridging therapy, 82 received cilta-cel) and 69 mITT (54 received bridging) CARTITUDE-1 pts matched MAMMOTH pts (Table). Among the pts in the MAMMOTH ITT cohort 34% received pomalidomide, 24% anti-CD38 MoAb, 19% carfilzomib and 35% cytotoxic chemotherapy in next therapy. ORR in the ITT cohorts was higher in CARTITUDE-1 (84% vs. 28%). Compared to their MAMMOTH counterparts, pts in CARTITUDE-1 ITT cohort had improved PFS (12 mo. 73% vs. 12%) and OS (12 mo. 83% vs 39%). Between the mITT cohorts, CARTITUDE-1 pts had superior ORR (96% vs. 30%), PFS (12 mo 79% vs. 15%) and OS (12 mo. 88% vs. 41%). **Conclusions:** In pts with RRMM beyond therapy with IMID, PI, and anti-CD38 MoAb, treatment with cilta-cel is associated with higher response rate and superior PFS and OS when compared to conventional treatment. Research Sponsor: Janssen.

	ITT (apheresis) CARTITUDE (N=95)	ITT matches, MAMMOTH (N=95)		mITT (treated) CARTITUDE (N=69)	mITT matches, MAMMOTH (N=69)	
Mean Age -years (sd)	62.4 (8.5)	62 (8.5)		62.6 (7.7)	62.7 (9.4)	
High cytogenetic risk	22%	24%		25%	23%	
Mean N lines of therapy (sd)	6.2 (3.0)	6.3 (2.4)		5.9 (2.9)	6 (1.9)	
Triple-class refractory	97%	96%		96%	96%	
Penta exposed	80%	76%		75%	75%	
Penta refractory	43%	42%		35%	42%	
ORR	84%	28%	P<0.001	96%	30%	P<0.001
PFS	HR=0.11, 95% C.I. 0.05-0.22		P<0.001	HR=0.02, 95% C.I. 0.01-0.14		P<0.001
OS	HR=0.20, 95% C.I. 0.10-0.39		P<0.001	HR=0.05, 95% C.I. 0.01-0.22		P<0.001

8031 **Poster Session**

Assessing financial difficulty in patients with multiple myeloma: Preliminary results of ALLIANCE A231602CD.

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Background: New orally administered anticancer treatments have launched in recent years, promising gains in survival and quality of life, but with high prices.Financial difficulties encountered over the course of cancer diagnosis and treatment is a growing concern. These difficulties include inability to pay for basic necessities, presence of medical debt, and high out of pocket burdens relative to income. The primary objective of this study was to estimate the proportion of patients with multiple myeloma (MM) who experience financial difficulties in the past 12 months.**Methods:** Data collection entailed a comprehensive, theoretically grounded telephone survey and companion medical chart abstraction. Subjects included individuals with a current diagnosis of MM whose current or recent treatment included pharmaceutical-based care and who were not enrolled in a treatment-based trial. Practices eligible to recruit respondents included 44 NCORP affiliates of the Alliance. 14 geographically diverse NCORP affiliates participated between 11/2019 and 6/2020. The primary endpoint of the study was the proportion of subjects who reported financial difficulty in the past 12 months, as measured by the EORTC QLQ-C30 item #28. This proportion and 95% Wilson score confidence interval were estimated for all MM patients who responded to the financial difficulty question ((# reported financial difficulty)/(total # in that category who answered the question)). NCI Central IRB approved this study. **Results:** 393 subjects were recruited. 304 subjects completed the survey (77.4% response rate). Mean age was 67.5 years (SD 9.8), 143 (46.4%) were female, 24 (7.8%) self-reported race as Black or African American', 82 (26.6%) reported insured by government insurance Medicare only, 116 (38.2%) reported highest education as high school or below, and 94 (30.5%) reported high income. Mean time from diagnosis to survey enrollment was 3.6 years (SD 4.5). 292 (95.1%) were currently receiving treatment and 192 (62.5%) reported currently receiving a pre-defined expensive' oral pharmaceutical-based cancer treatment. 20.2% (95% CI:16.1%, 25.0%) reported financial difficulties. **Conclusions:** This is the first national study to systematically assess the prevalence of financial difficulties and its correlates among MM patients. Approximately 1 in 5 surveyed patients reported financial difficulties. Results of this study aim to inform efforts to improve financial navigation and resources for cancer patients. Research Sponsor: U.S. National Institutes of Health, Leukemia and Lymphoma Society.

8032 **Poster Session**

5-Hydroxymethylcytosines in circulating cell-free DNA and overall survival in patients with multiple myeloma.

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Background: The epigenetic mark 5-methylcytosines (5mC) have been associated with poor prognosis and survival in multiple myeloma (MM), but the prognostic role of 5-hydroxymethylcytosines (5hmC) as marks of tissue-specific enhancers generated from 5mC through active demethylation is unknown. We showed that 5hmC can be profiled in circulating cell-free DNA (cfDNA) and is associated with relapse/death in another lymphoproliferative disorder diffuse large B-cell lymphoma. To date, no study has investigated genome-wide 5hmC profiles in cfDNA for its prognostic significance in MM. **Methods:** A total of 354 newly diagnosed MM patients at the University of Chicago Medical Center were prospectively enrolled between 2010-2017. Blood samples were collected at the time of diagnosis. Patients were followed through 31 December 2020 (avg. follow-up = 77.8 mths). We collected baseline clinical, laboratory, and cytogenetic data from electronic medical records. Vital status was ascertained in 351 of the 354 patients (deaths = 73) using the National Death Index. We profiled genome-wide 5hmC in cfDNA using the 5hmC-Seal and next-generation sequencing. The 5hmC-Seal data were mapped to the human genome reference (hg19) and annotated to gene bodies. Overall survival (OS) was defined as time from diagnosis until death from any cause. We used Cox proportional hazards model and the elastic net regularization to identify genes with modified 5hmC levels that are associated with OS. Patients were randomly divided into a training set (n = 264) and testing set (n = 87). **Results:** The median age at diagnosis was 61.8 years and 47% (n = 165) were males. We used the differential 5hmC enrichment levels of a preliminary four-gene marker panel (i.e., *YPEL1*, *VIPR2*, *PLAC8L1*, and *CYP2D6*) to compute a weighted prognostic score (wp-score). In the training set (deaths = 55), MM patients with high wp-score had worse OS (Hazard Ratio [HR] = 2.2, 95% Confidence Interval [CI]: 1.3-3.9; p = 0.004). The same trend was observed in the testing set (deaths = 18) (HR = 3.5, 95% CI: 1.1-10.6; p = 0.02). The 5hmC-based wp-score remained significantly associated with OS after controlling for standard prognostic factors, suggesting that 5hmC-based wp-score for this 4-gene panel is an independent prognostic factor for MM. We also explored population-specific 5hmC and wp-score. We found that 5hmC profiles in cfDNA differ between Blacks (n = 117) and Whites (n = 234). In addition, 5hmC marker genes associated with OS differ between Blacks (13 genes) and Whites (20 genes). **Conclusions:** Our results suggest that 5hmC in cfDNA at the time of diagnosis correlate with OS in MM and the 5hmC marker genes associated with OS differ between Blacks and Whites. These findings suggest that a plasma-derived cfDNA 5hmC-modified gene panel holds promise as a noninvasive approach for predicting prognosis in MM and may be integrated in clinical practice to improve precision care. Research Sponsor: U.S. National Institutes of Health.

8033 **Poster Session**

Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (belamaf).

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Background: Belantamab mafodotin (GSK2857916; belamaf; BLENREP) is a B-cell maturation antigen (BCMA)-targeting antibody–drug conjugate approved in the US and EU as a monotherapy for the treatment of adult patients with RRMM. Ocular events (OEs) during the pivotal DREAMM-2 trial (NCT03525678) included corneal exam findings (punctate keratopathy and microcyst-like epithelial changes), BCVA changes, and ocular symptoms. Dose reductions or delays based on corneal exam findings and BCVA were used to manage OEs. Here we performed a *post hoc* investigation of relationships between corneal exam findings, BCVA changes, and patient-reported ocular symptoms to explore if BCVA changes and symptoms could guide dosing, rather than corneal exams. **Methods:** Eye evaluations (including a corneal exam and BCVA assessment of Snellen visual acuity) were performed on all patients receiving single-agent belamaf (2.5 mg/kg) by ophthalmologists at baseline and prior to each belamaf dose. Changes in the corneal epithelium (Ker) and BCVA were both assessed as per protocol-defined criteria and assessment of grade (Gr) was based on the worse eye. BCVA grading was relative to baseline. Patient-reported ocular symptoms were reported as per the Common Terminology Criteria for Adverse Events. **Results:** In 12.5% of eye evaluations Gr 3–4 Ker was associated with minimal or no (Gr $\leq$1) BCVA changes. When patient-reported ocular symptoms were also considered, only 7.5% of evaluations found Gr 3–4 Ker with Gr $\leq$1 BCVA changes or ocular symptoms. Mild or no (Gr $\leq$2) Ker was associated with Gr $\leq$1 BCVA changes in 59.5% of evaluations, or in 38.8% of evaluations with no ocular symptoms reported. Overall, Gr 3–4 Ker were found in 24.9% of evaluations; by contrast, patients had Gr 2–4 BCVA changes or ocular symptoms in 53.7% of evaluations. Association of corneal epithelium changes (Ker) with BCVA changes and ocular symptoms. **Conclusions:** These findings highlight that BCVA changes and ocular symptoms should be further investigated to determine if they can be used as alternatives (eg, frequency of eye examinations based on symptoms) for the management of belamaf dosing to potentially reduce the burden on patients and healthcare professionals. Clinical trial information: NCT03525678. Research Sponsor: GlaxoSmithKline, Drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa.

