8000 **Oral Abstract Session**

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus elotuzumab and KRd in transplant-eligible patients with newly diagnosed multiple myeloma: Post-induction response and MRD results from an open-label randomized phase 3 study.

Stefan Knop, Thomas Stuebig, Miriam Kull, Richard Greil, Normann Steiner, Florian Bassermann, Axel Nogai, Marie von Lilienfeld-Toal, Snjezana Janjetovic, Karolin Trautmann-Grill, Max Bittrich, Monika Martha Engelhardt, Anette Hoferer, Sebastian Theurich, Mascha Binder, Niklas Zojer, Heinz A. Duerk, Monika Brueggemann, Swantje Held, Hermann Einsele, Deutsche Studiengruppe Multiples Myelom; Wuerzburg University Medical Center, Wuerzburg, Germany; Schleswig-Holstein University Hospital, Kiel Campus, Kiel, Germany; Ulm University Hospital, Dept. of Internal Medicine 3, Ulm, Germany; Hospital Salzburg Paracelus University, Salzburg, Austria; Medical University Innsbruck, Dept. of Internal Medicine V, Innsbruck, Austria; University Hospital rechts der Isar, Munich, Germany; Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität Zu Berlin, Medizinische Klinik m.S. Hämatologie, Onkologie Und Tumorimmunologie, Berlin, Germany; Jena University Hospital, Dept. of Hematology and Oncology, Jena, Germany; Helios Klinikum Berlin-Buch, Dept. of Hematology and Oncology, Berlin, Germany; Department of Hematology and Oncology, Dresden University Hospital Carl Gustav Carus, Dresden, Germany; University Hospital Medical Centre, Freiburg, Germany; Robert Bosch Hospital, Dept. of Hematology and Oncology, Stuttgart, Germany; Department of internal Medicine III, Hematology and Oncology, Gene Center, Cancer- and Immunometabolism Research Group, Ludwig-Maximilians University Munich, Mu, Munich, Germany; Department of Internal Medicine IV, Oncology/Hematology, Martin-Luther-University Halle-Wittenberg, Halle, Germany; Wilhelminen Cancer Research Institute, First Department of Medicine, Center for Oncology, Hematology, and Palliative Care, Clinic Ottakring, Vienna, Austria; St Barbara Hospital Hamm, Dept. of Hematology and Oncology, Hamm, Germany; Medical Department II, University Schleswig Holstein in the City Hospital Kiel, Kiel, Germany; Clinassess Inc., Leverkusen, Germany; Würzburg University Medical Center, Würzburg, Germany

Background: In medically fit patients with newly diagnosed (ND) multiple myeloma (MM), triplet or quadruplet induction regimens, high-dose chemotherapy (HDT) and autologous stem cell transplant (ASCT) remain a standard of care. Carfilzomib (K), lenalidomide (R) and dexamethasone (d, KRd) induction/consolidation has proven exceptionally effective. Elotuzumab (E), an anti-SLAMF-7 monoclonal antibody bears favorable tolerability in relapsed/refractory MM while its role in NDMM remains unclear. **Methods:** Transplant-eligible (TE) NDMM patients (pts) up to 70 years (yrs) were randomized 1:1 to receive six cycles (C) of KRd or E-KRd, (chemomobilisation for ASCT after C3), single (tandem, if <CR/high risk NDMM) HDT/ASCT, followed by four consolidation C (KRd/E-KRd) and R or ER maintenance. Induction (IND, 28-day C) consisted of K on D1/2, 8/9 and 15/16 (20 mg/m² IV on D 1/2 in C1 and 36 mg/m² thereafter), R (25 mg PO, D1-21) and d (36/40 mg D 1, 8, 15, 22). E was given on D 1, 8, 15, and 22 (C1/C2) and on D 1 and 15 (C3-6; 10 mg/kg IV). After IND, pts underwent restaging when bone marrow was analyzed for minimal residual disease (MRD) by next-generation flow cytometry. The first co-primary endpoint of the study was the rate of pts who were in ≥ VGPR and were MRD negative. The study is registered as NCT03948035. **Results:** 579 pts (574 of whom received treatment) were randomized between 08/2018 and 10/2021 at 52 sites and included in the intent-to-treat analysis. Median age was 60 (range, 31-71) yrs.15.4% had ISS stage III disease. 108/459 evaluable pts (23.5%) had high-risk cytogenetics (del[17p]; t[4;14]; t[14;16]; ≥ 3 1q21 copies). 525/574 pts (91.5%) completed 6 IND cycles. MRD negativity and ≥ VGPR was achieved in 145 of E-KRd (49.8%) and 102 (35.4%) of KRd patients, respectively (p=.0005). 212 (72.9%) of E-KRd versus 177 (62.5%) of KRd patients experienced treatment-emergent AEs (TEAEs) of ≥ grade 3. Febrile neutropenia occurred in 26 (6.4%) E-KRd versus 14 (4.9%) KRd pts. Grade 3/4 thrombocytopenia was seen in 36 (12.4%) E-KRd and 30 (10.6%) KRd pts. Pneumonia occurred in 24 E-KRd (8.2%) and 18 KRd (6.4%) pts. Grade 3/4 cardiac events occurred in 16 E-KRd (5.5%) and of grades 3 to 5 in 16 (5.7%) of KRd pts. 12 E-KRd (4%) and 9 KRd (3.2%) pts had COVID-19 infections with one grade 5 event each (0.3% and 0.4%, respectively). Three pts on E-KRd (1.0%) versus 7 on KRd (2.5%) died on induction due to infections (N=3), MM progression (2), AML (1), a cardiac event (N=1), other (N=3). **Conclusions:** In this study, the addition of elotuzumab to KRd significantly improved the rate of early, deep (≥ VGPR) MRD-negative remission in TE NDMM. E-KRd pts had slightly more TEAEs. Events were mainly hematotoxicity. To the best of our knowledge, this is the first study to show a benefit for the addition of elotuzumab to a front-line regimen. Clinical trial information: NCT03948035. Research Sponsor: AMGEN, Celgene, BMS.

8001 **Oral Abstract Session**

Maintenance therapy with carfilzomib, pomalidomide, and dexamethasone (KPd) in high-risk myeloma patients (pts): A phase 2 study with a safety run-in.

Ajay K. Nooka, Nisha S Joseph, Madhav V. Dhodapkar, Craig C. Hofmeister, Vikas Anand Gupta, Joel S Andrews, Charise Gleason, Anuja A Sharma, Bryan J Burton, Quanta R Cato, Ching Siong Tey, Manali Rupji, Yuan Liu, Ian McFadden, Rani Najdi, Lawrence H Boise, Jonathan L. Kaufman, Sagar Lonial; Winship Cancer Center of Emory University, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Winship Cancer Institute, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Winship Cancer Institute, Atlanta, GA; Biostatistics Shared Resource, Emory University, Atlanta, GA; Emory University, Atlata, GA; Amgen, Thousand Oaks, CA; Amgen Inc., Newbury Park, CA

Background: High-risk pts derive survival benefit from combination maintenance (PI and IMiD) strategies. We have evaluated the safety and efficacy of the next generation PI (carfilzomib) and IMiD (pomalidomide) in combination with dexamethasone in high-risk myeloma (NCT03756896). **Methods:** Newly diagnosed high-risk myeloma pts that have achieved ≥PR post-ASCT were included. High-risk myeloma was defined by the presence of t(4;14) in 27.6%, t(14;16) in 17.2%, del17p in 58.6% pts by FISH or CTG or presence of ≥20% circulating cells (pPCL) in 6.9%. Double-hit myeloma (as defined by presence of ≥2 high-risk cytogenetic abnormalities including gain of 1q) was seen in 58.6% of pts. Each cycle is 28 days. Carfilzomib 20/56 mg/m2 IV was given on days 1,8,15 and pomalidomide 2 mg PO on days 1 to 21 and dexamethasone 40 mg PO was administered on days of carfilzomib. Statistical analysis was conducted using SAS Version 9.4. **Results:** After the safety run in the first 3 pts, 26 additional pts were enrolled. Median age was 60 years (range, 46−75); 58.6% male and 58.6% black. At diagnosis, 65.5% had RISS stage 3 disease. 54.5% of whites and 64.7% of blacks had double-hit disease. Median time from diagnosis and from transplant to study entry was 9.3 (range, 6.08-12.42) and 2.89 (range, 2-8.51) months, respectively. At study entry, ≥CR and ≥VGPR rates were 24.1% and 68.9%, respectively, which deepened to 79.3% and 100% while on study. The median time to best response was 2.07 months (range, 1.22-14.26). Of the 15 pts with available MRD data, MRD (10^{-5}) and (10^{-6}) were achieved in 80% and 53.3%, respectively. After a median follow-up of 25.8 months, 36 month PFS was 63.2% (95% CI 38.3-80.3%) and 36 month OS was 72.4% (44.2-88.0%). Double-hit disease was an independent predictor for progression and death. Among these high risk patients, RISS did not show any statistical significance. While there is no PFS difference by race, the 36 month OS for black pts was inferior compared to whites (61.1% [23.1-84.7%] vs 85.7% [33.4%-97.9%], log rank 0.05). At data cut-off, 37.9% of pts were still receiving treatment; most common reason for permanent treatment discontinuation was progressive disease (27.6%). Among the 6 pt deaths, the most common cause of death was progressive disease (83.3%). Most common (≥20%) TEAEs were fever (37.9%), fatigue (34.5%), diarrhea (27.6% [G3/4, 3.4%]), nausea (24.1%), cough (20.7%), muscle cramps (20.1%), acneiform rash (20.1%). TEAEs of interest were cardiac (10.3% [G3/4, 3.4%]), cataracts (17.2% [G3/4, 17.2%]), neutropenia (6.9% [G3/4, 6.9%]) and anemia (10.3% [G3/4, 0%]). **Conclusions:** In pts with high-risk myeloma, KPd maintenance deepened responses. MRD negativity (10^{-5}) was attained in 80% of pts. Despite the encouraging results in this cohort of high-risk patients, PFS and OS among double-hit pts remains poor, warranting newer strategies aimed at remission sustenance. Clinical trial information: NCT03756896. Research Sponsor: Amgen.

8002 **Oral Abstract Session**

First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM).

Yael C Cohen, Daniel Morillo, Moshe E Gatt, Michael Sebag, Kihyun Kim, Chang-Ki Min, Albert Oriol, Enrique M Ocio, Sung-Soo Yoon, Maria-Victoria Mateos, Michael Chu, Paula Rodríguez-Otero, Irit Avivi, Yue Guo, Maria Krevvata, Michelle R. Peterson, Melissa Jo Beelen, Jill Vanak, Arnob Banerjee, Hila Magen; Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Hadassah Hebrew University Medical Center, Jerusalem, Israel; McGill University and MUHC, Montréal, QC, Canada; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Seoul St. Mary's Hospital, Seoul, South Korea; Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Marqués de Valdecilla University Hospital, Santander, Spain; Seoul National University College of Medicine, Seoul, South Korea; University Hospital of Salamanca, Salamanca, Spain; Alberta Health Services, Edmonton, AB, Canada; Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Janssen Research & Development, Spring House, PA; Chaim Sheba Medical Center, Ramat-Gan, Sackler Faculty of Medicine, Tel Aviv University, Ramat Gan, Israel

Background: Tec is the first BCMA-directed bispecific antibody approved for the treatment of triple-class exposed RRMM. Tal, a bispecific antibody targeting the novel myeloma antigen GPRC5D, has shown promising efficacy in pts with RRMM. Simultaneously targeting 2 validated myeloma target antigens, using tec + tal in combination may lead to improved outcomes by overcoming resistance mechanisms, such as antigen escape. Here, we report the first results from the phase 1b RedirecTT-1 trial (NCT04586426) in pts with RRMM. **Methods:** Enrolled pts had MM per International Myeloma Working Group 2016 criteria; were RR or intolerant to the last line of therapy (LOT); were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy; and had measurable disease. The primary objectives are to evaluate safety and to identify a recommended phase 2 regimen (RP2R) for the combination. Responses were investigator assessed. AEs were graded per CTCAE v5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT criteria. **Results:** As of Dec 12, 2022, 63 pts received tec + tal. Median (range) age was 67 y (39–81); median (range) prior LOT was 5 (1–11); 33% (15/45) had high-risk cytogenetics; 78% (49/63) were triple-class refractory; 63% (40/63) were penta-drug exposed; and 43% (27/63) had extramedullary disease (EMD; all bone independent). Median (range) duration of follow-up was 14.4 mos (0.5–21.9). The most common treatment-emergent AEs were CRS (81%; grade [gr] 3, 3%, no gr 4), neutropenia (76%; gr 3/4, 75%), and anemia (60%; gr 3/4, 43%). Dose-limiting toxicities (DLTs) were reported at dose level 1 (gr 3 herpetic stomatitis) and dose level 3 (gr 3 AST/ALT elevation). One ICANS event was reported at dose level 3. No DLTs were reported at the RP2R. Across all dose levels, overall response rate (ORR) was 84% (52/62) among all evaluable pts and 73% (19/26) among evaluable pts with EMD; rate of CR or better (≥CR) was 34% (21/62) and 31% (8/26), respectively. At the RP2R, ORR was 92% (12/13) among all evaluable pts and 83% (5/6) among evaluable pts with EMD; rate of ≥CR was 31% (4/13) and 33% (2/6), respectively. Median duration of response has not been reached. Updated data, with 19 additional pts at the RP2R, will be presented. **Conclusions:** In this first combination study of a BCMA- and GPRC5D-targeted bispecific antibody, tec + tal at the RP2R has a manageable safety profile consistent with each of the monotherapies. A 92% ORR was observed in pts with advanced RRMM at the RP2R, and an ORR of 83% was achieved in pts with EMD, a high-risk population with unmet need, supporting further evaluation of the combination. Clinical trial information: NCT04586426. Research Sponsor: Janssen Research & Development.