Ker + BCVA changes only (evaluations, n=773); n (%)	
Gr 3–4 Ker & Gr $\leq$1 BCVA	97 (12.5)
Gr 3–4 Ker & Gr 2–4 BCVA	96 (12.4)
Gr $\leq$2 Ker & Gr $\leq$1 BCVA	460 (59.5)
Gr $\leq$2 Ker & Gr 2–4 BCVA	120 (15.5)
Ker + BCVA changes or ocular symptoms (evaluations, n=773); n (%)	
Gr 3–4 Ker & (Gr $\leq$1 BCVA, no symptoms)	58 (7.5)
Gr 3–4 Ker & (Gr 2–4 BCVA, or symptoms)	135 (17.4)
Gr $\leq$2 Ker & (Gr $\leq$1 BCVA, no symptoms)	300 (38.8)
Gr $\leq$2 Ker & (Gr 2–4 BCVA, or symptoms)	280 (36.2)

8034 **Poster Session**

Isatuximab plus carfilzomib and dexamethasone in patients with relapsed multiple myeloma according to prior lines of treatment and refractory status: IKEMA subgroup analysis.

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Background: Patients (pts) with multiple myeloma (MM) often relapse and become refractory to successive lines of therapy, warranting better treatment options. The Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with Kd in pts with relapsed MM (RMM) (HR 0.53; 99% CI 0.32–0.89; P= 0.0007). We evaluated the efficacy and/or safety of Isa-Kd by number of prior lines of therapy (1 vs $>$ 1) and refractoriness to lenalidomide (Len) or bortezomib (Bor). **Methods:** Pts were randomized (3:2) to Isa-Kd (n = 179) or Kd (n = 123). Isa (10 mg/kg IV) was given weekly for 4 weeks, then every 2 weeks. K (20 mg/m^2 days 1-2, then 56 mg/m^2) was given twice-weekly 3 of 4 weeks, and d (20 mg) twice-weekly. The primary endpoint was PFS; key secondary endpoints were very good partial response or better (≥VGPR), minimal residual disease negativity (MRD-), and complete response (CR) rates. **Results:** Of the 302 randomized pts, 44.7% had 1 prior line, 55.3% had $>$ 1 prior line, 32.8% were Len-refractory, and 30.1% were Bor-refractory. PFS was improved with Isa-Kd vs Kd in pts who received 1 prior line and $>$ 1 prior line, as well as in pts refractory to Len, Len at last regimen, Bor, or Bor at last regimen (Table). The addition of Isa to Kd improved depth of response (≥VGPR, MRD-, and CR rates) in all subpopulations analyzed by prior treatment. Grade ≥3 treatment-emergent adverse events (TEAEs) were generally similar between the prior line subgroups (77.2% [Isa-Kd] vs 64.8% [Kd], 1 prior line; 76.5% [Isa-Kd] vs 69.1% [Kd], $>$ 1 prior line) and the overall safety population (76.8% [Isa-Kd] vs 67.2% [Kd]). Serious AEs were 62.0% vs 48.1% in the 1 prior line subgroup, and 57.1% vs 64.7% in the $>$ 1 prior line subgroup; TEAEs leading to discontinuations were 8.9% vs 11.1%, 1 prior line and 8.2% vs 16.2%, $>$ 1 prior line. **Conclusions:** The addition of Isa to Kd improved PFS and depth of response, irrespective of prior lines of therapy or refractory status, consistent with the benefit observed in the overall IKEMA study population. Isa-Kd had a manageable safety profile regardless of number of prior lines. Isa-Kd is a potential new treatment option for pretreated pts with RMM. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	n		PFS, HR (95% CI)	≥VGPR, %		MRD-, %		CR, %	
	Isa-Kd	Kd	-	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
Overall	179	123	0.53 (0.32-0.89)*	72.6	56.1	29.6	13.0	39.7	27.6
Number of prior lines as per randomization 1	80	55	0.59 (0.31-1.12)	75.0	61.8	33.8	18.2	41.3	36.4
>1	99	68	0.48 (0.29-0.78)	70.7	51.5	26.3	8.8	38.4	20.6
Refractory to Len Yes	57	42	0.60 (0.34-1.1)	66.7	35.7	24.6	9.5	38.6	11.9
Refractory to Len at last regimen Yes	36	31	0.69 (0.35-1.39)	72.2	38.7	27.8	9.7	47.2	12.9
Refractory to Bor Yes	52	39	0.62 (0.33-1.16)	55.8	51.3	17.3	10.3	28.8	17.9
Refractory to Bor at last regimen Yes	32	23	0.38 (0.16-0.92)	62.5	47.8	25.0	8.7	31.3	17.4

*99% CI.

8035 **Poster Session**

Daratumumab (DARA) maintenance therapy following DARA + cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction therapy in multiple myeloma (MM): End-of-study analysis of LYRA.

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Background: LYRA is a community practice-based, phase 2, single-arm study (NCT02951819) evaluating DARA + CyBorD as an immunomodulatory drug-sparing regimen in MM. The primary analysis demonstrated the safety and efficacy of DARA + CyBorD in newly diagnosed MM (NDMM) and relapsed MM (RMM), and an update showed that DARA maintenance therapy deepened responses. We present the final end-of-study analysis of LYRA. **Methods:** US pts aged ≥18 years with MM per IMWG criteria and ≤1 prior line of therapy received 4-8 induction cycles of DARA + CyBorD (cyclophosphamide 300 mg/m^2 PO weekly [QW]; bortezomib 1.5 mg/m^2 SC on Days [D] 1, 8, and 15; dexamethasone 40 mg PO or IV QW every 28 days; DARA IV 8 mg/kg on D1 and D2 of cycle [C]1, 16 mg/kg QW C1D8-C2, 16 mg/kg Q2W C3-6, and 16 mg/kg Q4W C7-8). After induction, eligible pts could receive autologous stem cell transplantation (ASCT). Pts received up to 12 maintenance cycles with DARA 16 mg/kg IV Q4W and were followed for up to 36 months after induction. **Results:** In total, 101 (NDMM, n = 87; RMM, n = 14) pts were enrolled; 36% of pts had high-risk cytogenetics. NDMM and RMM pts received a median of 6 and 8 induction cycles, respectively. Among NDMM pts, 44.8% (39/87) underwent ASCT and 72.4% (63/87) completed 12 months of maintenance. Rates of ≥VGPR and ≥CR were 82.1% and 48.7% in NDMM pts who underwent ASCT, and 70.2% and 29.8% in NDMM pts who did not (Table). With a median follow-up of 35.7 months, median progression-free survival (PFS) and overall survival (OS) were not reached for NDMM pts. Estimated 36-month PFS rates were 69.3% and 72.6% for NDMM pts who did and did not receive ASCT, respectively; estimated 36-month OS rates were 94.9% and 84.3% (Table). Among RMM pts, 7.1% (1/14) underwent ASCT and 50.0% (7/14) completed 12 months of maintenance; efficacy outcomes are shown in the Table. Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 62.0% of all pts, with the most common (≥10%) being neutropenia (14.0%). Serious TEAEs occurred in 33.0% of pts, the most common being pneumonia (4.0%) and pulmonary embolism (3.0%). TEAEs led to death in 2.0% of pts, all unrelated to study treatment. Infusion-related reactions occurred in 56.0% of pts; the majority were mild (4.0% of pts had grade 3/4 events). **Conclusions:** DARA used for induction with CyBorD and maintenance as monotherapy resulted in durable, deep responses in pts with NDMM or RMM, with a 3-year PFS rate of 70% in NDMM irrespective of ASCT status. With longer follow-up, no new safety concerns were identified. Clinical trial information: NCT02951819. Research Sponsor: Janssen Research & Development, LLC.

	NDMM who received ASCT (n = 39)	NDMM who did not receive ASCT (n = 47)	RMM (n = 14)
ORR, %	97.4	83.0	85.7
sCR	23.1	17.0	28.6
≥CR	48.7	29.8	64.3
≥VGPR	82.1	70.2	71.4
	(n = 39)	(n = 48)	(n = 14)
Estimated 36-mo PFS, % (95% CI)	69.3 (43.0-85.3)	72.6 (54.0-84.7)	31.7 (5.6-63.4)
Estimated 36-mo OS, % (95% CI)	94.9 (81.0-98.7)	84.3 (69.8-92.2)	50.0 (22.9-72.2)

8036 **Poster Session**

Characteristics of neurotoxicity associated with idecabtagene vicleucel (ide-cel, bb2121) in patients with relapsed and refractory multiple myeloma (RRMM) in the pivotal phase II KarMMa study.

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Background: Ide-cel, a BCMA-directed CAR T cell therapy, showed promising efficacy in patients (pts) with RRMM in the KarMMa study with an ORR of 73% and a CRR of 33% across target doses of 150–450 $\times$ 10^6 CAR+ T cells (Munshi NC, et al. *J Clin Oncol* 2020;38[suppl 15]. Abstract 8503). Associations of neurotoxicity (NT) with pt and disease characteristics, pt management, and impact on outcomes in the KarMMa study are reported here. **Methods:** Enrolled pts were triple-class exposed and refractory to their last regimen, with ide-cel given at target doses of 150, 300, or 450 $\times$ 10^6 CAR+ T cells after lymphodepletion (NCT03361748). Investigator-identified NT events were captured under the single preferred term of neurotoxicity and graded according to NCI CTCAE v4.03. Events were managed with corticosteroids (CS), anakinra (ANR), and tocilizumab (Toci) as needed. **Results:** Of 128 pts treated with ide-cel, NT was reported in 23 (18%); 12 pts (9%) had maximum grade (gr) 1 NT, 7 (5%) had gr 2, and 4 (3%) had gr 3. No gr 4 or 5 NT occurred. Most baseline characteristics were similar in pts with and without NT, including stage III disease (22% and 15%), high-risk cytogenetics (39% and 34%), and extramedullary disease (35% and 40%); exceptions were high tumor burden (65% and 48%) and sex (48% and 62% men). NT (any gr/gr 3) occurred in 0%/0%, 17%/1%, and 20%/6% of pts at doses of 150, 300, and 450 $\times$ 10^6 CAR+ T cells. Median time to onset was similar regardless of gr, and there were no late-onset events (Table). NT was managed with CS in 10 pts (43%), Toci in 3 (13%), and ANR in 1 (4%). Median (range) time to first use of CS was 2 d (1–6). ORR and DOR were similar in pts with and without NT (Table). All NT occurred in the proximity of cytokine release syndrome (CRS) events with the start date of NT events either overlapping with or occurring within 1 wk of the start of a CRS event. **Conclusions:** NT occurred early in the KarMMa study, was generally of short duration, and was mostly gr 1/2 with no gr $\geq$4 events. All NT was proximal to CRS. Pts with NT had a favorable ORR after ide-cel treatment. These results continue to demonstrate the durable efficacy and tolerability of ide-cel in pts with RRMM. Clinical trial information: NCT03361748. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, and bluebird bio.