8003 **Oral Abstract Session**

Talquetamab (tal) + daratumumab (dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Updated TRIMM-2 results.

Bhagirathbhai R. Dholaria, Katja Weisel, Maria-Victoria Mateos, Hartmut Goldschmidt, Thomas G. Martin, Daniel Morillo, Donna Ellen Reece, Paula Rodríguez-Otero, Manisha Bhutani, Anita D'Souza, Albert Oriol, Laura Rosiñol, Nizar J. Bahlis, Kalpana Bakshi, Lijuan Kang, Lien Vandenberk, Marie-Anne Damiette Smit, Ralph Wäsch, Niels W.C.J. van de Donk, Ajai Chari; Vanderbilt University Medical Center, Nashville, TN; University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; University Hospital of Salamanca, Salamanca, Spain; Medizinische Klinik V, Universitätsklinikum Heidelberg and Nationales Centrum für Tumorerkrankungen, Heidelberg, Germany; Helen Diller Family Comprehensive Cancer Center, San Francisco Medical Center, University of California, San Francisco, CA; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Princess Margaret Cancer Centre, Toronto, ON, Canada; Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; Levine Cancer Institute/Atrium Health, Charlotte, NC; Medical College of Wisconsin, Milwaukee, WI; Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Spain; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Antwerp, Belgium; Janssen Biologics Europe, Leiden, Netherlands; Freiburg University Medical Center, Freiburg, Germany; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; Mount Sinai School of Medicine, New York, NY

Background: Tal is a T-cell redirecting bispecific antibody (BsAb) targeting G protein–coupled receptor family C group 5 member D. Dara is an anti-CD38 mAb with direct on-tumor and immunomodulatory actions. Combining immunomodulatory effects of tal + dara may lead to synergistic efficacy. Initial TRIMM-2 (NCT04108195) results showed that SC tal RP2Ds, 0.4 mg/kg QW or 0.8 mg/kg Q2W, + SC dara had promising efficacy and increased CD38+/CD8+ T cells and proinflammatory cytokines. We report updated results with additional pts and longer follow-up. **Methods:** Pts had MM, ≥3 prior lines of therapy (LOT; including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double refractory to a PI and IMiD, and had not received anti-CD38 therapy in ≤90 d. Pts received tal RP2Ds with step-up dosing + dara 1800 mg per approved schedule. AEs were graded per CTCAE v5.0; cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Responses were assessed per IMWG criteria. **Results:** As of Dec 12, 2022 (N = 65), median follow-up was 11.5 mo (range 1.0–27.3). Median age was 63 y (range 37–81); 18% of pts had high-risk cytogenetics; 25% had extramedullary plasmacytomas. Median prior LOT was 5 (range 2–16): 63% penta-drug exposed; 58% triple-class refractory. Prior treatments included anti-CD38 (88% [77% refractory]), anti-BCMA (54% [38%]), BsAb (25% [25%]), and anti-BCMA CAR-T (17% [2%]) therapy. All pts had ≥1 AE (grade [Gr] 3/4 78%), most commonly CRS (78%; all Gr 1/2), dysgeusia (75%), dry mouth (55%), anemia (52%), fatigue (45%), and skin exfoliation (45%). CRS had a median time to onset of 1 d after the most recent dose with median duration of 2 d. 63% of pts had infections (Gr 3/4 22%; Gr 5 3% [n = 2 pneumonia, possibly related to tal + dara]). 38% of pts had neutropenia (Gr 3/4 26%). 85% had postbaseline IgG < 500 mg/dL; of these, 32% received IVIg. ICANS occurred in 3 pts (5%; all Gr 1/2 and resolved in 1–2 d). ORR was 78% (66% ≥VGPR; 45% ≥CR) across RP2Ds (100% in anti-CD38 naïve pts), and responses deepened over time. In pts exposed/refractory to prior therapy, ORRs were 75%/76% for anti-CD38, 74%/64% for anti-BCMA, and 75%/75% for BsAb. Median time to first response was 1 mo (range 0.9–8.3); at 12 mo, 86% of responders (89% of pts with ≥CR) still had responses. At data cutoff, 84% of responders remain on therapy (83%/82% anti-CD38 exposed/refractory). mPFS was 19.4 mo; 12-mo PFS and OS rates were 76% and 93%, respectively. **Conclusions:** Steroid-sparing tal + dara showed deep and durable responses with promising mPFS in heavily pretreated pts with RRMM, including pts refractory to anti-CD38/BCMA and T-cell redirecting therapy, suggesting combined immunomodulatory actions can yield robust responses in pts with refractory disease. The safety profile was clinically manageable; no new signals were identified with longer follow-up. Research Sponsor: Janssen Research & Development, LLC.

8004 **Oral Abstract Session**

Updated phase I study results of PHE885, a T-Charge manufactured BCMA-directed CAR-T cell therapy, for patients (pts) with r/r multiple myeloma (RRMM).

Adam Samuel Sperling, Benjamin Avi Derman, Sarah Nikiforow, Soo-Yeon Im, Shuntaro Ikegawa, Rao H. Prabhala, Diego Hernandez Rodriguez, Yifang Li, David S. Quinn, David Pearson, Dexiu Bu, Jennifer Mataraza, Jessica Liegel, Anita D'Souza, Lawrence Rispoli, Marc Credi, Jerome Ritz, Andrzej J. Jakubowiak, Serena De Vita, Nikhil C. Munshi; Dana-Farber Cancer Institute, Boston, MA; University of Chicago, Chicago, IL; Novartis Institutes for BioMedical Research, Cambridge, MA; Novartis Institutes for BioMedical Research, Basel, Switzerland; Beth Israel Deaconess Medical Center, Boston, MA; Medical College of Wisconsin, Milwaukee, WI

Background: B cell maturation antigen (BCMA) targeted CAR-T cells are approved for RRMM. Long manufacturing time and high clinical demand limit access. T-Charge, an innovative platform that reduces manufacturing time to $<$2 days and preserves T cell stemness, results in robust expansion and prolonged CAR T cell persistence. Here we report updated results from the Phase I trial of T-Charge manufactured, fully human, BCMA CAR-T PHE885 (NCT04318327). **Methods:** Eligible pts had RRMM after $\geq$2 prior lines of therapy (tx). Pts received fludarabine and cyclophosphamide (or bendamustine) for lymphodepletion (LD) prior to PHE885 infusion. Primary objective was safety. Secondary objectives were clinical response and cellular kinetics. **Results:** As of December 22, 2022, 46 pts received PHE885 at the following doses: 2.5e6 (n=4), 5e6 (n=13), 10e6 (n=20), 14.3e6 (n=1), and 20e6 (n=8) CAR T cells. PHE885 was manufactured for 61% of pts at a single academic institution; these pts proceeded from apheresis to LD in a median of 16 days. Median age at enrollment was 65 y (range [R] 45-81), median prior lines of tx was 4 (R 2-10). 37% of pts had extramedullary disease; 96% were triple refractory. Despite aggressive disease, only 28% of pts required bridging chemotherapy, predominantly influenced by quick production time. 96% of pts experienced any gr cytokine release syndrome (CRS); 11% had gr 3 CRS. Median time to CRS onset was 8 (R 2-16) days and median duration was 4 (R 1-19) days. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 22% of pts; 7% had gr 3 ICANS. Dose limiting toxicities were experienced by 13% of pts and included gr 4 neutropenia, gr 4 lipase increase, gr 3 serum amylase increase, gr 3 neurotoxicity, gr 3 transaminitis, and gr 3 ejection fraction reduction. The most common tx-related gr $\geq$3 AEs included anemia (54%), neutropenia (50%), and thrombocytopenia (37%). Geo-mean peak PHE885 expansion (C_{max}) was 276,000 copies/μg by qPCR and 70.6% of CD3+ T cells by flow cytometry (n=41). The PHE885 transgene was detected in 13/14 (93%) pts at 6 mo and 5/7 (71%) at 12 mo post infusion. T cells with early memory phenotype were preserved in the final product and persisted in pts post infusion. In 43 efficacy-evaluable pts, the ORR was 98%. At 10e6 dose (n=19), ORR was 100% and CRR was 42% (median follow-up of 4.9 mo [R 1.4-11.8]); 60% of 10 evaluable pts were MRD negative at 10^{-5} by NGS. Initial efficacy data at 20e6 and longer follow-up at active doses will also be presented. **Conclusions:** T-Charge manufactured PHE885 produced high response rates with no unexpected safety findings in heavily pretreated RRMM pts with aggressive disease. PHE885 expanded rapidly and showed durable persistence in vivo. Since conversion to CR/sCR has occurred as late as 18 months after infusion in this study, longer follow-up is ongoing to identify a recommended dose for future development. Clinical trial information: NCT04318327. Research Sponsor: Novartis.

8005 **Oral Abstract Session**

Updated results of a phase I, open-label study of BCMA/CD19 dual-targeting fast CAR-T GC012F for patients with relapsed/refractory multiple myeloma (RRMM).

Juan Du, Wei-Jun Fu, Hua Jiang, Baoxia Dong, Li Gao, Li Liu, Jian Ge, Aili He, Lu Li, Jing Lu, Xiequn Chen, Jia Liu, Qi Zhang, Jiaping He, Lianjun Shen, Lihong Weng, Hua Zhang, Wei Cao, Wenling Li; Shanghai Changzheng Hospital, Shanghai, Shanghai, China; Shanghai Changzheng Hospital, Shanghai, China; Xijing Hospital, Xi'an, China; The Second Affiliated Hospital of Army Medical University, Chongqing, China; Tangdu Hospital, Air Force Medical University, Xi'an, China; The First Affiliated Hospital of Anhui Medical University, Hefei, China; The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Gracell Biotechnologies Ltd, Shanghai, China; Gracell Biotechnologies, Ltd, Shanghai, China

Background: GC012F is a chimeric antigen receptor (CAR)-T cell therapy with B cell maturation antigen (BCMA) and CD19 dual-target developed on the novel FasT CAR-T platform enabling 22-36 h manufacturing. Our previous results were presented at ASCO and EHA 2022 for 29 pts (NCT04236011; NCT04182581), which demonstrated GC012F treatment led to deep and durable response in RRMM pts. Furthermore, initial results showed that GC012F showed considerable efficacy and safety in high-risk transplant-eligible newly diagnosed MM pts (Blood 2022; 140 (Supplement 1): 889–890). Here we present update on RRMM study with a longer median follow-up. **Methods:** From October 2019 to January 2022, 29 heavily pretreated RRMM pts (age 27-76) with a median of 5 prior lines therapies (range 2-9) received GC012F. 26 (89.7%) pts were high risk (HR- mSMART), 8 (27.6%) pts had EM disease, 24 (82.8%) pts were refractory to last therapy. 10 (34.5%) pts had received prior anti-CD38 and 11 (37.9%) pts were treated with auto-HSCT. After lymphodepletion over 2-3 days (30 mg/m^2/d, 300mg/m^2/d Flu/Cy), GC012F was administered as single infusion at 3 dose levels: 1x10^5/kg (DL1) n=2, 2x10^5/kg (DL2) n=10 and 3x10^5/kg (DL3) n=17. **Results:** At the time of data cut-off (January 30, 2023), 29 eligible pts had been evaluated for response with the last patient completed 12 months efficacy follow up. Overall response rate was 93.1% (27/29), stringent complete response rate was 82.8% (24/29), ≥very good partial response rate was 89.7% (26/29). All patients dosed (29/29) achieved MRD negativity by flow cytometry (sensitivity 10^{-4}-10^{-6}). To date 24/29 patients (82.8%) achieved MRD- sCR across all dose levels. According to the Kaplan-Meier method, the median duration of response (DOR) was 37.0 months (95%CI, 11.0-NR) and the median progression free survival (PFS) was 38.0 months (95%CI, 11.8-NR). Cytokine Release Syndrome (CRS) was reported in 25 (86.2%) pts, which was mostly ≤grade 2 (n=23, 79.3%) and 2 (6.9%) pts were grade 3. No ICANS was observed (Graded by ASBMT criteria). Median duration of CRS was 3 days (1-8 d). PK results showed no difference amongst dose levels DL1 to DL3. The median time of persistence was 410 days (range: 51-1183) and GC012F was still detectable in 23 (79.3%) pts at 6 months and in 16 (55.2%) pts at 12 months after infusion. sBCMA plasma levels started declining at day 4 in 80% (8/10) patients, falling sharply at day 10 in 100% (19/19), and reaching minimal levels from 30 to 60 days post infusion in 100% (29/29) patients. **Conclusions:** The updated results showed GC012F continues to provide deep and durable responses, and a very high MRD negativity ratein RRMM pts, including in pts refractory to anti-CD38, PIs and IMIDs. Based on these promising results of the study of GC012F for RRMM, further clinical studies will be conducted to confirm the efficacy of GC012F. Clinical trial information: NCT04236011; NCT04182581. Research Sponsor: Gracell Biotechnologies Ltd, Shanghai, China.