NT events	Gr 1 (n = 12)	Gr 2 (n = 7)	Gr 3 (n = 4)	Any gr (n = 23)
Time to onset, median (range), d	2 (1–10)	2 (1–4)	3 (1–4)	2 (1–10)
No. of events	13	7	4	24
Duration/event, %	69	43	25	54
1–5 d	31	29	0	25
6–10 d	0	14	75	17
>10 d	0	14	0	4
Ongoing	3 (1–9)	6 (1–26)	14 (2–22)	3 (1–26)
Median (range), d[a]				
CS / Toci / ANR, %	17 / 8 / 0	57 / 0 / 0	100 / 50 / 25	43 / 13 / 4

Efficacy	No NT (n = 105)	NT, any gr (n = 23)
Response, % (95% CI)		
ORR	73 (64.9–81.8)	74 (56.0–91.9)
CRR	35 (26.1–44.4)	22 (4.9–38.6)
PFS, median (95% CI), mo	8.9 (5.7–11.9)	6.1 (3.0–11.1)
DOR,[b] median (95% CI), mo	11.0 (8.0–11.3)	10.0 (4.0–NE)
OS, median (95% CI), mo	19.4 (18.0–NE)	NE (12.3–NE)

Data cutoff: 14 Jan 2020. NE, not estimable. [a]Ongoing NT excluded. [b]Among responders.

8037 **Poster Session**

ANCHOR (OP-104): Melflufen plus dexamethasone (dex) and bortezomib (BTZ) in relapsed/refractory multiple myeloma (RRMM)—Optimal dose, updated efficacy and safety results.

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Background: Development of resistance to standard treatments for RRMM highlights the need for novel therapies. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and rapidly releases alkylating agents inside tumor cells. Melflufen + dex showed clinical activity and an acceptable safety profile in HORIZON (Richardson et al. *J Clin Oncol*. 2020 Dec 9 [Epub]). This is an update of the BTZ arm of the phase 1/2a ANCHOR study (NCT03481556). **Methods:** Patients (pts) with RRMM were intolerant or refractory to a prior IMiD, with 1-4 prior lines of therapy (LoTs). Prior treatment with a proteasome inhibitor (PI) was allowed, but pts could not be refractory to PIs in the last LoT. Melflufen (30, 40, or 20 mg intravenously; d 1 of each 28-d cycle) was administered with BTZ (1.3 mg/m^2 subcutaneous) + oral dex (20 mg on d 1, 4, 8, and 11 and 40 mg on d 15 and 22; dex dose reduced if aged $\geq$ 75 y). The primary objective in phase 1 was to determine the optimal phase 2 dose of melflufen for this combination. **Results:** As of the data cutoff date (October 19, 2020), 13 pts received melflufen (30 mg, n = 6; 40 mg, n = 7) + dex and BTZ. In the 30 mg and 40 mg cohorts, respectively, median age was 78.5 y (range, 70-82) and 70.0 y (range, 61-76); median prior LoTs was 3.5 (range, 2-4) and 2.0 (range, 1-4); 33% and 50% of evaluable pts had high-risk cytogenetics; 83% and 71% were refractory to last LoT; 100% and 86% received a prior PI; 33% and 14% were refractory to PIs. In the 30 mg and 40 mg cohorts, respectively, median treatment duration was 6.5 mo (range, 1.4-29.0) and 8.7 mo (range, 2.1-19.6); 4 (67%) and 4 pts (57%) were still on treatment; 2 and 3 pts discontinued (30 mg: progressive disease [PD] and other [1 pt each]; 40 mg: adverse event [AE], lack of efficacy, and PD [1 pt each]). Confirmed overall response rate in the 30 mg and 40 mg cohorts, respectively, was 50% (1 very good partial response [VGPR] and 2 partial response [PR]) and 71% (1 complete response, 3 VGPR, and 1 PR). Most common grade 3/4 treatment-related AEs (TRAEs) were thrombocytopenia (30 mg: 50%; 40 mg: 100%) and neutropenia (30 mg: 33%; 40 mg: 71%); grade 3/4 nonhematologic TRAEs were infrequent; 3 pts discontinued study treatment due to treatment-emergent AEs (30 mg: cardiac failure chronic and osteolysis [1 pt each]; 40 mg: thrombocytopenia [1 pt]). Serious TRAEs occurred in 2 pts (33%) in the 30 mg cohort (neutropenia and pneumonia [1 pt], syncope [1 pt]) and 1 pt (14%) in the 40 mg cohort (thrombocytopenia and neutropenia). No dose-limiting toxicities occurred at either dose level. Fatal AEs occurred in 1 pt in the 30 mg cohort (cardiac failure chronic; unrelated to study treatment). **Conclusions:** ANCHOR determined that the optimal dose of melflufen is 30 mg + dex and BTZ; results showed clinical activity in heavily pretreated pts. Recruitment is ongoing; updated data will be presented. Clinical trial information: NCT03481556. Research Sponsor: Oncopeptides AB.

8038 **Poster Session**

Once weekly selinexor, carfilzomib, and dexamethasone (XKd) in carfilzomib nonrefractory multiple myeloma (MM) patients.

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Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL in combination with low dose dexamethasone (dex) ± bortezomib (BOR) is FDA approved for previously treated MM. The synergy of SEL with the PI BOR has been confirmed in the phase 3 BOSTON study in MM patients (pts) with 1-3 prior therapies; once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS), time to next therapy, and overall response rate (ORR) as compared to standard twice weekly BOR/dex (Vd), despite XVd using 40% less BOR and 25% less dex than standard Vd. We hypothesized that the addition of QW SEL to the PI carfilzomib (CAR)-dex (XKd) would be an active and tolerable regimen in pts with heavily pretreated MM. **Methods:** In the XKd arm of the multi-arm Phase 1b/2 STOMP study, SEL at 80 or 100 mg QW was evaluated in combination with CAR at 56 or 70 mg/m^2 QW plus dex at 40 mg QW in pts with heavily pretreated MM not refractory to CAR. Study objectives were to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) and assess the safety and activity of the XKd regimen. **Results:** As of 4Jan2021, 27 pts were enrolled: 18 (67%) were male, median age 71 years (range 50-76), and median of 4 (range 1-8) prior lines of therapy. All 27 pts were previously treated with BOR, 26 (96%) lenalidomide (LEN), 19 (70%) pomalidomide (POM), 18 (67%) daratumumab (dara). The majority (67%) of pts were triple-class pretreated (PI, IMiD, and anti-CD38 mAb), and 44% had triple-class refractory MM. Nine pts (33%) had MM quad-refractory to BOR, LEN, POM, and dara. Common hematologic treatment-related adverse events (TRAEs) (total, grade ≥3) included thrombocytopenia (74%, 56%), anemia (59%, 19%), and neutropenia (30%, 7%). Non-hematologic TRAEs included nausea (67%, 4%), fatigue (52%, 7%), and anorexia (52%, 4%). RP2D was identified as SEL 80 mg QW, CAR 56 mg/m^2 QW, and dex 40 mg QW. As of 3Feb2021, ORR was 78% (21/27) with 5 pts reaching CR (19%), 8 VGPR (30%), and 8 PR (30%). Median PFS was 23.7 months. Among 18 pts pretreated with dara, ORR was 67% and median PFS 23.7 months. In 9 pts whose MM was refractory to BOR, LEN, POM, and dara, ORR was 67% with 4 VGPR (44%). **Conclusions:** In pts with heavily pretreated MM, weekly XKd is highly active with an ORR of 78% and deep responses (≥VGPR 48%) with an overall PFS of 23 months. All AEs including grade 3/4 thrombocytopenia can be managed with appropriate supportive care and dose modifications. These data support further investigation of XKd in pts with previously treated MM including those previously treated with dara. Research Sponsor: Karyopharm Therapeutics.

8039 **Poster Session**

Phase Ib trial of vactosertib in combination with pomalidomide in relapsed multiple myeloma: A corticosteroid-free approach by targeting TGF-β signaling pathway.

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Background: Immunosuppression and osteoclast activation are two hallmarks of the bone marrow environment in Multiple Myeloma (MM). Corticosteroids have been used historically as part of anti-myeloma regimens due to their anti-plasma cell activity, however they potentially could suppress immune system and activate osteoclast further; therefore there is an unmet need for corticosteroid-free approaches in the era of emerging anti-cancer immunotherapy modalities. There is an abundance of Transforming Growth Factor-beta (TGF-β), a crucial cytokine in suppression of immune system as well as catabolic bone remodeling, in the MM microenvironment. Vactosertib (Vacto) is a small molecule TGF-β type I receptor inhibitor that has shown single agent activity against myeloma in the syngeneic 5T33MM murine mouse model. Here, we report the phase Ib trial of Vacto in combination with pomalidomide (Pom) without any corticosteroids (NCT03143985). **Methods:** pts with relapsed MM with at least two lines of therapies enrolled on a 3 + 3 dose escalation design and received Vacto, 60 mg/d, 120 mg/d, 100 mg BID and 200 mg BID in combination with standard dose of Pom (4mg) without corticosteroids. The primary objectives of the study was to assess safety and recommended phase 2 dose. Vacto tablets, taken once or twice daily for 5 days followed by 2 days without treatment, is administered in 28-day cycles, until progression of disease or intolerable toxicity. **Results:** 15 pts were enrolled on the study (Table). The most common non-hematologic adverse event (AE) was grade II fatigue and pain in one pt, one episode of grade III renal failure that took less than 7 days to get back to baseline on another patient, sinus bradycardia that reversed to sinus rythem and an Afib that was rate controlled with beta blocerks. No grade IV non-hematologic AE was observed. Three pts had grade III hematologic AE, no grade IV hematologic AE. Three out of 15 pts experienced progression of disease (PFS-6: 80%). **Conclusions:** The phase Ib data shows safety of this agent in combination with Pom. The efficacy assessment (PFS-6: 80%) is higher than the historical control (PFS-6: 20% in randomized Phase II study by Richardson et al. Blood. 2014) with Pom only (PFS-6: 20%) or Pom with corticosteroids (PFS-6: 40%). Further advancement of this agent in clinical trial pipelines for MM is planned. Clinical trial information: NCT03143985. Research Sponsor: Medpacto Inc.