8006 **Oral Abstract Session**

LINKER-MM1 study: Linvoseltamab (REGN5458) in patients with relapsed/refractory multiple myeloma.

Hans C. Lee, Naresh Bumma, Joshua Ryan Richter, Madhav V. Dhodapkar, James E. Hoffman, Attaya Suvannasankha, Jeffrey A. Zonder, Mansi R. Shah, Suzanne Lentzsch, Joseph J. Maly, Jing Christine Ye, Ka Lung Wu, Michelle DeVeaux, Dhruti Chokshi, Anita Boyapati, Anasuya Hazra, Karen Rodriguez-Lorenc, Glenn Scott Kroog, Yariv J. Houvras, Sundar Jagannath; The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Icahn School of Medicine at Mount Sinai, New York, NY; Emory University School of Medicine, Atlanta, GA; University of Miami Health System, Miami, FL; Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN; Karmanos Cancer Institute, Detroit, MI; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Columbia University Medical Center, New York, NY; Norton Cancer Institute, Louisville, KY; University of Michigan, Ann Arbor, MI; Ziekenhuis Netwerk Antwerpen Stuivenberg, Antwerp, Belgium; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Linvoseltamab is a BCMA×CD3 bispecific antibody with encouraging efficacy and a manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM) (Bumma et al. ASH 2022). Two Phase (Ph) 2 full dose cohorts (50 mg and 200 mg) in the LINKER-MM1 (NCT03761108) trial were studied to optimize dose selection. **Methods:** Ph 2 enrolled adults with MM who progressed on/after ≥3 lines of therapy (LoT) including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody (Ab), or were at least triple class (IMiD/PI/anti-CD38 Ab) refractory. A protocol amendment permitted pts who progressed during 4–12 wks on 50 mg to dose escalate to 200 mg. Primary endpoint was objective response rate (ORR). Key secondary endpoints included duration of response (DoR) and minimal residual disease status. **Results:** As of 1 Sept 2022, 252 pts have enrolled (Ph 1: 73; Ph 2: 179 [200 mg: 75; 50 mg: 104]). Median age was 66 yrs (range 37–90), 12% had extramedullary plasmacytomas, 12% high-risk cytogenetics, 37% bone marrow plasma cell percentage (BMPC) ≥50%. Median soluble BCMA concentration (sBCMA) was 0.43 mg/L (range 0–10.2), median prior LoT: 5 (range 1–16), and 81% were ≥triple class refractory. Numerically higher efficacy was observed with 200mg, including in high disease burden subgroups; ORR was 64% (200 mg cohort; n = 58, includes 12 Ph 1 pts) and 50% (50 mg cohort; n = 104). Subgroup analyses showed higher ORR in the 200 mg cohort versus 50 mg for sBCMA ≥0.4 mg/L (52% vs 37%), BMPC > 67% (64% vs 35%) and revised ISS stage III (71% vs 27%). Median DoR was not reached for both cohorts (median follow-up: 2.3 months [200 mg], 4.7 months [50 mg]). Probability of maintaining response at 6 months was 89% (200 mg) and 85% (50 mg). Eight pts dose escalated from 50 to 200 mg; 6 (75%) achieved a response. Treatment-emergent adverse events (TEAEs) occurred in 95% (Grade [Gr] ≥3: 66%) of pts in the 200 mg cohort (n = 87, includes 12 Ph 1 pts) and 100% (Gr ≥3: 80%) in the 50 mg cohort. The most common TEAEs were cytokine release syndrome (200 mg: 37% [Gr 3: 1%]; 50 mg: 53% [Gr 3: 2%]), fatigue (200 mg: 32% [Gr ≥3: 0]; 50 mg: 33% [Gr ≥3: 0]) and anemia (200 mg: 28% [Gr ≥3: 24%]; 50 mg: 40% [Gr ≥3: 36%]). Grade ≥3 ICANS occurred in 2 pts (2%) in the 200 mg cohort and 1 pt (1%) in the 50 mg cohort. TEAEs leading to treatment discontinuation occurred in 7% (200 mg cohort) and 8% (50 mg cohort) of pts. Infections occurred in 43% (Gr ≥3: 26%) in the 200 mg cohort and 59% (Gr ≥3: 31%) in the 50 mg cohort. **Conclusions:** Linvoseltamab 200 mg showed better efficacy compared with 50 mg, including in pts with high disease burden. The 200 mg dose had consistent efficacy across high-risk subgroups and induced responses in pts who progressed on 50 mg. Safety was consistent across Ph 2 doses. The recommended linvoseltamab dose for further development is 200 mg. Updated data with longer follow-up and complete enrollment of the 200 mg cohort will be presented at the meeting. Clinical trial information: NCT03761108. Research Sponsor: Regeneron Pharmaceuticals, Inc.

8007 **Oral Abstract Session**

A phase 3, open-label, randomized study to evaluate the efficacy and safety of single-agent belantamab mafodotin (belamaf) compared to pomalidomide plus low-dose dexamethasone (Pd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): DREAMM-3.

Katja Weisel, Vania TM Hungria, Atanas Radinoff, Sosana Delimpasi, Gabor Mikala, Tamas Masszi, Jian Li, Marcelo Capra, Morio Matsumoto, Neal Sule, Mary Li, Astrid McKeown, Wei He, Shelley Bright, Brooke Currie, Julia Boyle, Joanna Opalinska, Meletios A. Dimopoulos; University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; Clinica São Germano, São Paulo, Brazil; University Hospital Sveti Ivan Rilski, Sofia, Bulgaria; General Hospital Evangelismos, Athens, Greece; South Pest Central Hospital, National Institute for Haematology and Infectious Diseases, Budapest, Hungary; Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary; Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; Centro Integrado de Hematologia e Oncologia, Hospital Mãe de Deus, Porto Alegre, Brazil; National Hospital Organization, Shibukawa Medical Center, Shibukawa, Japan; GSK, Upper Providence, PA; GSK, Stevenage, United Kingdom; GSK, Waltham, MA; GSK, Rockville, MD; GSK, London, United Kingdom; National and Kapodistrian University of Athens School of Medicine, Athens, Greece

Background: Belamaf, an antibody-drug conjugate targeting B-cell maturation antigen, induces cell death by direct cell kill and immune-mediated mechanisms. The DREAMM-2 trial (NCT03525678) showed rapid, deep and durable responses to belamaf monotherapy in pts with RRMM. The Phase 3, open-label, randomized, multicenter DREAMM-3 trial (NCT04162210) evaluated belamaf monotherapy vs Pd in adult pts with RRMM at second relapse (third line) or later. **Methods:** Pts were randomized (2:1) to belamaf 2.5 mg/kg Q3W or Pd (pom 4 mg PO daily on days 1–21 of 28 day cycle; dex, 40mg PO [20mg if >75 years]) Q1W. The primary endpoint was progression free survival (PFS). **Results:** 325 pts were enrolled (belamaf n=218, Pd n=107). Median (range) age was 68 (38–90) years; 57% were male. Median (range) duration of exposure for belamaf was 4.1 (0.4, 22.9) months (mo) and 5.3 (0.4, 24.0) for Pd. Median (range) duration of follow-up was 11.5 (0.6, 24.2) mo for belamaf and 10.8 (0.0, 26.4) mo for Pd. Median PFS was longer for belamaf (11.2 [6.4, 14.5] mo) vs. Pd (7.0 [4.6, 10.6] mo). There was no statistically significant difference in PFS between the 2 treatment groups, (HR 1.03 [95% CI: 0.72, 1.47]), based on the stratified Cox model (p=0.558). Belamaf induced deeper responses vs Pd (Table). Median duration of response (DoR) was more durable for belamaf than for Pd (Table). At 12 mo, the probability (95% CI) of maintaining response was 0.768 (0.641, 0.854) for belamaf and 0.484 (0.258, 0.679) for Pd. Median PFS2 was 18.7 mo (95% CI 14.5, NR) for belamaf and 12.7 mo (9.3, 21.1) for Pd. PFS2 rate at 6 mo was 73% for belamaf and 76% for Pd. Overall survival (OS) data were immature (37.5% overall maturity) at this analysis; median OS was 21.2 mo (95% CI 18.7, NR) for belamaf and 21.1 mo (15.1, NR) for Pd (HR 1.14 [95% CI 0.77, 1.68]; p=0.746). Adverse events (AEs) were reported in 97% and 93% of patients (Table). The safety profile was consistent with previous reports for belamaf and Pd. **Conclusions:** Belamaf monotherapy did not demonstrate PFS superiority when compared to a doublet (Pd). However, median PFS was longer for belamaf monotherapy and belamaf induced deeper, more durable responses than Pd. No new safety signals were observed. Subgroup analyses and PRO outcomes will be reported. Belamaf continues to be investigated in combination with established and novel agents. Research Sponsor: GSK(207495).

Efficacy and safety.

	Belamaf (ITT n=218, safety n=217)	Pd (ITT n=107, safety n=102)
ORR, n (%)	89 (41)	38 (36)
≥VGPR, n (%)	55 (25)	9 (8)
MRD- ≥VGPR, n (%)	15 (7)	0
DoR, months, median (95% CI)	NR (17.9, NR)	8.5 (7.6, NR)
Any AE, n (%)	211 (97)	95 (93)
Serious AEs, n (%)	94 (43)	40 (39)
Fatal AEs, n (%)	16 (7)	11 (11)
Grade 3–4 AEs, n (%)	164 (76)	71 (70)
AEs leading to discontinuation, n (%)	33 (15)	17 (17)

8008 **Oral Abstract Session**

Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma (RRMM) and prior B-cell maturation antigen (BCMA)-directed therapies: A pooled analysis from MagnetisMM studies.

Ajay K. Nooka, Alexander M. Lesokhin, Mohamad Mohty, Ruben Niesvizky, Christopher Maisel, Bertrand Arnulf, Sarah Marie Larson, Asya Varshavsky Yanovsky, Xavier P Leleu, Lionel Karlin, David H. Vesole, Nizar J. Bahlis, Carlos Fernández de Larrea, Noopur S. Raje, Eric Leip, Umberto Conte, Mohamed Elmeliegy, Andrea Viqueira, Salomon Manier; Winship Cancer Institute, Emory University Hospital, Atlanta, GA; Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY; Sorbonne University, Hôpital Saint-Antoine, and INSERM UMRs938, Paris, France; Weill Cornell Medical College - New York Presbyterian Hospital, New York, NY; Baylor University Medical Center, Dallas, TX; Hôpital Saint-Louis, Paris, France; University of California Los Angeles Medical Center, Los Angeles, CA; Fox Chase Cancer Center, Philadelphia, PA; Centre Hospitalier Universitaire de Poitiers, Poitiers, France; Centre Hospitalier Lyon Sud, Lyon, France; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; Hospital Clínic de Barcelona, Barcelona, Spain; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Pfizer Inc., Cambridge, MA; Pfizer Inc., New York, NY; Pfizer Inc., San Diego, CA; Pfizer SLU, Madrid, Spain; Lille University Hospital, Lille, France

Background: Studies in the MagnetisMM program (MM-1, NCT03269136; MM-3, NCT04649359; MM-9, NCT05014412) enrolled pts treated with prior BCMA-directed therapies. A pooled analysis from these studies evaluated the efficacy and safety of elranatamab in pts with RRMM and prior exposure to BCMA-directed therapy. **Methods:** Eligible pts received at least 1 PI, 1 IMiD, 1 anti-CD38 antibody, and 1 BCMA-directed therapy (ADC and/or CAR-T cells). Pooled analysis included pts in MM-1 (n = 13) who received SC elranatamab 215−1000 μg/kg; MM-3 (n = 64) and MM-9 (n = 9) who received the RP2D, SC 76 mg QW. Efficacy endpoints were assessed by investigator per IMWG criteria. TEAEs were graded by CTCAE (MM-1, v4.03; MM-3 & MM-9, v5.0); CRS and ICANS were graded by ASTCT criteria. Results include data up through ~10 months after last pt initial dose in all pooled studies. **Results:** In total, 86 pts were included. Median age was 66.0 y (range, 40−84); 47.7% male. At baseline, 69.8% had an ECOG PS ≥1; 24.4% had high risk cytogenetics; 54.7% had extramedullary disease. Pts received a median of 7.0 (3−19) prior lines of therapy, including BCMA-directed ADC (67.4%), CAR T-cells (41.9%), 9.3% received both. 96.5% and 54.7% of pts were triple-class and penta-drug refractory, respectively; among pts who received ADC and CAR-T cells respectively, 79.3% and 27.8% were refractory to ADC and CAR-T cells. After a median follow-up of 10.3 mo (0.3−32.3), median duration of treatment was 3.3 mo (0.03−30.4). At data cut-off, 24.4% of pts remained on treatment; most common reason for permanent treatment discontinuation was progressive disease (44.2%). ORR was 45.3% (95% CI 34.6−56.5), with ≥CR achieved in 17.4% of pts. ORR for pts with prior BCMA-directed ADC and CAR-T cells was 41.4% (95% CI 28.6−55.1) and 52.8% (95% CI 35.5−69.6), respectively. Among responders, median time to objective response was 1.9 mo (0.3−9.3). Median DOR was not reached by 10 mo; the DOR rate at 9 mo was 72.4% (95% CI 54.7−84.2). DOR rate (95% CI) for pts with prior BCMA-directed ADC and CAR-T cells were 67.3% (43.1−83.0) and 78.9% (53.2−91.5) at 9 mo, respectively. Median PFS was 4.8 mo (95% CI 1.9−7.7), and median OS was not reached by 10 mo, with a rate of 60.1% (95% CI 48.9−69.6) at 9 mo. Most common (≥25% of pts) TEAEs were CRS (65.1% [G3 1.2%]), anemia (59.3% [G3/4, 46.5%]), neutropenia (44.2% [G3/4, 40.7%]), thrombocytopenia (40.7% [G3/4, 29.1%]), diarrhea (33.7% [G3/4, 0%], and lymphopenia (32.6% [G3/4, 30.2%]). ICANS was reported in 5.8% (G3, 2.3%) of pts. **Conclusions:** In pts with RRMM and prior exposure to BCMA-directed therapies, elranatamab was efficacious and well tolerated; no new safety signals were observed vs the BCMA-naïve population. Results support treatment with elranatamab in pts with RRMM post BCMA-directed therapy. Clinical trial information: NCT03269136, NCT04649359, NCT05014412. Research Sponsor: Pfizer.

8009 **Poster Discussion Session**

CARTITUDE-1 final results: Phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma.

Yi Lin, Thomas G. Martin, Saad Zafar Usmani, Jesus G. Berdeja, Andrzej J. Jakubowiak, Mounzer E. Agha, Adam D. Cohen, Abhinav Deol, Myo Htut, Alexander M. Lesokhin, Nikhil C. Munshi, Elizabeth O'Donnell, Carolyn Chang Jackson, Tzu-min Yeh, Arnob Banerjee, Enrique Zudaire, Deepu Madduri, Christopher delCorral, Lida Bubuteishvili-Pacaud, Sundar Jagannath; Mayo Clinic, Rochester, MN; University of California, San Francisco, San Francisco, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute, Nashville, TN; University of Chicago, Chicago, IL; UPMC Hillman Cancer Center, Pittsburgh, PA; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; City of Hope Comprehensive Cancer Center, Duarte, CA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Massachusetts General Hospital, Harvard Medical School, Boston, MA; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Spring House, PA; Legend Biotech USA Inc., Somerset, NJ; Mount Sinai Medical Center, New York, NY

Background: Heavily pretreated patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with standard of care therapy have median overall survival (OS) of ~12 months (mo). In the single-arm, phase 1b/2 CARTITUDE-1 study (NCT03548207), pts received a single infusion of ciltacabtagene autoleucel (cilta-cel), a CAR-T cell therapy targeting BCMA. At the final protocol-specified analysis (27.7-mo median follow-up [MFU]), overall response rate (ORR) was 98%, with 83% stringent complete response (CR); 27-mo rates of progression-free survival (PFS) and OS were 55% and 70%, respectively. Here, we report study closeout results. **Methods:** Eligible pts received ≥3 prior lines of therapy (LOT) or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD); and had received prior PI, IMiD, and anti-CD38 antibody therapy. Primary endpoint was ORR and safety; secondary endpoints included PFS, OS, and minimal residual disease (MRD) negativity at 10^{-5}. **Results:** 97 pts received cilta-cel (median age 61 years [y]; median 6 prior LOT; 42% penta-drug refractory; 88% triple-class refractory; 99% refractory to last LOT). As of October 14, 2022, MFU was 33.4 mo (range, 1.5-45.2). Median (m) duration of response was 33.9 mo (95% CI, 25.5–not estimable [NE]). mPFS was 34.9 mo (95% CI, 25.2–NE), with an estimated 47.5% progression free and alive at 36 mo. mOS was not reached (NR), with an estimated 62.9% survival at 36 mo. Of 49 MRD-evaluable pts, 26 had MRD negativity sustained for ≥12 mo, of which 20 had sustained MRD-negative ≥CR. mPFS was NR in these subgroups (Table). 18 pts were MRD negative with ≥CR at 24 mo post infusion. No new safety signals and no new neurotoxicity events were reported since the 27.7-mo MFU. 6 new cases of second primary malignancy were reported, including 2 cases of basal cell carcinoma and 1 case each of myelodysplastic syndrome, B-cell lymphoma, melanoma, and prostate cancer. 5 additional deaths occurred (progressive disease [PD], n=3; pneumonia and sepsis, n=1 each [both unrelated to cilta-cel]), for a total of 35 (PD, n=17; unrelated to cilta-cel, n=12; related, n=6). **Conclusions:** Longer mPFS was observed after a single infusion of cilta-cel than any previously reported therapy in heavily pretreated pts with RRMM. Achieving CR and/or sustained MRD negativity was associated with prolonged PFS. Pts continue to be followed for safety and survival in the 15-y CARTINUE long-term study (NCT05201781; MMY4002). Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC; Legend Biotech USA Inc.

PFS at ~3-y MFU.

Subgroup	n	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All pts	97	34.9 (25.2–NE)	54.2%	47.5%
≥CR	76	38.2 (34.9–NE)	66.8%	59.8%
6-mo sustained MRD negativity[a]	34	32.2 (25.1–NE)	68.6%	45.7%
12-mo sustained MRD negativity[a]	26	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative CR[a]	20	NR (NE–NE)	78.5%	NE

[a]≥2 MRD-negative assessments, 6 or 12 mo apart, with no MRD-positive samples in that interval.

8010 **Poster Discussion Session**

Long-term remission and survival in patients with relapsed or refractory multiple myeloma after treatment of LCAR-B38M CAR-T: At least 5-year follow-up in LEGEND-2.

Jian-Qing Mi, Wan-Hong Zhao, Li-Juan Chen, Wei-Jun Fu, Bai-Yan Wang, Jie Xu, Jie Liu, Shi-Wei Jin, Han Zhu, Juan Du, Hua Jiang, Huabin Sun, Yehui Jia, Xiao-Hu Fan, Jian-Yong Li, Jian Hou, Zhu Chen, Wang-Gang Zhang, Ai-Li He, Sai-Juan Chen; State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine, Shanghai Institute of Hematology, Ruijin Hospital Affiliated With Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Hematology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Department of Hematology, Jiangsu Province Hospital, First Affiliated Hospital of Nanjing Medical University, Nanjing, China; Department of Hematology, Changzheng Hospital, The Second Military Medical University, Shanghai, China; Janssen Research & Development, Raritan, NJ; Nanjing Legend Biotech Inc., Nanjing, China; Department of Hematology, Renji Hospital Affiliated With Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: LCAR-B38M CAR-T cells express a structurally differentiated CAR construct containing a 4-1BB costimulatory domain and 2 BCMA-targeting single-domain antibodies designed to confer avidity. LEGEND-2 was a first-in-human phase 1 study of LCAR-B38M conducted in China, which showed encouraging efficacy and manageable safety in 74 patients (pts) with RRMM. The US phase 1b/2 CARTITUDE-1 and Chinese phase 2 CARTIFAN-1 trials of ciltacabtagene autoleucel, which expresses the same CAR as LCAR-B38M, confirmed the efficacy observed in LEGEND-2. Here, we present ≥5-y FU data from LEGEND-2, the longest FU for any BCMA-targeted CAR-T cell therapy study. **Methods:** Study design was previously published. Pts underwent lymphodepletion with cyclophosphamide (cy) 300 mg/m^2 (n=66) or cy 250 mg/m^2 plus fludarabine 25 mg/m^2 (n=8) prior to receiving LCAR-B38M at a median dose of 0.51×10^6 (range, 0.07-2.10 $\times 10^6$) CAR-positive T cells/kg in a single (n=9) or 3 split (n=65) infusions. **Results:** Pts were enrolled from 30 Mar 2016 to 26 Nov 2017. As of 30 Nov 2022, median FU was 65.4 mo (range, 0.4-78.8). 74 pts had received LCAR-B38M (median age, 54.5 y; 60.8% male; median [range] 3 [1-9] prior lines of therapy [LOT]; 44.6% ISS stage I; 28.4% ISS stage III; 29.7% with extramedullary disease [EMD]; 35.7% cytogenetic high risk). No new CAR-T cell-related toxicities were reported in the analysis. ORR (87.8%), CR rate (73.0%), MRD-negative CR rate (67.6%), median DOR (23 mo), and median PFS (18 mo) were mature and the same as previously reported; median OS was previously not reached. At 65.4-mo median FU, median OS was 55.8 mo, with 33 (44.6%) pts alive and 13 (17.6%) still disease-free. Compared with pts with progressive disease (PD) or who died, pts without PD were more likely to have baseline ECOG performance status (PS) 0, IgG type MM, ISS stage I MM, numerically shorter time from diagnosis, fewer prior LOT, no light chain MM, and no EMD (Table). **Conclusions:** At ≥5-y FU in LEGEND-2, median OS was 55.8 mo and 18% of pts with RRMM were disease-free, raising the possibility of a cure in this heavily pretreated pt population. Our data suggest that pts who are less heavily pretreated or have good functional status may experience greater benefit, potentially being cured, from LCAR-B38M CAR-T cell therapy. Clinical trial information: NCT03090659. Research Sponsor: Key Research and Development Plan of ShaanXi Province, Project 2018SF-002 awarded to W–H Zhao, Project 2017ZDXM-SF-25–6 (Approval No. 2018ZDXM-SF-039) awarded to A-L He; National Natural Science Foundation of China (No. 81970189) awarded to J Xu.

Baseline characteristics of pts with and without PD/death.

	Without PD n=13 median FU, 66.8 mo (range, 61.1-76.1)	With PD/Death n=61 median FU, 64.6 mo (range, 0.4-78.8)
Male / female	61.5% / 38.5%	60.7% / 39.3%
Median age (range), y	53 (35-68)	55 (27-74)
ECOG PS 0	61.5%	36.1%
MM type: IgG / light chain	76.9% / 0%	37.7% / 31.1%
EMD	0%	36.1%
ISS stage I	61.5%	41.0%
Median time from diagnosis (range), y	3 (1-9)	4 (1-9)
Median # prior LOT (range)	2 (1-6)	3 (1-9)
Median dose (range), $\times 10^6$ cells/kg	0.432 (0.16-1.58)	0.523 (0.07-2.10)

8011 **Poster Discussion Session**

Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM).

Niels W.C.J. van de Donk, Philippe Moreau, Alfred L. Garfall, Manisha Bhutani, Albert Oriol, Ajay K. Nooka, Thomas G. Martin, Laura Rosiñol, Maria-Victoria Mateos, Nizar J. Bahlis, Rakesh Popat, Britta Besemer, Joaquin Martinez-Lopez, Amrita Y. Krishnan, Michel Delforge, Danielle Trancucci, Raluca Verona, Tara Stephenson, Katherine Chastain, Surbhi Sidana; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; Hematology Clinic, University Hospital Hôtel-Dieu, Nantes, France; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Levine Cancer Institute/Atrium Health, Charlotte, NC; Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Winship Cancer Center of Emory University, Atlanta, GA; University of California, San Francisco, San Francisco, CA; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; University College London Hospitals NHS Foundation Trust, London, United Kingdom; University of Tuebingen, Tuebingen, Germany; Hematología Hospital 12 de Octubre, Madrid, Spain; City of Hope Comprehensive Cancer Center, Duarte, CA; University of Leuven, Leuven, Belgium; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Spring House, PA; Stanford University School of Medicine, Stanford, CA

Background: Teclistamab is the first approved off-the-shelf BCMA×CD3 bispecific antibody for the treatment of patients (pts) with RRMM based on data from the pivotal phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098). Moreau et al (*NEJM* 2022) reported rapid, deep, and durable responses: overall response rate (ORR) was 63% (39% ≥complete response [CR] rate), with a median duration of response (mDOR) of 18.4 mo, and median progression-free survival (mPFS) of 11.3 mo after a median follow-up (mFU) of 14.1 mo. Here, we present updated results with extended follow-up of ~2 y (22 mo). **Methods:** Eligible pts were aged ≥18 y, had documented MM (per IMWG 2016 criteria), and had received ≥3 prior lines of therapy (LOT), including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. Pts received teclistamab 1.5 mg/kg QW (the recommended phase 2 dose [RP2D]), with the option to switch to Q2W dosing if they achieved ≥partial response after ≥4 cycles of therapy in phase 1 or ≥CR for ≥6 months in phase 2. The primary endpoint was ORR (assessed per IMWG 2016 criteria by computerized algorithm). AEs were graded per CTCAE v4.03. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. **Results:** As of Dec 9, 2022, 165 pts had received teclistamab at the RP2D (median age, 64 y; 58% male; 26% high-risk cytogenetics; 12% International Staging System stage III). Pts had a median of 5 prior LOT (range, 2–14): 92% daratumumab exposed; 78% triple-class refractory; 81% daratumumab-refractory; and 90% refractory to last LOT. At 22 mo mFU, 43% of pts achieved ≥CR, mDOR was 24 mo (95% CI, 16.2–not estimable [NE]), mDOR in pts achieving ≥CR was not reached (95% CI, 24.0–NE), mPFS was 12.5 mo (95% CI, 8.8–17.2), and median overall survival was 21.9 mo (95% CI, 16.0–NE). Hematologic AEs (any grade [gr]/gr 3/4) included neutropenia (72%/65%), anemia (54%/38%), thrombocytopenia (42%/22%), and lymphopenia (35%/33%). Infections occurred in 78% of pts (52% gr 3/4); key infections included respiratory (56%), COVID-19 (27%), other viral (10%), GI (8%), fungal (5%), PJP (4%), and hepatitis B (0.6%). CRS occurred in 72% of pts (0.6% gr 3; no gr 4/5); 5 (3%) pts reported 9 ICANS events (all gr 1/2; all resolved). 1 pt in phase 1 required a teclistamab dose reduction due to neutropenia. 6 treatment-related deaths have occurred (3 due to COVID-19). Of the 49 pts who remain on study, ~90% have received Q2W dosing. **Conclusions:** After ~2 y mFU, pts receiving teclistamab demonstrated deep and durable responses regardless of refractory status, with mPFS of 12.5 mo and mDOR of 24 mo (not reached in those achieving ≥CR). These long-term follow-up data support teclistamab as a safe and effective off-the-shelf BCMA bispecific therapy for pts with RRMM. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

8012 **Poster Discussion Session**

Safety and efficacy of standard of care (SOC) ciltacabtagene autoleucel (Cilta-cel) for relapsed/refractory multiple myeloma (RRMM).