Patients' characteristics.

Parameter	60 mg/d			120 mg/d			100 mg BID			200 mg BID				
Age	70	77	70	64	64	69	75	56	77	70	56	66	72	69	67
Gender	F	F	M	F	M	M	F	F	F	M	F	M	F	M	M
lines of therapy	3	4	3	5	3	2	3	1	4	2	2	2	2	4	3
Bony lesions	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Response assessment	MR	PR	SD	MR	SD	PD	PR	PD	MR	PD	SD	PR	PR	PR	SD

PR: Partial response, MR: Minimal response, SD: Stable disease, PD: Progressive disease.

8040 **Poster Session**

Using mobile wearables to establish sleep bioprofiles in newly diagnosed multiple myeloma (MM) patients.

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Background: Passive monitoring using wearables can objectively measure sleep over extended time periods. MM patients (PTs) are susceptible to fluctuating sleep patterns due to pain and dexamethasone (dex) treatment. In this prospective study, we remotely monitored sleep patterns on 40 newly diagnosed MM (NDMM) PTs while administering electronic PT reported outcome (ePRO) surveys. The study aim was to establish sleep bioprofiles during therapy and correlate with ePROs. **Methods:** Eligible PTs for the study had untreated NDMM and assigned to either Cohort A – PTs $<$ 65 years or Cohort B – PTs $\geq$ 65 years. PTs were remotely monitored for sleep 1-7 days at baseline [BL] and continuously up to 6 therapy cycles. PTs completed ePRO surveys (EORTC - QLQC30 and MY20) at BL and after each cycle. Sleep data and completed ePRO surveys were synced to Medidata Rave through Sensorlink technology. Associations between sleep measurement trends and QLQC30 scores were estimated using a linear mixed model with a random intercept. **Results:** Between Feb 2017 - Sep 2019, 40 PTs (21 M and 19 F) were enrolled with 20 in cohort A (mean 54 yrs, 41-64) and 20 in cohort B (mean 71 yrs, 65-82). Regimens included KRd 14(35%), RVd 12(30%), Dara-KRd 8(20%), VCd 5(12.5%), and Rd 1(2.5%). Sleep data was compiled among 23/40 (57.5%) PTs. BL mean sleep was 578.9 min/24 hr for Cohort A vs. 544.9 min/24 hr for Cohort B (p = 0.41, 95% CI -51.5, 119.5). Overall median sleep trends changed for cohort A by -6.3 min/24 hr per cycle (p = 0.09) and for cohort B by +0.8 min/24 hr per cycle (p = 0.88). EPRO data trends include global health +1.5 score/cycle (p = 0.01, 95% CI 0.31, 3.1), physical +2.16 score/cycle (p $<$ 0.001, 95% CI 1.26, 3.07), insomnia -1.6 score/cycle (p = 0.09, 95% CI [-3.47, 0.26]), role functioning +2.8 score/cycle (p = 0.001, 95% CI 1.15, 4.46), emotional +0.3 score/cycle (p = 0.6, 95% CI -0.73, 1.32), cognitive -0.36 score/cycle (p = 0.44, 95% CI -1.29,0.56), and fatigue -0.36 score/cycle (p = 0.4, 95% CI -1.65, 0.93). No association between sleep measurements and ePRO were detected. Difference in sleep on dex days compared to all other days during the sample cycle period for cohort A was 81.4 min/24 hr (p = 0.004, 95% CI 26, 135) and for cohort B was 37.4 min/24 hr (p = 0.35, 95% CI -41, 115). **Conclusions:** Our study provides insight into wearable sleep monitoring in NDMM. Overall sleep trends in both cohorts do not demonstrate significant gains or losses, and these trends fit with HRQOL ePRO insomnia responses. Upon further examination, we demonstrate objective differences (younger PTs) in intra-cyclic sleep measurements on dex days compared to other cycle days (less sleep by $>$ 1 hr). For older patients, less variation in sleep profiles was detected during dex days, possibly due to higher levels of fatigue or longer sleep duration. Sleep is an integral part of well-being in the cancer patient. Future studies should continue to characterize sleep patterns as it relates to HRQOL. Research Sponsor: None.

8041 **Poster Session**

LocoMMotion: A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma (RRMM) receiving ≥3 prior lines of therapy.

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Background: Multiple myeloma (MM) remains incurable despite advances in medical treatment that have improved survival. Even with these improvements, most patients with MM eventually progress through standard drug classes of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 monoclonal antibodies (mAbs), and others. There are currently no prospective data on real-world standard-of-care (SOC) in patients who progress after PIs, IMiDs, and anti-CD38 mAbs. Here, we present interim results from LocoMMotion (NCT04035226), the first prospective efficacy and safety study of real-life SOC in patients with RRMM. **Methods:** Eligible patients (aged ≥18 years [y]) with a diagnosis of MM were enrolled between August 2019 and October 2020 from 75 sites across 9 European countries and the US. Patients were included if they received ≥3 prior lines of therapy or were double-refractory to a PI and IMiD, had measurable disease at screening, received at least a PI, an IMiD, and anti-CD38 mAb with documented progressive disease since their last line of therapy, and had an ECOG PS score of 0 or 1. Responses were assessed per International Myeloma Working Group response criteria. A Response Review Committee assessed the overall response rate (ORR, primary objective) of real-life current SOC. Secondary objectives of the study included additional efficacy and safety evaluation of real-life SOC. **Results:** The data cut-off was November 4, 2020 for the first interim analysis of 225 patients with a median follow-up of 3.7 months (range: 0–12.7), 22 (9.8%) patients were from the US and 203 (90.2%) were from Europe. Median age was 68 y (range: 41–89), 124 (55.1%) were male, 162 (72.0%) had a baseline ECOG PS score of 1, and median time since initial MM diagnosis was 6.0 y (range: 0.3–22.8). Patients had received a median of 4.0 (range: 2–13) prior lines of therapy; all patients were triple-class exposed, 166 (73.8%) were triple-class refractory, and 208 (92.4%) were refractory to last line of therapy. The ORR with real-life SOC salvage therapy was 20.1% (95% CI: 15.0–26.0) in the response-evaluable population (n = 219). Treatment-emergent adverse events (TEAEs) were reported in 148 (65.8%) patients, 95 (42.2%) were grade ≥3. The most common grade ≥3 TEAEs were anemia, thrombocytopenia, and neutropenia. Fifteen deaths (6.7%) occurred due to TEAEs during the study. Treatment is ongoing in 121 (53.8%) patients. **Conclusions:** The interim results of this first, prospective study of real-life SOC treatment in heavily pretreated, triple-class exposed patients with RRMM demonstrate that patients continue to progress after multiple lines of therapy and have poor outcomes. Therefore, there is a need for new treatments with novel mechanisms of action for this patient population. Clinical trial information: NCT04035226. Research Sponsor: Janssen-Cilag International NV, Pharmaceutical/Biotech Company.

8042 **Poster Session**

Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis.

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Background: A prespecified interim efficacy analysis of the Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) + carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; *P*= 0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD-) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile. This subgroup analysis of IKEMA examined efficacy and safety in pts with high-risk cytogenetics [t(4;14), del(17p), and t(14;16)] and/or gain(1q21). **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n = 179) or Kd (n = 123). High-risk cytogenetics was assessed by central laboratory analysis and defined as ≥1 of the following: del(17p): 50% cutoff; t(4;14) or t(14;16): 30% cutoff. Assessment of gain(1q21) was prespecified as ≥3 copies: 30% cutoff. **Results:** Of the randomized pts, 23.5% (Isa-Kd) and 25.2% (Kd) had ≥1 high-risk cytogenetic abnormality (CA); 26.3% (Isa-Kd) and 25.2% (Kd) had isolated gain(1q21). The addition of Isa to Kd improved PFS for pts with ≥1 high-risk CA and standard-risk pts (Table); pts with t(4;14) (HR 0.549; 95% CI, 0.232–1.301) had a more pronounced treatment effect than pts with del(17p) (HR 0.837; 95% CI, 0.281–2.496). A clear PFS benefit with Isa-Kd was also seen for pts with isolated gain(1q21) and gain(1q21) combined with other high-risk CA (Table). The trend toward improved CR, ≥very good partial response (VGPR), and MRD- rates with the addition of Isa was more pronounced in pts with gain(1q21) than in pts with high-risk CA alone. Grade ≥3 treatment-emergent adverse events (TEAEs) were more common with Isa-Kd vs Kd, but the incidence of serious and fatal TEAEs was similar with both arms for high-risk pts (Table). **Conclusions:** The addition of Isa to Kd improved PFS in pts with high-risk CA and disease response in pts with gain(1q21) isolated or combined with high-risk CA, with a manageable safety profile, consistent with the benefit observed in the overall IKEMA population. Isa-Kd is a potential new treatment option for the difficult-to-treat subgroup of pts with RMM and high-risk cytogenetics. Funding: Sanofi. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	High Risk		Standard Risk		Isolated Gain(1q21)		Gain(1q21) + High-Risk CA	
%	Isa-Kd n = 42	Kd n = 31	Isa-Kd n = 114	Kd n = 77	Isa-Kd n = 47	Kd n = 31	Isa-Kd n = 25	Kd n = 19
PFS HR vs Kd (95% CI)	0.724 (0.361–1.451)		0.440 (0.266–0.728)		0.462 (0.219–0.972)		0.678 (0.299–1.537)	
CR	23.8	22.6	46.5	26.0	46.8	22.6	32.0	26.3
≥VGPR	57.1	54.8	78.9	54.5	80.9	51.6	64.0	52.6
MRD-	21.4	22.6	36.0	11.7	36.2	9.7	28.0	21.1
Grade ≥3 TEAEs	85.7	63.3	76.1	76.6	78.3	67.7	88.0	66.7
Serious TEAEs	64.3	66.7	57.5	59.7	63.0	51.6	60.0	66.7
Fatal TEAEs	0	0	4.4	5.2	6.5	3.2	0	0
TEAEs leading to definitive discontinuation	4.8	10.0	9.7	18.2	10.9	19.4	0	0

8043 **Poster Session**

Ixazomib (IXA), carfilzomib (CAR), elotuzumab (ELO) or daratumumab (DAR) with lenalidomide and dexamethasone (LEN+DEX) versus LEN+DEX only in relapsed/refractory multiple myeloma (R/R MM): A comparative cost-effectiveness analysis.