Doris K. Hansen, Krina K. Patel, Lauren C. Peres, Mehmet H. Kocoglu, Leyla Shune, Gary Simmons, Christopher J. Ferreri, Shebli Atrash, Ricardo Daniel Parrondo, Saurabh Chhabra, Patrick Costello, Shonali Midha, Melissa Alsina, Peter M. Voorhees, Myo Htut, Douglas W. Sborov, Jack Khouri, Murali Janakiram, Yi Lin, Surbhi Sidana; Department of Blood & Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL; MD Anderson Cancer Center, Houston, TX; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; Division of Hematologic Malignancies and Cellular Therapeutics (HMCT), University of Kansas Medical Center, Kansas City, KS; Virginia Commonwealth University Massey Cancer Center, Richmond, VA; Levine Cancer Institute, Charlotte, NC; Mayo Clinic Florida, Jacksonville, FL; Mayo Clinic, Phoenix, AZ; Dana-Farber Cancer Institute, Palm Beach, FL; Dana-Farber Cancer Institute, Boston, MA; H. Lee Moffitt Cancer Center, Tampa, FL; City of Hope Comprehensive Cancer Center, Duarte, CA; The University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Cleveland Clinic Taussig Cancer Center, Cleveland, OH; City of Hope Comprehensive Cancer Center, Durante, CA; Mayo Clinic, Rochester, MN; Stanford University School of Medicine, Stanford, CA

Background: Cilta-cel was FDA approved in 2022 for the treatment of RRMM. We evaluated the outcomes of patients treated with intended SOC cilta-cel. **Methods:** 12 US academic medical centers contributed data to this retrospective study. As of 12/31/2022, 177 patients were leukapheresed and 139 received cilta-cel. **Results:** The table describes the study population compared to the CARTITUDE-1 trial. More patients in our study had extramedullary disease (EMD, 35%) and high-risk cytogenetics (41%). 55% of the patients would not have met eligibility criteria for CARTITUDE-1. Common reasons for ineligibility were cytopenias (19%), prior BCMA therapy (14%), organ dysfunction (12%), oligosecretory disease (13%), and plasma cell leukemia (8%). 83% of the patients received bridging chemotherapy (overall response rate, ORR: 28%). Lymphodepletion included fludarabine (Flu) + cyclophosphamide (Cy): 81%, bendamustine: 11%, Cy: 4%, and cladribine + Cy: 4%. Median CAR-T cells infused were 0.6 million/kg (range: 0.1-0.9), and 19% of patients were treated on an expanded access protocol (EAP). Median follow-up was 2.3 months (range: 0-8). Cytokine release syndrome (CRS) was seen in 81% (≥ grade 3: 7%) and immune effector cell-associated neurotoxicity syndrome (ICANS) in 22% (≥ grade 3: 8%) of patients. Tocilizumab, steroids, and anakinra were used in 61%, 44%, and 10% of patients, respectively. Delayed neurotoxicity (NT) was seen in 9% (cranial nerve palsy: 8, Parkinsonism: 2, others: 3). Grade ≥ 3 cytopenias at day ≥ 30 were seen in 75% of patients. Infections were seen in 32% of patients. Day 30 (N=115) and best response rates (N=118) were: ≥ partial response (PR), 75/80%; ≥ very good PR, 44/62%; and ≥ complete response (CR), 26/40%, respectively. In the non-EAP FluCy population (N=88), best ORR/≥CR were 89/49%. 17 patients died by data cut-off, 4 due to disease progression and 13 (9%) due to non-relapse mortality (NRM) (grade 5 CRS: 3, infection: 6, CRS/infection: 1, grade 5 ICANS: 1, delayed NT: 2). **Conclusions:** Patients treated with intended SOC cilta-cel had a favorable ORR (80%) despite a larger proportion of patients having high-risk features relative to trial patients and limited follow-up. Response rates were higher in patients receiving conforming products with FluCy conditioning (89%). Delayed NT and NRM were seen in 9% of patients. Results will be updated with continued follow-up. D.K.H., K.K.P, M.J., Y.L. & S.S. contributed equally. Research Sponsor: None.

Comparison of patient characteristics and outcomes by intended SOC vs. CARTITUDE-1 trial participants.

	Intended SOC, N=139	CARTITUDE-1, N=97
Median age, yrs	64	61
ECOG PS 0 or 1	91%	96%
Extramedullary disease	35%	13%
High-risk cytogenetics	41%	24%
Median prior regimens	6 (2-18)	6 (4-8)
Penta-refractory disease	36%	42%
Grade ≥ 3 CRS and ICANS	7%, 8%	4%, 2%
Delayed NT/Parkinsonism	9%/1.4%	12%/6%
Best ORR/≥CR	All: 80%/40% Non-EAP FluCy: 89%/49%	98%/83%

8013 **Poster Discussion Session**

Impact of bridging therapy (BT) on outcome of relapsed refractory multiple myeloma (RRMM) with Ide-cel CAR T-cell therapy: Real-world experience from the US myeloma CAR T consortium.

Aimaz Afrough, Hamza Hashmi, Doris K. Hansen, Surbhi Sidana, Chul Ahn, Danai Dima, Ciara L. Freeman, Omar Alexis Castaneda Puglianini, Mehmet H. Kocoglu, Shebli Atrash, Peter M. Voorhees, Leyla Shune, Gary Simmons, Douglas W. Sborov, Christopher J. Ferreri, Charlotte Burton Wagner, Krina K. Patel, Jack Khouri, Larry D. Anderson, Jr, Yi Lin; Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Medical University of South Carolina, Charleston, SC; H. Lee Moffitt Cancer Center, Tampa, FL; Stanford University School of Medicine, Stanford, CA; University of Texas Southwestern Medical Center, Dallas, TX; Department of Hematology and Medical Oncology, Taussig cancer institute, Cleveland Clinic, Cleveland, OH; Moffitt Cancer Center, Tampa, FL; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; Levine Cancer Institute, Charlotte, NC; The University of Kansas Medical Center, Kansas City, KS; Virginia Commonwealth University Massey Cancer Center, Richmond, VA; The University of Utah Huntsman Cancer Institute, Salt Lake City, UT; The University of Texas MD Anderson Cancer Center, Houston, TX; Cleveland Clinic Taussig Cancer Center, Cleveland, OH; Mayo Clinic, Rochester, MN

Background: Ide-cel is an FDA-approved treatment for RRMM patients (pts). However, there is limited data on how BT for disease control during its manufacturing process affects clinical outcomes. **Methods:** Eleven US academic centers contributed data to this analysis without involvement from the manufacturer. By 5/1/2022, 235 pts had undergone leukapheresis, with 214 infused with a median follow up of 9 months (mos). BT was given between leukapheresis and CAR-T infusion. **Results:** In this analysis, 79% of pts (n = 170) received BT, which included alkylator-based in 35.5%, steroid and/or IMiD/Ab combos (IMiD combos) in 14%, PI combinations (PI combos) in 12%, and selinexor in 10%. BT recipients had higher ECOG PS 2-4, R-ISS 2-3, ferritin, and CRP before lymphodepleting (LD) chemo, however, no difference among BT subgroups. No difference in prior lines of therapy or penta-refractory between BT and No BT (NBT) groups or BT subgroups. Median cycle of the BT was 1 (1-7), with overall response rate (ORR) of 12%, with no difference among BT subgroups. Incidence and severity of CRS and ICANs were comparable in BT and NBT. However, pts who received BT had a longer median hospital stay compared to NBT, particularly in the alkylator/selinexor subgroups. There were no significant difference in cytopenias at day 90 post CAR-T between the BT and NBT or BT subgroups. For the 73% (n = 157) evaluable for day 90 response, there was no difference in the complete or ORR between the BT and NBT groups (41% vs. 52%; p = .2 and 84% vs. 87.5%, p = .8, respectively). Median PFS was worse at 8.1 mos in BT vs 11.5 mos in NBT (p = .03). Among BT subgroups, PFS was the longest with IMiD combos with median PFS not reached (NR), comparable to NBT, and was significantly longer than all other BT subgroups (p = 0.01). The median OS was 13.8 mos with BT and NR in NBT (p = .002). In BT subgroup analysis, alkylators had a shorter OS, although, this was not significant (p = .06). There was no significant difference in PFS and OS in relationship to response to BT (p = .6 and p = .9, respectively). **Conclusions:** Pts without BT had longer PFS and OS post ide-cel, likely reflective of less aggressive disease. Those who received BT with steroid/IMiD and Ab combos had similar PFS as NBT. However, BT choice is complicated by disease severity and should be evaluated per patient circumstances. Research Sponsor: None.

Patient's characteristics and outcomes based on BT.

	BT			Type of BT				
	Yes (N = 170)	No (N = 44)	P	Alkylator (N = 76)	IMiD combos (N = 30)	PI combos (N = 25)	Selinexor (N = 21)	P
Median Age, yrs	63	65	.4	63	63.5	63	66	.8
ECOG > 1	21%	2%	**.002**	24%	13%	13%	19%	.5
EMD	47%	36%	.2	54%	27%	48%	57%	.052
R-ISS 2- 3	82%	55%	**.002**	82%	95%	90%	79%	.4
High-risk cytogenetic	36%	19%	.07	39%	38%	37.5%	31.5%	.9
Ferritin > 300 ng/mL prior LD	59%	32%	**.001**	63%	50%	52%	62%	**.5**
CRP > 5 mg/L prior LD	25%	9%	**.02**	30%	20%	32%	10%	**.1**
Median hospital stay, days	10	8	**< .001**	10.5	9	9	11	.6
Median PFS, mos	8.1	11.5	**.03**	6.9	NR	6.4	9.7	**.01**

Plasma cell leukemia: A multicenter retrospective study of 150 patients.

Iloabueke Gabriel Chineke, Betsy C. Wertheim, Denise Roe, Ashley Larsen, Douglas W. Sborov, Victoria Vardell, Damian Jonathan Green, Dominique Degraff, Michaela Liedtke, Maire Okoniewski, Mohammed Wazir, Omar Nadeem, Ashley Paquin Shubert, Rebecca Wang Silbermann, Levanto Gershon Schachter, David Coffey, Timothy Martin Schmidt, Matthew Brunner, Sandy Wai Kuan Wong, Krisstina L. Gowin; The University of Arizona Cancer Center, Arizona, AZ; University of Arizona Cancer Center, Tucson, AZ; The University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Department of Internal Medicine, University of Utah, Salt Lake City, UT; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Washington, Seattle, WA; Stanford Cancer Center, Stanford, CA; Brigham and Women's Hospital, Boston, MA; UMass Memorial Medical Center, Worcester, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Oregon Health & Science University, Portland, OR; OHSU Knight Cancer Institute, Portland, OR; Sylvester Comprehensive Cancer Center, Miami, FL; University of Wisconsin School of Medicine and Public Health, Madison, WI; University of Wisconsin-Madison Carbone Cancer Center, Madison, WI; University of California San Francisco, San Francisco, CA

Background: Despite the use of novel induction regimens, stem cell transplantation (SCT), and maintenance therapy, plasma cell leukemia (PCL) remains a challenging disease with a dismal prognosis. Currently, there is no agreed standard of care management for PCL. We conducted a multicenter retrospective analysis of the clinical presentation, treatment, and outcomes of 150 patients with PCL. **Methods:** Data of patients diagnosed with pPCL or sPCL between 01/2010 and 01/2021 were entered into a study-specific REDCap database from 7 different U.S. academic sites. PCL was defined as $\geq$ 5% circulating plasma cells. Clinical data included baseline patient characteristics, clinical presentation, treatment, therapeutic response, and survival outcomes. Overall survival (OS) curves were plotted using the Kaplan-Meier method. Cox proportional hazards regression tested associations between patient characteristics and OS, generating hazard ratios (HR) and 95% confidence intervals (CI), adjusted for PCL type (primary or secondary) and SCT. **Results:** The analytical cohort included 93 pPCL and 57 sPCL patients. Median age at diagnosis was 60 years. High-risk cytogenetics were found in 56.7% of the patients where it was documented. Of the 79 patients with a documented induction regimen, 58.2% received a proteasome inhibitor triplet, 22.8% received a VTD-Pace like conventional chemotherapy, and 3% received a daratumumab quadruplet regimen. SCT (autologous or allogeneic) was done in 56.1% of the patients. The median OS for all patients, those with pPCL, and those with sPCL was 20.3, 36.6, and 3.2 months, respectively. Secondary PCL was associated with worse survival outcomes compared with pPCL (HR, 2.46; 95% CI, 1.51-3.98; $p<0.001$) (Table). Median OS was better in patients treated with a proteasome inhibitor triplet regimen vs VTD PACE-like combination (28.2 versus 12.6 months). OS was prolonged among patients who underwent any type of SCT compared with those who did not undergo SCT (44.0 versus 5.7 months, $p<0.001$). **Conclusions:** This multicenter retrospective study is one of the largest PCL analyses performed to date and reveals the clinical practice patterns of treatment and survival of PCL patients across the U.S. in the novel treatment era. The survival analysis reinforces the poor prognosis in sPCL patients and the continued need for novel treatment approaches in this patient population. While limited by retrospective design, this analysis suggests prolonged survival with transplantation in both pPCL and sPCL. Research Sponsor: None.

Associations with survival (any survival, n=150).

Characteristics	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
PCL type (primary/secondary)	4.69 (3.10 - 7.10)	2.46 (1.51 - 3.98)	< 0.001
Any transplant	0.17 (0.11 - 0.28)	0.23 (0.14 - 0.38)	< 0.001
Extramedullary disease	1.57 (0.98 - 2.50)	1.09 (0.64 - 1.88)	0.749

8015 **Poster Discussion Session**

Disparities in multiple myeloma: A global perspective on drug toxicity trends.

Majid Jaberi-Douraki, Xuan Xu, Beth Faiman, Gerald Wyckoff, Jim Riviere, Jack Khouri, Sandra Ann Mazzoni, Remya Ampadi Ramachandran, Nuwan Millagaha Gadara, Mobina Golmohammadi, Louis Williams, Christy Joy Samaras, Jason Neil Valent, Faiz Anwer, Shahzad Raza; DATA Consortium, Computational Comparative Medicine, Department of Mathematics, Kansas State University–Olathe, Olathe, KS; Kansas State University–Olathe, Olathe, KS; Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH; University of Missouri Kansas City, Kansas City, MO; Kansas State University, Olathe, KS; Cleveland Clinic Taussig Cancer Center, Cleveland, OH; Taussig Cancer Center, Cleveland Clinic, Ohio, OH; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Myeloma Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: The FDA Adverse Event Reporting System (FAERS) is one of the largest pharmacovigilance databases containing information on adverse events (AEs) received from manufacturers, consumers and healthcare professionals. The purpose of this study is to evaluate the global disparities in multiple myeloma (MM) through data mining of FAERS. **Methods:** We examined AEs associated with FDA-approved MM drugs from 2003-2022 from FAERS and the Medical Dictionary for Regulatory Activities. Patient data were then stratified based on age, sex (F/M) and 6 geographical regions. We evaluated the reporting odds ratio (ROR) combined with a 95% confidence interval for the elevated incidence of AEs. **Results:** The data curation provided 381,378 patients with information from North America (NA), Europe (EU), Asia (AS), Africa (AF), Oceania (OC) and Latin America & the Caribbean (LA), merged from 129 countries and 27 phenotypic systems and organs categories when the number of AEs happened more than 0.1% of the total. Cardiotoxicities (n=23160) and vascular toxicities (n=26716) were seen more in NA (M) (ROR=1.16±0.02 and EU (M) (ROR=1.11± 0.03) compared to the rest of the World. Nephrotoxicity (n=17486) was reported more in AF (M) (ROR=2.92±0.41) compared to AS (M) (ROR≥1.17± 0.12), EU (M) (ROR≥1.34± 0.13) and NA (M) (ROR=1.09± 0.03). Peripheral neuropathies (n=14786) were frequent among EU (F) (ROR=1.09±0.07) and OC (M) (ROR=1.08± 0.04). Mortality was higher among AS and EU (ROR≥2.15± 0.93) compared to NA and OC. There were 18,222 secondary neoplasms in FAERS. Skin neoplasms (n=4650) more frequently occurred in OC and EU (ROR≥1.70 ±0.16). Breast neoplasms (n=694) were the highest in EU (F) (ROR=4.01+0.63) and lowest in OC (F) (ROR<1). Gastrointestinal neoplasms (n=1564) were more common among AS, EU and OC (M) with (ROR≥2.23±0.47). Lymphomas (n=542) were predominant in AS(M) (ROR=2.21±0.98) and OC (M) (ROR=3.35±2.23). Leukemias (n=3896) cases were significantly higher in EU (M) (ROR=4.08 ± 0.40) and EU (F) (3.11 ± 0.26). Respiratory tract and mediastinal neoplasms (n=796) were more common in AS, EU and OC(M) where ROR≥1.36±0.33. More phenotypic characterization are tabulated below. **Conclusions:** FAERS can be used to assess cancer disparity from a global perspective. Our results indicates that certain AEs are influenced by gender and geographical location. These disparities in MM AEs may be the result of factors such as genetics, dosing/regimen, comorbidities, age and sex. These variables must be investigated for improved patient care, strategies for AE reduction, mortality reduction and optimal allocation of healthcare resources. Research Sponsor: None.

Phenotypic Characterization	Sex	NA (n=308177)	EU (n=40761)	AS (n=16467)	AF (n=363)	OC (n=2166)	LA (n=3919)
Age	F	70	69	71	**59.5**	68	67
	M	69	68	69	60	68	65
Reproductive neoplasms	F	2.1±1.2	**4.95±2.5**	**4.2±1.6**	Data not available	1.34±1.1	1.69±1.2
Prostate neoplasms	M	**2.11±0.98**	**4.39±0.65**	1.25±0.39	2.80±2.40	**3.53±0.49**	1.35±0.84

8016 **Poster Discussion Session**

Investigation into aberrant B cell repertoire in myeloma on humoral immunity and patient survival.

Lakshmi Bhavani Potluri, Hannah Seah, Vaishnavi Reddy Bade, Arthur Krogman, Shree Acharya, Andreea Mihaela Negroiu, Srikanth Talluri, Lakshmi Manasa Vempati, Pradyumna Iragavarapu, Saem Lee, Mariateresa Fulciniti, Mehmet Kemal Samur, Paul G. Richardson, Philippe Moreau, Herve Avet-Loiseau, Kenneth Carl Anderson, Rao H. Prabhala, Nikhil C. Munshi; Wayne State Univ/DMC Sinai Grace Hospital, Detroit, MI 48235, Detroit, MI; Dana-Farber Cancer Institute, Boston, MA; Boston University Medical Center, Boston, MA; Hematology Department, CHU Nantes, Nantes, France; University Hospital of Santa Maria, Nantes, France

Background: B cells are critical to inhibiting tumor progression, as they generate tumor-reactive antibodies; promote anti-tumor killing capacity of NK cells and phagocytosis of macrophages/DCs; and enrich priming of T cells against the tumor. Multiple myeloma (MM) is a B-cell-derived malignancy, and its survival is partly driven by a deficiency in the immune response. Yet, the abnormalities of the B-cell-mediated humoral responses in MM are ill defined. **Methods:** We investigated B cell composition in bone marrow (BM) from patients with newly diagnosed MM (NDMM, N = 170), relapsed refractory MM (RRMM, N = 140) and healthy donors (HD, N = 21) by multi-color flow cytometry. **Results:** We observed that B1b cells was significantly reduced by 45% ($p = 0.004$) in NDMM patients compared to HD. B1b cells are important in generating long-lasting protective antibodies, particularly against vaccines, in a T cell independent fashion. Similarly, B2 cells, which can produce all antibody types, were significantly reduced in the periphery of NDMM and RRMM patients. Within the B2 cell population, germinal center (GC) matured B cells were significantly reduced in both BM and periphery of MM patients, as shown by significantly higher expression of Fas receptor. Because of deficiencies in the GC-maturation of these B cells, their ability to switch from IgM to IgG was also significantly decreased. On the other hand, the population of regulatory B cells (Bregs) were significantly elevated by 2.3-fold ($p < 0.05$) in the BM and periphery of NDMM and periphery of RRMM patients. However, the ability of Breg cells to produce suppressive cytokines, like IL-10, was significantly reduced ($p = 0.03$), indicating impaired suppressive functional capacity. We investigated whether this dysregulated B cell homeostasis impacts myeloma patient survival following treatment. We found that a higher proportion of Bregs and a lower percent of B1a in BM and periphery prior to treatment was associated with favorable progression-free survival (PFS) in both NDMM and RRMM patients. We hypothesized that reduction of B2 cells and their inability to have GC-based maturation could impair antibody generation against acute infections and tumor neoantigens. Therefore, we evaluated MM patients' ability to produce antibodies against hepatitis B surface antigen-based vaccination. We observed that only 31% of MM patients (N = 32) respond to the vaccine compared to 90% of HD. Furthermore, MM patients' antibody titers were significantly lower (< 120 IU/L) compared to > 5000IU/L in HD. **Conclusions:** All together, these results show that in MM patients, vaccine-responsive populations of B cells are reduced, with fewer mature B cells with limited repertoires in GC to fight against acute infections, and with a high number of dysregulated regulatory B cells. These results indicate that compromised B cell functionality in MM patients could impact therapeutic outcome. Research Sponsor: U.S. National Institutes of Health.

8017 **Poster Discussion Session**

Final results of pilot trial to evaluate anti-PD1 and 8 Gy in 1 fx for relapsed refractory multiple myeloma.

Mohammad Khurram Khan, Tahseen Nasti, Troy Kleber, Josh Qian, Jeffrey M. Switchenko, Clayton B Hess, Jonathan L. Kaufman, Ajay K. Nooka, Madhav V. Dhodapkar, Dabedochukwu Obiekwe, Sagar Lonial, Rafi Ahmed; Emory University, Atlanta, GA; Department of Microbiology and Immunology, Emory Vaccine Center, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Emory University, Department of Biostatistics and Bioinformatics, Atlanta, GA; Dignity Health, Grass Valley, CA; Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA; Winship Cancer Institute - Emory, Atlatna, GA

Background: Single agent Immune-Checkpoints, such as Anti-PD1, have not be successful. A pilot phase 1, 2 trial (NCT03267888) was conducted to see if radiotherapy (RT) and anti-PD1 (Pembrolizumab) could provide early signals of safety and response. **Methods:** Inclusion criteria included patients $>$ 18 years of age, ECOG 0-1, able to give informed consent, have relapsed/refractory myeloma, and have $\geq$1 osseous and/or extra-osseous lesion that could undergo RT. Patients had to be candidates for anti-PD1 based on organ function testing, have measurable disease per International Myeloma Working Group Criteria (IMWG), and/or have progressive disease on serial staging PET/CT. IRB approval was obtained. RT (8 Gy in 1 fx) was given on day 0, cycle 1 followed by pembrolizumab (200 mg/kg iv on day 2 or 3, then every 3 weeks +/- 7 days) for 2 years or until progression. Primary endpoint was toxicity. Secondary endpoints were IMWG response, abscopal response, overall survival (OS), and immunological changes on serial blood collections. Patients were assessed at 3, 6, and 12 months for progression free survival (PFS) using IMWG and serial PET/CT scans. Patients with stable disease were continued on the trial. Patients that progressed were censored. Standard statistical analysis was performed, and included Kaplan-Meier to estimate OS and PFS. **Results:** From June, 2018 until October, 2021, 32 patients were screened and 25 were enrolled. Of the enrolled patients, 76% were Caucasian, 64% had ECOG 1, and the mean age was 60 years. Prior to enrollment, the median number of prior lines of therapy that a patient had filed was 5.0 (range: 2 – 11). There was no grade 2 or higher radiation related toxicity within the irradiated volume using CTCAE 4.0. Only one case of $\geq$ grade 3 (fevers) pembrolizumab-related toxicity was noted. Abscopal response, defined as improvement of a non-targeted lesion, was noted in 5 of 25 patients (20%). IMWG showed robust reduction in the paraproteins and other myeloma labs, suggesting response to radiotherapy and anti-PD1. A total of 8 patients showed response. Of those responding patients, 5 were post CarT cell patients, suggesting that the most benefit may be in post CarT cell patients. None of the post CarT cell patients were noted to have cytokine release syndrome and/or neurotoxicity. Of the responding patients, some of these were associated to have a robust CD 8 T cell activation. The 6 and 12 month PFS for the entire cohort was 31.8% and 22.7%, respectively. The 6 and 12-month OS for the entire cohort was 68% and 64%, respectively. Those that were post CarT, there was a higher 6 month PFS (50%) and OS (71.4%). **Conclusions:** Combination therapy of single-fraction, low-dose radiation therapy with pembrolizumab appears to be safe and shows early promise of efficacy in MM pts progressing following CarT therapy. Larger trials are warranted in the relapsed/refractory myeloma patients. Clinical trial information: NCT03267888. Research Sponsor: Merck Pharmaceutical.

A phase 1 study of belantamab mafodotin in combination with standard of care in newly diagnosed multiple myeloma: An interim analysis of DREAMM-9.