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Background: IXA, CAR, ELO and DARin combination with LEN+DEXhave been found superior in efficacy compared to LEN+DEX in the management of R/R MM. Applying indirect treatment comparisons from a network meta-analysis (NMA), this economic evaluation aimed to estimate the comparative cost-effectiveness and cost-utility of these four triplet regimens in terms of progression-free survival (PFS). **Methods:** In the absence of direct treatment comparison from a single clinical trial, NMA was used to indirectly estimate the comparative PFS benefit of each regimen. A 2-state Markov model simulating the health outcomes and costs was used to evaluate PFS life years (LY) and quality-adjusted life years (QALY) with the triplet regimens over LEN+DEX and expressed as the incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR). Probability sensitivity analyses were conducted to assess the influence of parameter uncertainty on the model. **Results:** The NMA revealed that DAR+LEN+DEX was superior to the other triplet therapies, which did not differ statistically amongst them. As detailed in the Table, in our cost-effectiveness analysis, all 4 triplet regimens were associated with increased PFSLY and PFSQALY gained (g) over LEN+DEX at an additional cost. DAR+LEN+DEX emerged the most cost-effective with ICER and ICUR of $667,652/PFSLYg and $813,322/PFSQALYg, respectively. The highest probability of cost-effectiveness occurred at a willingness-to-pay threshold of $1,040,000/QALYg. **Conclusions:** Our economic analysis shows that all the triplet regimens were more expensive than LEN +DEX only but were also more effective with respect to PFSLY and PFSQALY gained. Relative to the other regimens, the daratumumab regimen was the most cost-effective. Research Sponsor: None.

Results of probabilistic sensitivity analysis: ICER (i$ / PFSLYg) / ICUR (i$/PFSQALYg).

CAR+LEN+DEX				
$4,265,380 / -$7,108,967	**IXA+LEN+DEX**			
$3,129,200 / $391,150	$4,549,425/ -$1,654,336	**ELO+LEN+DEX**		
-$37,723 / -$31,436	$492,566/$747,970	$53,986/ $52,566	**DAR+LEN+DEX**	
$1,479,497/ $1,834,576	$943,750/ $876,339	$1,424,507/ $2,513,835	$667,652/ $813,322	**LEN+DEX**

LEN Lenalidomide, DEX Dexamethasone, CAR Carfilzomib, IXA Ixazomib, ELO Elotuzumab, DAR Daratumumab, ICER Incremental cost-effectiveness ratio, ICUR Incremental cost-utility ratio, g gained, i$ incremental dollars, PFS Progression-free survival, LY Life-year, QALY Quality-adjusted life year.

8044 **Poster Session**

ISB 1342: A first-in-class CD38 T cell engager for the treatment of relapsed refractory multiple myeloma.

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Background: ISB 1342 is a bispecific antibody heterodimer based on the Ichnos proprietary Bispecific Engagement by Antibodies based on T cell receptor (BEAT) platform. ISB 1342 is a first-in-class CD38 T cell engager under investigation in subjects with relapsed multiple myeloma refractory to proteasome inhibitors (PIs), immunomodulators (IMiDs) and daratumumab (study ISB 1342-101). **Methods:** ISB 1342 was engineered with a single chain variable fragment (scFv) arm that specifically recognizes a cluster of differentiation (CD)3-epsilon (CD3ε) and a fragment antigen binding (Fab) arm which specifically recognizes CD38 and does not compete with daratumumab. By co-engaging CD3ε on T cells and CD38 on tumor cells, ISB 1342 redirects T cells to kill CD38-expressing tumor cells. This mechanism of action is differentiated from existing monospecific CD38 targeting therapies and was designed to overcome resistance to daratumumab in multiple myeloma. **Results:** *In vitro,* ISB 1342 killed a large range of CD38-expressing tumor cell lines (EC50:12 to 90 pM) with 8 to 239-fold superior efficacy than daratumumab. ISB 1342 was also able to efficiently kill CD38 low-intermediate-expressing tumor cells that were poorly killed by daratumumab. ISB 1342 retained the potency to kill CD38 low-intermediate-expressing tumor cells when used in sequential or concomitant combination with daratumumab. In addition, the presence of soluble CD38 or glucocorticoid did not impact ISB 1342 killing potency. ISB 1342 was constructed with a double LALA mutation that dampens the binding to Fcγ receptors and C1q. Consistently, ISB 1342 showed only residual Fc-mediated effector functions and its mechanism of tumor cell killing critically relies on the engagement and the activation of T lymphocytes. ISB 1342 showed a favorable on target specificity profile *in vitro* and was unable to activate T cells in the absence of CD38 positive target cells. Further, ISB 1342-induced tumor cell killing was not associated with a detectable T cell fratricide *in vitro*. Finally, the potency of ISB 1342 was assessed *in vivo* in a therapeutic model of a subcutaneously established Daudi tumor co-xenografted with human PBMCs. In marked contrast to daratumumab, which induced only a partial tumor control, ISB 1342 induced complete tumor eradication when injected intravenously weekly at 0.5 mg/kg. As anticipated, the ISB 1342 control molecule (ISB 1342_13DU) made of an irrelevant CD38 binder failed to control tumor growth. The release of the Granzyme A and B, TNF-alpha and CXCL-10 in the tumor micro-environment one week post-treatment was strongly and significantly increased by ISB 1342 but not by daratumumab and ISB 1342_13DU; this represents a correlate of anti-tumor immunity associated with ISB 1342 efficacy *in vivo*. **Conclusions:** Hence the higher potency of ISB 1342 relative to daratumumab supports the ongoing clinical development in multiple myeloma patients. Research Sponsor: Glenmark and Ichnos Sciences.

8045 **Poster Session**

Comparison of outcomes with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 versus real-world standard of care (RW SOC) for patients (pts) with triple-class exposed relapsed/refractory multiple myeloma (RRMM).

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Background: Pts with RRMM who are triple-class exposed (to immunomodulatory drugs [IMiDs], proteasome inhibitors [PIs] and an anti-CD38 antibody) cycle through multiple salvage regimens with progressively worse outcomes. CARTITUDE-1 (NCT03548207) is a single-arm phase 1b/2 study evaluating cilta-cel, a chimeric antigen receptor T-cell therapy with 2 B-cell maturation antigen–targeting single-domain antibodies, in pts with RRMM who received ≥3 prior lines of therapy (LOT) or were double refractory to an IMiD and PI, were triple-class exposed, had ECOG score of 0 or 1, and had disease progression ≤12 mo after the last LOT. Here, we compare efficacy outcomes for pts who received cilta-cel in CARTITUDE-1 (N = 97) with pts treated with SOC in a synthetic cohort from RW clinical practice. **Methods:** The Flatiron database, a primarily US community-based MM registry (Sep 2020 data cutoff), was used to identify a RW pt cohort who met CARTITUDE-1 (Sep 2020 data cutoff) eligibility criteria, including organ function. Progression-free/overall survival (PFS/OS) were compared between the cilta-cel–treated US pts and RW SOC cohort, using inverse probability of treatment (tx) weighting (IPTW) propensity scores adjusting for unbalanced baseline covariates of prognostic significance. Sensitivity analyses were conducted using multivariate Cox regression models and propensity score matching. **Results:** Baseline characteristics were similar between the 2 cohorts after propensity score weighting (Table). SOC tx regimens in the RW cohort primarily included pomalidomide (33%), carfilzomib (32%), daratumumab (13%), elotuzumab (16%), and ixazomib (8%). Pts had improved PFS and OS with cilta-cel (N = 97; median follow-up 12.4 mo) vs RW SOC (N = 196; median follow-up 9.2 mo) with a reduction in risk of progression/death and death by 84% and 78%, respectively (Table). Cilta-cel treatment benefit was robust across sensitivity analyses. **Conclusions:** Cilta-cel shows significantly better efficacy outcomes over RW SOC for PFS and OS, highlighting its potential as an effective tx option in pts with triple-class exposed RRMM. Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC.

	CARTITUDE-1 N = 97	RW Cohort Observed N = 196	RW Cohort IPTW-Adjusted N = 102
Baseline characteristic, %			
Age < 65 y	64	41	67
< 6 y since MM diagnosis	46	81	44
High-risk cytogenetics*	24	18	22
ISS stage III	14	32	11
Prior LOT > 4	66	69	73
Time to progression on last LOT ≤4 mo	50	29	52
Triple-class refractory only†	45	43	43
Outcomes			
PFS, HR (95% CI)‡		0.17 (0.11, 0.26)§	0.16, (0.10, 0.27)§
OS, HR (95% CI)‡		0.26 (0.15, 0.46)§	0.22 (0.11, 0.45)§

*del17p, t(14;16), t(4;14); †At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody; ‡CARTITUDE-1 vs RW cohort; §$P \leq 0.0001$. CI, confidence interval; HR, hazard ratio.