Saad Zafar Usmani, Michał Mielnik, Ja Min Byun, Aránzazu Alonso Alonso, Al-Ola A. Abdallah, Mamta Garg, Hang Quach, Chang-Ki Min, Wojciech Janowski, Enrique M. Ocio, Katja Weisel, Albert Oriol, Irwindeep Sandhu, Paula Rodríguez-Otero, Karthik Ramasamy, Jacqueline L. Egger, Danae Williams, Jie Ma, Morrys C. Kaisermann, Marek Hus; Memorial Sloan Kettering Cancer Center, New York, NY; Katedra i Klinika Hematoonkologii i Transplantacji Szpiku, Lublin, Poland; Seoul National University Hospital, Seoul, South Korea; Hospital Quirón Madrid, Madrid, Spain; University of Kansas Medical Center, US Myeloma Research Innovations Research Collaborative (USMIRC), Westwood, KS; Leicester Royal Infirmary, Leicester, United Kingdom; St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, VIC, Australia; Seoul St. Mary's Hospital, Seoul, South Korea; Calvary Mater Newcastle, Newcastle, Australia; Hospital Universitario Marqués de Valdecilla (IDIVAL), Universidad de Cantabria, Santander, Spain; University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; Institut Català d'Oncologia and Institut Josep Carreras - Hospital Universitari Germans Trias i Pujol (HUGTP), Badalona, Spain; Hospital Universitario Marqués de Valdecilla (IDIVAL), Universidad de Cantabria, Santander, Spain; University of Alberta, Edmonton, AB, Canada; Clínica Universidad de Navarra, Pamplona, Spain; Churchill Hospital, Headington, Oxford, United Kingdom; GSK, Stevenage, United Kingdom; GSK, Upper Providence, PA; GSK, Waltham, MA; Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland

Background: Belantamab mafodotin (belamaf) is a B-cell maturation antigen-binding antibody-drug conjugate that eliminates myeloma cells via direct cell killing and anti-myeloma immune responses. DREAMM-9 (NCT04091126) is an ongoing Phase 1, randomized, dose and schedule evaluation study. It aims to evaluate belamaf plus bortezomib, lenalidomide, and dexamethasone (VRd) in adult patients (pts) with transplant-ineligible (TI) newly diagnosed MM (NDMM) and to establish the recommended dose for future development of belamaf combination therapies in the 1st-line setting. Herein, we report updated interim-analysis data. **Methods:** Belamaf dose cohorts (Co1–7) are shown in the Table. VRd was given every 3 weeks (Q3W) until cycle 8, and Rd Q4W thereafter. Following safety data from Co2–5, Co6–7 were opened in parallel (randomized 1:1) and have shorter follow-up (Table). Safety was the primary endpoint; efficacy and tolerability were secondary endpoints. Minimal residual disease (MRD) was assessed by next-generation sequencing (10^{-5}). **Results:** As of data cutoff (Oct 20, 2022), 93 pts were treated across Co1–7. Median age (range) was 73 (51–88) years, 55% of pts were male, and 84% were white. The most commonly reported non-ocular adverse events (AEs) across all Co were thrombocytopenia (46%), constipation (36%), diarrhea (34%), and peripheral sensory neuropathy (31%). Overall, belamaf-related Grade ≥3 AEs occurred in 35% of pts and led to belamaf dose reductions in 7% and dose delays in 63% of all treated patients. Grade ≥3 ocular AEs (keratopathy and visual acuity [KVA] scale) occurred in 53% of all pts and led to dose reductions in 12% and dose delays in 52% of overall pts. Fatal AEs occurred in 7 pts, all unrelated to study treatment. Efficacy results and ocular AEs are summarized in the Table: 100% of pts responded in Co1 (1.9 mg/kg Q3/4W) and Co3 (1.9 mg/kg Q6/8W). Median time to very good partial response or better (≥VGPR) ranged from 2.1 to 3.1 months (mo) across cohorts. Highest MRD negativity (MRD[-]) rates (≥VGPR) were seen in Co1 (83%) and Co3 (67%). **Conclusions:** This updated interim analysis demonstrates that belamaf plus VRd has no new safety signals and provides early and deep anti-myeloma responses in pts with TI NDMM, with high MRD[-] rates. Clinical trial information: NCT04091126. Research Sponsor: GSK (209664).

Summary.

Cohorts	1 1.9 mg/kg Q3/4W n=12	2 1.4 mg/kg Q6/8W n=12	3 1.9 mg/kg Q6/8W n=12	4 1.0 mg/kg Q3/4W n=15 (Safety population n=14)	5 1.4 mg/kg Q3/4W n=13	6 1.4 mg/kg then 1.0 mg/kg Q9/12W n=14	7 1.9 mg/kg then 1.4 mg/kg Q9/12W n=15 (Safety population n=14)
Grade ≥3 ocular AEs (KVA; N=91), %	83	58	92	57	85	7	0
Median follow-up, mo	27.6	16.0	16.2	15.3	15.2	2.5	2.0
ORR, %	100	92	100	80	92	79	53
≥CR	75	83	83	53	62	14	7
VGPR	17	8	17	20	23	21	27
PR	8	0	0	7	8	43	20
MR/SD	0	8	0	7	0	7	7
MRD[-], %							
≥CR	75	33	58	33	46	7	0
≥VGPR	83	33	67	33	46	14	7

8019 **Poster Discussion Session**

Changing spectrum of infection with BCMA and GPRC5D targeting bispecific antibody therapy in patients with relapsed refractory multiple myeloma (RRMM).

Abhishek Janardan, Hammons Lindsay, Aniko Szabo, Vineel Bhatlapenumarthi, Evanka Annyapu, Binod Dhakal, Ravi Kishore Narra, Samer Al Hadidi, Sabarinath Venniyil Radhakrishnan, Divaya Bhutani, Sharmilan Thanendrarajan, Janz Siegfried, Maurizio Zangari, Suzanne Lentzsch, Frits van Rhee, Anita D'Souza, Rajshekhar Chakraborty, Carolina D. Schinke, Meera Mohan; Medical College of Wisconsin, Milwaukee, WI; Medical college of Wisconsin, Milwaukee, WI; Froedtert & Medical College of Wisconsin, Division of Biostatistics, Milwaukee, WI; University of Arkansas Medical Sciences, Little Rock, AR; Wayne State University, Detroit, MI; University of Arkansas for Medical Sciences, Little Rock, AR; Columbia University Irving Medical Center, New York, NY; Columbia University Medical Center, New York, NY; Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR

Background: There is a paucity of granular data on infection risk with bsAb targeting BCMA and GPRC5D in RRMM. **Methods:** We identified and followed 80 patients treated with bsAb therapy at 3 institutions in early-phase clinical trials between 2019 and 2022. Baseline demographic, disease and infection-specific variables were collected from the beginning of treatment to the last follow-up or 3 months after the study exit. **Results:** A total of 86 treatment courses were included, 56 patients received BCMA bsAb,15 GPRC5D bsAb combination with CD38MoAb + / -IMiD (GPRC5Dc), and 15 GPRC5D bsAb monotherapy (GPRC5Dm). The median age was 70 (45-91) years and 48% (n = 41) were females. Racial/ethnic minorities accounted for 27% (n = 24) of patients included. A total of 117 infections were observed, 89 in the BCMA group, 24 in the GPRC5Dc group and 4 with GPRC5Dm.The infection rate per 100 days in recipients of BCMA bsAb and GPRC5D bsAb were 0.56 and 0.40 (p = 0.34), respectively. There was a greater incidence of high-grade infections (≥ grade 3) with BCMA bsAb treatment compared to GPRC5D bsAb (p = 0.01). Grade 5 events were observed in 8% (n = 7) of patients treated with BCMA bsAb compared to none with GPRC5D bsAb. The proportion of bacterial, viral, and fungal infection in the BCMA group were 56% (n = 50), 37% (n = 37), and 7% (n = 6) respectively and that in GPRC5D group were 46% (n = 13), 43% (n = 12), 11% and (n = 3) respectively. Of the infections during BCMA bsAb therapy, 76% (n = 67) required hospitalization compared to 54% (n = 15) with GPRC5D bsAb (p = 0.02). At 18 months, the cumulative incidence of all-grade infection in the BCMA and GPRC5D group were 72% and 47%, respectively (p = 0.05). The cumulative incidence of ≥ grade 3 infection at 18 months was higher at 60% with BCMA bsAb compared to 29% with GPRC5D bsAb (p = 0.01). The cumulative mean number of recurrent infections by 18 months with BCMA bsAb was 3.2 (95% CI 2.33-4.58) and 1.4 (95% CI 0.77-2.60) with GPRC5D bsAb (p = 0.25). In multivariate analysis, the use of BCMA bsAb, GPRC5D combination therapy and prior infections with bsAb therapy was associated with a significantly higher risk of all-grade and grade≥3 infections. **Conclusions:** There is a significant risk of infections with bsAb therapy in RRMM with higher cumulative incidence of infection, higher grade infection and infections that require hospitalization with BCMA bsAb compared to GPRC5D bsAb. There were seven grade 5 events noted, all in patients treated with BCMA bsAb. Additionally, GPRC5D combination therapy with CD38MoAb +/- IMiDs conferred a higher risk of infections compared to GPRC5D monotherapy. Research Sponsor: None.

Analysis of infections and parameters of humoral immunity in patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with talquetamab (tal) monotherapy in MonumenTAL-1.

Paula Rodríguez-Otero, Carolina D. Schinke, Ajai Chari, Brea Lipe, Noa Lavi, Leo Rasche, Deeksha Vishwamitra, Sheri Skerget, Raluca Verona, Xuewen Ma, Sheetal Khedkar, Brandi Hilder, Tara J. Masterson, Michela Campagna, Thomas Renaud, Jaszianne A. Tolbert, Christoph Heuck, Marie-Anne Damiette Smit, Niels W.C.J. van de Donk; Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR; Mount Sinai School of Medicine, New York, NY; University of Rochester Medical Center, Rochester, NY; Rambam Health Care Campus, Haifa, Israel; University Hospital of Würzburg, Würzburg, Germany; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Madrid, Spain; Janssen Research & Development, Raritan, NJ; Janssen Biologics Europe, Leiden, Netherlands; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands

Background: Infection, a key complication of MM, may be due to patient, disease, or treatment-related factors. Immunotherapies that impact normal immune cells may increase risk of infection. Tal, a bispecific antibody with clinical benefit in pts with RRMM, targets G protein–coupled receptor family C group 5 member D (GPRC5D), a protein of unknown function with significantly higher expression on malignant versus normal plasma cells. We report the infection profile and immune function with tal in the phase (ph) 1/2 MonumenTAL-1 study (NCT03399799/NCT04634552). **Methods:** Pts had RRMM, were intolerant to/progressed on established therapies (ph 1), or had ≥3 prior lines of therapy (ph 2; ≥1 proteasome inhibitor/immunomodulatory drug/anti-CD38 antibody). Subcutaneous tal was given at 0.4 mg/kg QW or 0.8 mg/kg Q2W. Infections (graded by CTCAE v4.03) were treated per local guidelines. B-cell subpopulations and IgG levels were assessed from whole blood and serum samples, respectively. **Results:** We evaluated 339 pts on tal QW or Q2W, of whom 51 had prior T-cell redirection therapy (pTCRT); infection rates are shown in the table (median follow-up, 15.9, 10.1, and 13.1 mo, respectively). New-onset infections were most prevalent during cycles 1–2. Grade (gr) 3/4 infections observed in >2 pts were pneumonia (3.5%) and UTI (2.1%) on tal QW; pneumonia (2.1%) and COVID-19 (2.1%) on tal Q2W; and pneumonia (5.9%) with pTCRT. Opportunistic infections were observed in 3.5%, 4.1%, and 5.9% of pts, respectively. Less than 1.5% of pts died from infections: COVID-19 pneumonia (n=2) and one each due to septic shock, fungal sepsis, and unknown etiology. Hypogammaglobulinemia rates by IgG values were 64.3% (tal QW), 65.5% (tal Q2W), and 70.6% (pTCRT); IVIg use was 14.7%, 12.4%, and 15.7%, respectively. CD19+ B-cell levels were stable, and there was a trend toward increased non-clonal IgG over time. **Conclusions:** Roughly 20% of pts had gr 3/4 infections on tal (most frequently cycles 1–2), with low rates of opportunistic infections, discontinuation, and death. Infection rates, particularly rates of fatal infections, appear lower with tal than with BCMA-targeted T-cell–based therapies. A trend toward increased non-clonal IgG suggests potential recovery of humoral immunity accompanies rapid, deep, and durable responses to tal. These results distinguish tal as an important emerging therapy for RRMM. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

Pts, n (%)	Tal 0.4 mg/kg QW (n=143)	Tal 0.8 mg/kg Q2W (n=145)	pTCRT (n=51)
Infections			
Any Gr	83 (58.0)	94 (64.8)	36 (70.6)
Gr 3/4	31 (21.7)	23 (15.9)	13 (25.5)
Led to death	3 (2.1)	2 (1.4)	0
Led to discontinuation	2 (1.4)	0	1 (2.0)
Led to dose interruption	44 (30.8)	43 (29.7)	16 (31.4)
Gr 3/4 neutropenia	44 (30.8)	32 (22.1)	27 (52.9)
Any infection + concomitant Gr 3/4 neutropenia	11 (7.7)	3 (2.1)	9 (17.6)
Gr 3/4 infection + concomitant Gr 3/4 neutropenia	4 (2.8)	1 (0.7)	1 (2.0)

8021 **Poster Session**

Busulfan, melphalan, and carfilzomib (BuMelCar) conditioning for autologous stem cell transplant (ASCT) in multiple myeloma: Phase I/II data.