8046 **Poster Session**

Health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM) treated with pomalidamide and dexamethasone ± subcutaneous daratumumab: Patient-reported outcomes (PROs) in APOLLO.

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Background: APOLLO (NCT03180736) is a phase 3 trial of pomalidomide and dexamethasone (Pd) ± subcutaneous daratumumab (1800 mg, co-formulated with recombinant human hyaluronidase PH20 in 15 mL) in patients with RRMM and ≥1 prior line of therapy including lenalidomide and a proteasome inhibitor. After 16.9 months (mo) median follow-up, D-Pd significantly reduced the rate of progression or death by 37% relative to Pd. Patients with RRMM have reduced HRQoL compared with age- and sex-matched populations. Here, we present PROs from the APOLLO trial. **Methods:** Patients were randomized 1:1 to D-Pd or Pd and treated in 28-day cycles until disease progression/unacceptable toxicity. PROs were assessed on Day 1 of each cycle using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30), EORTC QLQ Multiple Myeloma Module 20-item (MY20), and EuroQol 5-dimensional descriptive system. PRO analyses were performed on patients from the intent-to-treat population with a baseline (BL) and ≥1 post-BL assessment. Treatment effect was assessed by a mixed effects model with repeated measures. Time to worsening was estimated using the Kaplan-Meier method. **Results:** A total of 304 patients were included (151 D-Pd, 153 Pd). Median treatment duration was 11.5 mo with D-Pd vs 6.6 mo with Pd. At Cycle 16 (Cyc 16), 63 and 40 patients remained on treatment in the D-Pd and Pd groups, respectively. Compliance rates for PRO instruments were high and comparable between groups. Patients treated with D-Pd had a reduction in pain (maximum improvement: 6.8 points at Cyc 12) measured with the EORTC QLQ-C30 and no mean change in disease symptoms or the treatment side effects subscales of the EORTC QLQ-MY20. Group mean physical and emotional functioning were unchanged from BL with D-Pd but worsened in the Pd group (maximum worsening: 6.4 at Cyc 4 and 9.1 points at Cyc 14). The proportion of patients with a meaningful improvement from BL was 55.0% vs 49.0% for disease symptoms, 43.0% vs 35.3% for physical functioning, and 41.7% vs 31.4% for emotional functioning with D-Pd vs Pd, respectively. Median time to worsening was ~4 mo, except for the disease symptoms subscale (~10 mo); there were no differences between groups. **Conclusions:** When daratumumab was added to Pd, patients did not experience any decrements in HRQoL while on treatment, but some patients experienced reductions in pain as well as clinically meaningful improvements in symptoms and emotional/physical function. These findings complement the clinical benefits of D-Pd in RRMM patients and further support its use in this RRMM population. Clinical trial information: NCT03180736. Research Sponsor: Janssen Research & Development, LLC, Other Foundation.

8047 **Poster Session**

Teclistamab and talquetamab modulate levels of soluble B-cell maturation antigen in patients with relapsed and/or refractory multiple myeloma.

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Background: B-cell maturation antigen (BCMA, CD269) is a single transmembrane protein that is selectively expressed in the B-cell lineage and is a validated target for multiple myeloma. BCMA exists as both surface protein and as a free soluble form (sBCMA). γ-secretase activity at the transmembrane domain leads to a shed BCMA protein fragment of approximately 6 kilodalton that can exist as free circulating sBCMA in blood. Teclistamab and talquetamab are CD3 bispecific antibodies that have been developed to recruit $CD3^+$ T-cells to $BCMA^+$ or $GPRC5D^+$ multiple myeloma (MM) cells, respectively. The objective of this work was to evaluate sBCMA in relapsed and/or refractory MM patients in response to treatment with teclistamab or talquetamab. **Methods:** Serum samples from relapsed and/or refractory MM patients in teclistamab and talquetamab phase 1 studies (64007957MMY1001 and 64407564MMY1001) were collected (at various timepoints between baseline and cycle 4 or end of treatment) and analyzed for sBCMA by an electrochemiluminescence ligand binding assay. Soluble BCMA data were quantitatively analyzed in reference to patient's tumor burden and response, as well as pharmacokinetic data. **Results:** Teclistamab and talquetamab modulated levels of sBCMA in patients with high ($\geq$ 50%) and low ($<$ 50%) frequency of tumor plasma cells (TPCs), as well as in high and low risk cytogenetic groups. In cycle 3, majority of the responders had reduction in sBCMA [88% (50 out of 57) for teclistamab and 98% (49 out of 50) for talquetamab] compared to baseline. On the contrary, non-responders (progressive disease, stable disease, or minimal response) seemed to show an increase in sBCMA [80% (33 out of 41) for teclistamab and 49% (24 out of 49) for talquetamab] from baseline. Patients with deep responses tend to have higher magnitude of sBCMA reduction compared to others. Based on few patients who responded to teclistamab or talquetamab and then relapsed, sBCMA seemed to have an initial reduction followed by an increase in the levels. Soluble BCMA corelated with % bone marrow TPCs. Majority of patients with plasmacytoma (limited data) seemed to have high sBCMA; suggesting sBCMA could be a comprehensive marker for tumor burden. Teclistamab preliminary population pharmacokinetic analysis showed that sBCMA did not appear to impact teclistamab exposure, suggesting that sBCMA was not acting as a sink for teclistamab. **Conclusions:** Teclistamab and talquetamab induced changes in levels of sBCMA that correlated with clinical activity, further supporting clinical development of these bispecific antibodies. Lastly, the results support that sBCMA is a potential surrogate marker of myeloma tumor burden, and as a valuable marker for response in MM patients. Clinical trial information: NCT03145181 and NCT03399799. Research Sponsor: Janssen Research & Development, LLC.

Melflufen plus dexamethasone (dex) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) exposed/refractory to prior alkylators: A pooled analysis of the O-12-M1 and HORIZON studies.

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Background: Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and rapidly releases alkylating agents inside tumor cells. Melflufen has a mechanism of action distinct from other alkylating agents (Slipicevic et al. AACR 2020. Abs. 1843). In the O-12-M1 (NCT01897714) and HORIZON (OP-106; NCT02963493) studies, melflufen plus dex showed meaningful efficacy and a clinically manageable safety profile in pts with RRMM (Richardson et al. *Lancet Haematol.* 2020;7:5; Richardson et al. *J Clin Oncol*. 2020;Dec 9 [Epub]). This pooled analysis examines pts from these studies exposed to prior alkylators. **Methods:** Both the O-12-M1 and HORIZON studies included pts with RRMM who received ≥ 2 prior lines of therapy (LoTs) and had a primary endpoint of overall response rate (ORR). Secondary endpoints included progression-free survival (PFS) and safety. Data from the 2 studies were pooled and analyzed according to previous exposure and refractoriness to alkylators before study entry. Refractoriness to prior alkylator therapy was defined as disease that failed to achieve a minimal response or progressed while on therapy, or within 60 d of last therapy. **Results:** Of 202 pts (HORIZON: n = 157, cutoff January 14, 2020; O-12-M1: n = 45, cutoff October 29, 2019), 178 (88%) had been exposed to alkylators in ≥ 1 prior LoT (see Table for subgroups). Pts exposed and refractory to alkylators in ≥ 2 LoTs had the highest number of pts refractory to an alkylator in the last LoT (61%), and 82% were refractory to an alkylator within 12 mo of study entry. Meaningful response rates were seen in all subgroups, except for pts who were exposed and refractory to alkylators in ≥ 2 prior LoTs (see Table). PFS trended toward being shorter with higher exposure and refractoriness to prior alkylators. Results should be interpreted with caution due to limited pt numbers. Grade 3/4 adverse events (AEs) were similar between pts exposed to prior alkylators (O-12-M1: 85%; HORIZON: 89%) and the overall population (O-12-M1: 84%; HORIZON: 89%). The most common AEs were hematologic, but were mostly reversible and clinically manageable. Nonhematologic AEs were infrequent and primarily grade 1/2. **Conclusions:** Melflufen in combination with dex showed meaningful efficacy and a clinically manageable safety profile in pts with RRMM exposed/refractory to prior alkylators. Clinical trial information: NCT02963493 and NCT01897714. Research Sponsor: Oncopeptides AB.

Efficacy by subgroup.

Patients		n	ORR, % (95% CI)	Median PFS, (95% CI), mo
Total		202	29.7 (23.5, 36.5)	4.4 (3.7-5.1)
Alkylator exposed	**Alkylator refractory**			
0	NA	24	50.0 (29.1, 70.9)	7.1 (3.7-9.0)
≥ 1	0	62	33.9 (22.3, 47.0)	5.3 (4.2-7.9)
1	1	43	23.3 (11.8, 38.6)	4.6 (3.0-6.5)
≥ 2	1	40	35.0 (20.6, 51.7)	3.7 (2.4-4.9)
≥ 2	≥ 2	33	9.1 (1.9, 24.3)	3.1 (1.7-4.0)

NA, not applicable.

8049 **Poster Session**

Prognostic impact of depth of response in Waldenström macroglobulinemia patients treated with fixed duration chemoimmunotherapy.

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Background: The treatment paradigm of Waldenström macroglobulinemia (WM) continues to evolve as new therapies expand our options for this indolent and incurable disease. While more profound responses are generally associated with longer treatment-free intervals, the impact of depth of response from fixed duration therapy in WM patients' survival needs further evaluation. In this international, multicenter cohort study, we report the prognostic impact of depth of response in WM. **Methods:** 319 WM patients treated with frontline fixed duration therapy [Dexamethasone/Rituximab/Cyclophosphamide (DRC), Bendamustine/Rituximab (BR), or Bortezomib/Dexamethasone/Rituximab (BDR)] were included. Response at the completion of therapy (6 months) was used in a landmark analysis for progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) (defined as time from 6 months post treatment response to event or censor). Response was defined by modified IWWM-6 criteria. Associations between clinical variables and outcomes were evaluated using Cox proportional-hazard models. **Results:** The median age at the time of treatment initiation was 64 years (range: 29-94), 59% were men, and risk category by International Prognostic Scoring System (IPSS)-WM was low (n=67, 23%), intermediate (n=83, 29%), and high-risk (n=141, 48%). Evaluable responses at 6 months from frontline therapy [DRC (n=105; 41%), BR (n=83; 32%), BDR (n=68; 27%)] were available in 256 patients and included in the landmark analysis. Median follow-up was 63 months (95% CI: 59-70). The rate of major response (PR or better) at 6 months was 74% for the entire cohort. Five-year PFS rates from completion of therapy for patients who attained major response vs. those who did not were 71% and 43%, respectively ($p<0.001$). Five-year TTNT rates for patients who attained major response vs. not were 84% and 54%, respectively ($p<0.001$). Five-year OS rates for patients who attained major response vs. not were 92% and 77%, respectively ($p<0.001$). In multivariable analyses including other WM prognostic factors evaluated at initiation of frontline therapy, attaining a major response at 6 months was associated with superior PFS (HR 0.33, $p<0.001$), TTNT (HR 0.23, $p<0.001$), and OS (HR 0.31, p=0.001–Table). **Conclusions:** Achieving a major response at 6 months after frontline chemoimmunotherapy emerges as a significant prognostic factor for PFS, TTNT and OS in patients with WM. Research Sponsor: Mayo Clinic Division of Hematology for abstract submission fee and analysis software.

Multivariable Cox models for OS.

	HR (95% CI)	p-value
Major response at 6 months	0.3 (0.1-0.6)	0.002
Age > 65 years	5.2 (1.9-14)	0.001
Hemoglobin level ≤11.5 g/dl	1.2 (0.5-2.7)	0.57
Platelet count ≤100,000/uL	1.6 (0.5-4.7)	0.36
Serum β2-microglobulin ≥3 mg/l	1.3 (0.6-2.7)	0.47
Serum IgM level >7,000 mg/dl	0.2 (0.03-2.0)	0.21
Bone marrow involvement ≥50%	0.5 (0.2- 1.3)	0.19

HR: Hazard ratio; CI: Confidence interval.

8050 **Poster Session**

An animal model of MGUS/SMM to investigate the role of cellular senescence in progression to MM.

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Background: Multiple Myeloma (MM) is an incurable cancer of plasma cells that arises from precursor stages, monoclonal gammopathy of undetermined significance (MGUS) and/or smoldering MM (SMM). Mechanisms for the transformation of MGUS/SMM to MM are not fully known. There is no approved therapy for MGUS/SMM and research is limited by a lack of animal models. Here, we describe the use of a novel animal model of disease progression derived from patients with MGUS/SMM to study the impact of cellular senescence (CS) on the development of MM. **Methods:** CD 138+ plasma cells and CD138- stromal cells were isolated via magnetic beads from bone marrow aspirates of patients with MGUS/SMM and co-cultured CD138+/CD138- with different ratios. For the animal model CD138+/CD138- cells from MGUS/SMM patients were injected into the tibias of NSG mice (1:10). After 4 weeks, CD138+ cells were harvested and again co-transplanted into the tibia of a 2^{nd} NSG mouse with the CD138- cells (1:10). Mice underwent serial imaging and tibias were histologically examined after 4 weeks in the 2nd mouse. CS gene expression was compared by RNAseq between patients with SMM and healthy older adults. The primary CD138- cells were stained for SA-β-gal. Human mesenchymal stem cells (hMSCs) induced by H_2O_2 for CS vs control were co-cultured with CD138+ cells. Patient derived CD138- cells were treated with anti-senolytic drugs, dasatinib (D) and quercetin (Q) and cell growth in co-culture with CD138+ plasma cells was measured. D+Q treated patient-derived CD138+/CD138- cells were co-transplanted into our NSG mouse model and followed with serial imaging. **Results:** CD138- stromal cells from patients with MGUS/SMM support the growth of CD138+ plasma cells (10:1). CD138- cells were found to gain CD138+ expression, suggesting another source for the plasma cell growth. Imaging of our mouse model showed the development of lytic lesions in the tibias of 5/5 mice versus no lytic lesions in mice transplanted with CD138+ cells alone. Staining of the lytic lesions revealed CD138+ plasma cells. Our RNA seq showed significantly increased expression of CS genes, CDKN2A, p16 and p19 (3 fold) in CD138- cells of SMM patients and confirmed by qPCR (8 fold) compared to healthy older adults. The primary stromal cell culture from MGUS/SMM patients showed the presence of SCs by SA-β-gal staining. H_2O_2 induced senescent hMSCs stimulate cell survival and growth of CD138+ cells. CD138- cells cultured with conditioned media from H_2O_2 induced hMSCs demonstrated more CD138+ cells than vehicle treated CD138- cells. Conversely, D + Q pre-treated CD138- cells lost the ability to promote CD138+ cells in co-culture. Our animal model treated with D+Q showed less bone erosion in tibias compared to untreated mice. **Conclusions:** Our work demonstrates a novel animal model for studying disease progression in patients with MGUS or SMM and demonstrates a role for CS in MM disease progression. Research Sponsor: University of Rochester.

TPS8051 **Poster Session**

LIGHTHOUSE (OP-108): A phase 3 study of melflufen in combination with dexamethasone (dex) and daratumumab (dara) versus dara in relapsed/refractory multiple myeloma (RRMM) patients (pts).

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Background: Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and rapidly releases alkylating agents inside tumor cells. Melflufen + dex showed clinical efficacy and was well tolerated in pts with heavily pretreated RRMM (HORIZON; Richardson et al. *J Clin Oncol.* 2020 Dec 9 [Epub]). The ongoing phase 1/2 ANCHOR study (OP-104) established the optimal dose for melflufen + dex and dara, showing meaningful clinical activity and manageable safety at both melflufen doses tested in pts with RRMM (Ocio et al. ASH 2020. Oral 417). The aim of this study (OP-108; NCT04649060) is to evaluate the efficacy and safety of melflufen + dex and dara vs dara in pts with RRMM previously treated with an IMiD and a proteasome inhibitor (PI), similar to the indication for dara monotherapy. **Methods:** Pt enrollment has begun (N = 240 planned). Pts must be $\geq$ 18 y, double refractory to (or intolerant of) an IMiD and a PI or had $\geq$ 3 prior lines of therapy (LoTs) including an IMiD and a PI, have measurable disease, and Eastern Cooperative Oncology Group performance status $\leq$ 2. Pts with primary refractory disease and refractoriness to an anti-CD38 antibody are excluded. Pts will be randomized 1:1 to open-label melflufen + dex and dara (Arm A) or single-agent dara (Arm B) until progressive disease [PD] or unacceptable toxicity, stratified by prior LoT number. Pts in Arm B with PD can opt to receive Arm A triplet therapy. Arm A: melflufen 30 mg intravenously on d 1 of each 28-d cycle; dex 40 mg/wk orally (20 mg if aged $\geq$ 75 y); dara 1800 mg subcutaneously on d 1, 8, 15, and 22 of cycle 1 and 2, d 1 and 15 of cycles 3-6, and d 1 of cycles 7+. Arm B: dara at the same dosage as Arm A. Primary objective: superiority (*P* value from the 2-sided statistical test $<$ 0.05; upper limit of the 2-sided 95% CI for the hazard ratio $<$ 1) of progression-free survival (PFS) in pts treated with triplet therapy vs dara. An estimated sample of 240 pts with 160 expected events (PD or death) and 15% assumed dropout rate would provide 90% power at a 2-sided log rank test at 5% significance level to detect a hazard ratio for death of 0.6. Key secondary endpoints: overall response rate (ORR; $\geq$ partial response [PR]), duration of response, and safety. Response will be assessed by a blinded independent review committee based on International Myeloma Working Group criteria. Other secondary endpoints: clinical benefit rate ($\geq$ minimal response), time to response, time to progression, time to next treatment, and overall survival. Exploratory endpoints include: minimal residual disease in pts achieving $\geq$ very good PR, PFS following next line of treatment (PFS-2), pt-reported outcomes, pharmacokinetics, translational biomarkers, response rate in pts with extramedullary disease, and efficacy (including ORR) in Arm B pts who receive Arm A triplet therapy after PD. Clinical trial information: NCT04649060. Research Sponsor: Oncopeptides AB.

TPS8052 **Poster Session**

ECOG-ACRIN EAA181: Effective quadruplet utilization after treatment evaluation (EQUATE)—a randomized phase 3 trial for newly diagnosed multiple myeloma (NDMM) not intended for early autologous transplantation.

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Background: The monoclonal antibody (MoAb) daratumumab (dara) has been approved for treatment of newly diagnosed Multiple Myeloma (NDMM) in combination with lenalidomide (len) and dexamethasone (DRd) in patients who are not eligible to undergo stem cell transplantation (SCT). Ongoing trials are examining the role of adding bortezomib (Btz) to DRd, but it remains unclear if all patients benefit from a quadruplet regimen. Availability of sensitive assays to detect measurable/minimal residual disease (MRD) in MM and emerging data demonstrating significant prognostic value for attaining MRD negativity, offers an unprecedented opportunity to develop individualized treatment approaches. An important question is to identify who benefits from adding a fourth drug to the MoAb-IMiD triplet, thus individualizing therapy based on depth of response. We hypothesize that prolonged intensive therapy with the addition of Btz for consolidation and maintenance after DRd induction therapy for NDMM will improve survival outcomes with a more pronounced effect when used in MRD positive patients. **Methods:** Patients with NDMM, R-ISS Stage I or II, who are not eligible to undergo SCT or those willing to defer SCT to first relapse and have not received more than 1 cycle of any NDMM therapy will be enrolled, provided they have measurable disease, adequate organ and marrow function, have received no more than once cycle of therapy for MM and significant peripheral neuropathy or chronic obstructive pulmonary disease. Importantly, a dominant clone should be identified by lymphotrack assay for future MRD monitoring. Once enrolled, induction therapy will be in 28 day cycles consisting of daraSC (1800 mg) weekly for 2 cycles, every other week for cycles 3-6 and then every 4 weeks for 9 cycles, along with len 25 mg days 1-21 of each cycle and dex 40 mg (20 mg for those $>$ 75 years) weekly. At end of 9 cycles (induction), patients will undergo MRD testing by next generation sequencing and will be classified into MRD positive or negative subgroups. Using MRD as an integral biomarker, the trial employs a randomized biomarker-stratified design as proposed by Freidlin et al. to determine efficacy for each MRD subgroup. Patients will be stratified by MRD status and R-ISS stage and randomized to receive 9 cycles of consolidation with DRd, without (control arm) or with (experimental arm) Btz (1.3 mg/m2 weekly for 3 of 4 weeks), followed by DR maintenance until progression The primary endpoint is consolidation OS. Sample size considerations rest on estimates of MRD subgroup prevalence at the end of induction and operating characteristics establishing the treatment effect within the MRD positive subgroup as primary and MRD negative subgroup as key secondary. The total accrual goal is 1450 patients. Clinical trial information: NCT04566328. Research Sponsor: CTEP.

TPS8053 **Poster Session**

KarMMa-4: Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T-cell therapy in high-risk newly diagnosed multiple myeloma.

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Background: High-risk (R-ISS stage III) newly diagnosed multiple myeloma (NDMM) has a poor prognosis (median PFS, 29 mo), highlighting the need for novel disease-targeting approaches (Palumbo A, et al. *J Clin Oncol* 2015;33:2863-2869). Ide-cel, a BCMA-directed CAR T cell therapy, demonstrated deep, durable responses in heavily pretreated patients (pts) with relapsed and refractory MM (RRMM; Raje N, et al. *N Engl J Med* 2019;380:1726-1737; Munshi NC, et al. *J Clin Oncol* 2020;38[suppl 15]. Abstract 8503), including those with high-risk (R-ISS stage III) RRMM. In this population, earlier use of ide cel—when there may be more bone marrow reserve, more healthy peripheral blood mononuclear cells, a less compromised immune status, and less extensive disease to debulk before cell therapy—may result in improved outcomes vs standard therapies and offer an opportunity to replace transplant with CAR T cell therapy. **Methods:** KarMMa-4 (NCT04196491), a multicenter, open-label, phase 1, single-arm study, is currently evaluating ide-cel in pts with high-risk NDMM, defined as R-ISS stage III (ISS stage III [serum $_2$ microglobulin $\geq$ 5.5 mg/L] and cytogenetic abnormalities t(4;14), del(17p), and/or t(14;16) by interphase FISH; or ISS stage III and serum LDH $>$ ULN). Pts must have received $\leq$ 3 cycles of the induction regimens listed below, be aged $\geq$ 18 years, and have ECOG PS 0-1. Nonsecretory MM and CNS involvement are exclusion criteria. Pts can enroll between induction cycles 1 and 3. Permitted cycle 1 regimens are carfilzomib + lenalidomide (LEN) + dexamethasone (DEX) ± daratumumab (DARA; KRd ± DARA), LEN + bortezomib (BOR) + DEX ± DARA (RVd ± DARA), or cyclophosphamide + BOR + DEX (CyBorD). Induction cycles 2-4 are limited to KRd or RVd, with DEX omitted during cycle 3. Pts will undergo T cell collection via leukapheresis after cycle 3, and ide-cel will be manufactured during cycle 4. Stem cell collection for future use may be conducted after cycle 3 (following leukapheresis) or 4 (before lymphodepletion). Ide-cel is infused after 2 days of rest following lymphodepletion with 3 days of fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2. LEN-based maintenance may be provided upon bone marrow recovery or 90 days after ide-cel infusion, whichever is later. Dose-limiting toxicity and safety are the primary endpoints. Secondary endpoints include complete response (CR) rate and overall response rate, duration of response, time to CR, time to start of maintenance, feasibility of initiating maintenance, PFS, overall survival, and pharmacokinetics. Exploratory endpoints include LEN maintenance safety, minimal residual disease, immunogenicity and biomarkers. The starting ide-cel target dose is 450 $\times$ 10^6 CAR+ T cells, with dose escalation/de-escalation (150, 300, and 800 $\times$ 10^6 CAR+ T cells). Upon determination of optimal target dose, 12 pts will be enrolled in the dose-expansion phase. Clinical trial information: NCT04196491. Research Sponsor: Celgene, a Bristol-Myers Squibb Company and bluebird bio.

TPS8054 **Poster Session**

Subcutaneous daratumumab (DARA SC) plus lenalidomide versus lenalidomide alone as maintenance therapy in patients (pts) with newly diagnosed multiple myeloma (NDMM) who are minimal residual disease (MRD) positive after frontline autologous stem cell transplant (ASCT): The phase 3 AURIGA study.

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Background: DARA, a human anti-CD38 IgGκ monoclonal antibody, is approved in many countries as monotherapy in relapsed/refractory MM (RRMM) and in combination with standard of care (SoC) in RRMM and NDMM. However, no clinical studies have yet compared DARA maintenance versus SoC maintenance. The ongoing phase 3 AURIGA study will evaluate the addition of DARA to lenalidomide maintenance among pts with NDMM who are MRD positive after SoC induction and ASCT. The primary endpoint is the conversion rate to MRD negativity after 1 year of maintenance therapy. **Methods:** This open-label, multicenter, randomized phase 3 study will enroll approximately 214 pts in the United States aged 18-79 years with NDMM who receive $\geq$4 cycles of induction followed by ASCT. Pts must enroll within 6 months of ASCT, be nave for anti-CD38 treatment, have a very good partial response or better per IMWG criteria, and be MRD positive at a threshold of 10^{-5} by next generation sequencing (NGS) within 30 days of screening. Pts will be stratified by cytogenetic risk (high vs standard/unknown) and randomized 1:1 to 28-day cycles of lenalidomide maintenance (10 mg PO; D1-28 [dose increasing to 15 mg if tolerated]) ± DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA; QW Cycle 1-2, Q2W Cycles 3-6, Q4W C7+). Treatment will continue for up to 36 cycles or until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint is MRD conversion rate after 12 months of maintenance treatment, defined as the proportion of pts who achieve MRD negativity (10^{-5}) by NGS. Additional MRD assessments occur after 18, 24, and 36 months of maintenance. While MRD negativity is associated with improved long-term outcomes for pts with MM and is an emerging, validated prognostic factor, this study is among the first to use MRD negativity as a primary study endpoint. Importantly, MRD negativity allows for earlier efficacy assessment than traditional endpoints such as progression-free survival (PFS) and overall survival (OS). Secondary endpoints include overall MRD conversion rate at any time, sustained MRD negativity lasting $\geq$12 months, PFS, OS, response rates, duration of complete response, changes in health-related quality of life, and safety. Due to the COVID-19 pandemic, this study has been amended to improve enrollment access by allowing up to 12 months from start of induction therapy to ASCT to mitigate against ASCT delays and to allow greater flexibility for screening and laboratory assessments. Clinical trial information: NCT03901963. Research Sponsor: Janssen Research & Development, LLC.

TPS8055 **Poster Session**

A randomized, open-label, phase 3 study of low-dose selinexor and lenalidomide (Len) versus len maintenance post autologous stem cell transplant (ASCT) for newly diagnosed multiple myeloma (NDMM): ALLG MM23, Sealand.

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Background: Len maintenance post ASCT is standard of care for patients (pts) with NDMM. Deep responses (CR or better) post ASCT correlates with better progression free survival (PFS). In a meta-analysis of len maintenance post ASCT (McCarthy PL et al. J Clin Oncol. 2017), only 10.7% of pts achieve CR post ASCT, and 72% of pts who discontinued len maintenance did so because of progressive disease (PD). Selinexor is a selective inhibitor of nuclear export that blocks exportin 1, thus retaining tumour suppressor proteins within the nucleus while blocking proto-oncoprotein translation. It is approved in combination with bortezomib and dexamethasone (dex) for pts with MM who have had at least 1 prior line of treatment, or with dex for pts with penta-refractory MM by the FDA. The oral bioavailability and weekly schedule of selinexor makes it suitable in combination with len for maintenance therapy. Given the encouraging activity (ORR 92%) and tolerability of selinexor, len and dex from the phase 1b/2 STOMP study, we hypothesise that combination low-dose selinexor and len (XR) will be well tolerated and effective, increasing CR and MRD negativity rate post ASCT, thus prolonging PFS compared to len. **Methods:** ALLG MM23 SeaLAND, is an ongoing randomised, multi-centre, phase 3 trial. Eligible pts ($>$ 17 years of age) have measurable disease, have undergone 3-6 cycles (C) of induction containing a proteasome inhibitor (PI) and/or immunomodulatory drug and recovered post melphalan-conditioned ASCT with adequate haematopoiesis, renal and liver function, and with ECOG performance status. Registration occurs prior to ASCT with screening between 75 to 115 days post ASCT. The study includes a lead-in safety phase of 20 patients with XR: Len 10mg daily days 1 to 21 and Selinexor 40mg weekly in a 28-day cycle. If well tolerated, Selinexor escalates to 60mg po weekly from C2 and Len to 15mg po daily from C4. Two safety reviews will occur after the 10^{th} and 20^{th} patients completes C2, respectively. Upon meeting safety criteria, a sample size of 290 pts will be randomised 1:1 to XR or lenalidomide (R). Therapy will continue until PD. The primary endpoint is PFS at 3 years post randomisation. Secondary endpoints include ORR and MRD-negativity rate (International Myeloma Working Group Response Criteria), PFS on next treatment line (PFS2), OS, safety and tolerability, quality of life, and cost effectiveness. Main analysis occurs after 232 patients complete 3-years of follow-up. Exploratory objective is to correlate immunological and molecular profiles to treatment response and resistance. ALLG MM23 SeaLAND is a multisite bi-national investigator-initiated trial lead by Australia and New Zealand's national cooperative group, the Australasian Leukaemia & Lymphoma Group. Clinical trial registration: ACTRN12620000291987p. Clinical trial information: 12620000291987. Research Sponsor: Karyopharm Therapeutics Inc.