Joseph Allan Norton, Patrick Hagen, Stephanie Tsai, Scott E. Smith, Mary Lee, Loredana Campo, David Oldenburg, Patrick J. Stiff; Loyola University Medical Center, Maywood, IL

Background: Melphalan-200 high dose chemotherapy for ASCT has been the standard of care for multiple myeloma (MM) for over 30 years. Newer combination regimens such as Busulfan and Melphalan (BuMel) have demonstrated improved progression free survival (PFS) but with increased transplant related morbidity including mucositis and infections. Our group previously demonstrated that adding a proteasome inhibitor (bortezomib) to BuMel further increased PFS with mucositis ameliorated by Palifermin. Building on this effectiveness, we added carfilzomib to the BuMel backbone in a Phase I/II manner focused on safety and initial effectiveness of this novel regimen. **Methods:** This phase I/II open-label dose-escalation/expansion study (NCT03795597) enrolled patients with relapsed or high risk first remission MM. Patients received Busulfan over 4 days at a target total AUC of 20,000 mM-min followed by melphalan at 140mg/m2. Patients received 4 total doses of IV carfilzomib, 2 before melphalan and 2 after, with the final 2 doses escalated based on toxicity. Palifermin was given on days -11,-10, 0, and +1. Once MTD was determined, 10 more patients were treated at that level. Primary objective was safety and secondary outcomes were response to treatment at day 100 including MRD, engraftment kinetics, PFS, and OS. **Results:** Patients were predominantly male (79%) with median age 60.95 years. Median KPS was 80 and median HCT-CI was 2. The carfilzomib MTD was 36 mg/m2. One SAE of grade V ischemic colitis was seen at the 45 mg/m2 dose level. Toxicity at 36 mg/m2 yielded a similar pattern to our prior bortezemib containing regimen with grade 1 NSVT in 2 patients and hypertension in another. With a median follow up of 22 months, only 1 of the 13 MTD patients has progressed at 33mo. 2-year PFS and OS are both 100%. Analysis at D+100 showed 69% of MTD patients were MRD negative regardless of genetics. **Conclusions:** This novel BuMelCar ASCT regimen is safe and tolerable and appears to lead to a high % of MRD negative disease at D+100, which other studies correlate to a high PFS at 2 years. A comparison study with mel 200 is warranted to test whether BuMelCar can improve transplant outcomes especially in high-risk patients. Clinical trial information: NCT03795597. Research Sponsor: Amgen.

Toxicity of BuMelCar by dose levels.

		Carfilzomib		Dose Level				
		27	27	36	36	45	45	45
		All Grades	Grade III/IV	All Grades	Grade III/IV	All Grades	Grade III/IV	Grade V
Toxicity	GI	3 (100)	1 (33.33)	13	2 (15.38)	3 (100)	1 (33.33)	0 (0)
	Mucositis/Esophagitis	2 (66.67)	0 (0)	10 (76.92)	4 (30.76)	2 (66.67)	0 (0)	0 (0)
	Infection	0 (0)	0 (0)	3 (23.08)	0 (0)	1 (33.33)	1 (33.33)	0 (0)
	FN	2 (66.67)	2 (66.67)	10 (76.92)	10 (76.92)	3 (100)	3 (100)	0 (0)
	Cardiac Toxicity	0 (0)	0 (0)	2 (15.38)	0 (0)	1 (33.33)	1 (33.33)	0 (0)
	Electrolyte Abnormality	3 (100)	0 (0)	13 (100)	1 (7.69)	3 (100)	0 (0)	0 (0)
	Other	3 (100)	0 (0)	12 (92.30)	1 (7.69)	2 (66.67)	0 (0)	1 (33.33)

8022 **Poster Session**

Treatment patterns for extramedullary multiple myeloma and outcomes with CAR-T therapy and bispecific antibodies.

Saurabh Zanwar, Matthew Ho, Prashant Kapoor, Moritz Binder, Francis Buadi, Angela Dispenzieri, David Dingli, Amie L. Fonder, Morie A. Gertz, Wilson I. Gonsalves, Suzanne R. Hayman, Yi Lisa Hwa, Miriam A. Hobbs, Taxiarchis Kourelis, Martha Lacy, Nelson Leung, Eli Muchtar, Rahma M. Warsame, S. Vincent Rajkumar, Shaji Kumar; Mayo Clinic, Rochester, MN; Mayo Clinic (Rochester, MN), Rochester, MN; Mayo Clinic Department of Pediatric and Adolescent Medicine, Rochester, MN; Division of Hematology, Mayo Clinic, Rochester, MN

Background: Extramedullary Multiple Myeloma (EMM) is an aggressive entity with a dismal prognosis. Immune effector therapies (IETs), including chimeric antigen receptor T-cell (CAR-T) therapies and bispecific T-cell engaging antibodies (BsAb), have demonstrated excellent efficacy in relapsed/refractory MM with limited data for efficacy in EMM. Here, we report the treatment outcomes for patients with EMM. **Methods:** We identified 299 patients with EMM diagnosed between 01/01/2000 and 12/31/2021 after excluding solitary plasmacytomas, paraskeletal MM and primary plasma cell leukemia. The IMWG criteria were used for response definition. **Results:** Of the 299 patients, 204 (68%) patients had secondary EMM (sEMM) and 95 (32%) patients had primary EMM (pEMM). For sEMM (n=204), the median progression free survival (PFS) with initial therapy was 2.9 (95% CI: 2.4-3.2) months. Initial treatment strategies for sEMM were heterogenous and demonstrated in the table; 44% patients achieved ≥partial response (PR) with initial treatment for sEMM. The median PFS in patients with ≥PR was 5.8 (95%CI: 4.5-6.9) months vs 1.8 (95%CI: 1.4-2; p <0.0001) months for <PR. For patients with pEMM (n=95), the median PFS was 12.9 (95% CI: 6.7-18) months; the median PFS was 17.4 (95%CI: 12.9-25.4) months for patients with ≥PR versus 1 month (95% CI: 0.8-2) in patients with <PR. Thirty patients (all sEMM and triple class refractory) were treated with IET after development of EMM: 18 with BCMA-directed CAR-T, 10 with BsAbs, and 2 with both CAR-T and BsAbs. In patients receiving CAR-T therapy, 75% (15/20) achieved ≥PR with 40% (n=8) achieving MRD negative (by flowcytometry) complete response. Fifteen (75%) patients receiving CAR-T had progressive disease (PD); 7 with systemic and EMM PD and 4 patients each with isolated EMM or systemic PD. The median PFS for patients treated with CAR-T was 4.9 months [3.1- not reached (NR)]. Among patients achieving a ≥PR with CAR-T, the median PFS was 5.8 (95%CI: 4.7-NR) months vs 1.4 months [(95%CI: 0.8-NR), p<0.001] for <PR. Among patients treated with BsAbs (10-BCMA, 1 each against FcRH5 and GPRC5D), 33% (4/12) achieved a ≥PR. Ten (83%) patients had PD on BsAb; 8 with both EMM and systemic PD and 1 patient each with isolated EMM or PD. The median PFS with BsAb was 2.9 months (95%CI: 2.2-NR). **Conclusions:** Patients with EMM continue to have dismal outcomes with conventional therapies. High response rates were noted with CAR-T therapy, but these tend to be short-lived. Research Sponsor: None.

PFS with initial treatment for secondary EMM.

Groups	n	Median PFS (95%CI), months	P value
Proteasome Inhibitor (PI) plus IMiD based combination without CD38 antibody(Ab)]	24	2.2 (1.9-5.2)	0.078
CD38 Ab-combination (including with PI or IMiD)	36	4.5 (2.5-7.6)	
CAR-T or BsAb	12	3.9 (1.9-NA)	
VDT-PACE like and alkylator combinations	59	2.9 (2.4-3.5)	
Either PI or IMiD-based combination without CD38 Ab	34	3.1 (2.2-5.1)	
Other therapies	13	1.5 (0.8-NA)	

8023 **Poster Session**

Plinabulin to shorten neutropenia and improve quality of life peri-autologous hematopoietic cell transplant.

Gunjan L. Shah, Danielle Hanley, Ambika Datta, Alyssa Kamrowski, David J. Chung, Gaurav K. Gupta, Hani Hassoun, Elizabeth Hoover, Malin Hultcrantz, Neha Korde, Oscar Boutros Lahoud, Heather Jolie Landau, Alexander M. Lesokhin, Michael Scordo, Urvi A Shah, Carlyn Rose Co Tan, Saad Zafar Usmani, Ramon W. Mohanlal, Sergio Giralt; Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; BeyondSpring Pharmaceuticals, Inc., New York, NY

Background: Plinabulin is a selective immunomodulating microtubule-binding agent, which prevents chemotherapy induced neutropenia (CIN) via a mechanism of action different from that of G-CSF analogues. It has been studied for CIN and anti-solid tumor activity in phase 3 trials. To decrease the period of myelosuppression and obligate neutropenia after high dose melphalan with autologous hematopoietic stem cell transplantation (AHCT) for patients with multiple myeloma, we studied the addition of plinabulin to standard growth factors. **Methods:** To achieve the primary objective of reducing the duration of absolute neutropenia post AHCT, 40mg of intravenous plinabulin was given 1-3 hours after stem cell infusion (Day 0) with pegfilgrastim on Day +1 in this pilot trial (NCT05130827). Secondary objectives include the safety, tolerability, and toxicity profile of plinabulin in combination with pegfilgrastim, neutrophil and platelet engraftment rate, disease response, progression free and overall survival, patient reported outcome (PRO) assessment of symptom burden, and plinabulin pharmacokinetic profiling. Exploratory objectives include transfusion requirements, phenotypic characterization of neutrophil population through day 30, and analysis of cytokine levels early post AHCT. **Results:** Between January 2022 and February 2023, 15 patients with median age of 64 (range 54-74) and 33% female received plinabulin after melphalan 140 (n = 4) or 200mg/m2 (n = 11). Median CD34+ cells/kg infused was 4.12 x 10^6 (range 2.18 – 7.85). Half of the patients had hypertension immediately after the plinabulin infusion, which is a known toxicity and resolved within a few hours. Median WBC on Day 0, 1, and 2 was 7.67(3.6 – 11.5), 5.2 (3.2 – 13.6), and 17.1 (5.1-59.1), respectively. Of the 14 patients who have engrafted to date, median time to ANC $>$ 0.5 x 10^9 cell/L was 11 days (range 9-16) with median days from AHCT to ANC $<$ 0.5 of 5 days (range 5-6). The median number of days of ANC $<$ 0.1 and $<$ 0.5 were 2 (range 1-5) and 5 days (range 4-9), respectively. For the 7 patients who had a fever, the median time to fever was 8 days from AHCT (range 8-12), and all except one were peri-engraftment. Median length of stay was 17 days (range 15-21). Median pRBC and platelet transfusions were 0 (range 0-3) and 3 (range 0-11), respectively. **Conclusions:** Plinabulin appears well tolerated without additional major toxicities post AHCT and provided a high WBC on Day +2 and decreased rate of neutropenic fever. Plinabulin PK, quality of life data, and PROs will be presented. Adjusting the schedule of plinabulin to later post AHCT pre engraftment may further shorten the duration of neutropenia using this novel mechanism of action. Clinical trial information: NCT05130827. Research Sponsor: Beyond Spring; Institutional Funds.

8024 **Poster Session**

Prognostic value of month 1 bone marrow and PET MRD status in CAR-T therapy for myeloma.

Radhika Bansal, Jeffrey Babcock, Larissa Brunaldi, Saurabh Chhabra, Ricardo Daniel Parrondo, Morie A. Gertz, Matthew Hathcock, David Dingli, Prashant Kapoor, Taxiarchis Kourelis, Joselle Cook, Suzanne R. Hayman, Rahma M. Warsame, Moritz Binder, Rafael Fonseca, Peter Leif Bergsagel, Sikander Ailawadhi, Shaji Kumar, Stephen M Broski, Yi Lin; Division of Hematology, Mayo Clinic, Rochester, MN; Department of Radiology, Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Mayo Clinic, Phoenix, AZ; Mayo Clinic Florida, Jacksonville, FL; Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ; Mayo Clinic, Scottsdale, AZ; Mayo Clinic, Jacksonville, FL; Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

Background: Minimal residual disease (MRD) is prognostic for survival in multiple myeloma (MM). MRD is usually assessed in the bone marrow (BM) by flow cytometry or NGS. MRD by FDG PET/CT provides a global representation of the tumor burden, including response assessment of extramedullary disease. We examined MRD status in MM pts using both BM and PET/CT at Mayo Clinic. **Methods:** Medical records were reviewed retrospectively for MM pts who received CAR-T between 4/2018 and 12/2022. All PET/CT scans were assessed by radiologists. BM MRD was assessed by flow cytometry with a sensitivity of 10^{-5}. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier method. **Results:** Among the 157 CAR-T pts, including 89 pts who received FDA-approved CAR-T, median age was 63 years, 59% (92/157) were males, 42% (66/157) had high risk cytogenetics with median of 5 prior lines of therapy, 36% (57/157) had plasmacytoma. Incidence of CRS was 83%, 5% grade $\geq$ 3 CRS. Incidence of ICANS was 19%, 4% grade $\geq$ 3 ICANS. CR/sCR rate was 37%. One hundred and thirty-seven pts (87%) had evaluable BM at month (mo) 1, 85% (117/137) were BM MRDneg at mo 1. Baseline demographics were comparable between the two groups except age, % BM plasma cells and use of bridging therapy. Among the MRDneg pts, CR/sCR rate was 44% (51/117) and 95% (111/117) had sFLC below normal. At median follow-up of 13.8 months, median PFS among pts with BM MRDneg at 1 mo was 12 mo (95% CI: 11, 30) vs 3 mo (95% CI: 2, 7) for BM MRDpos ($p<0.001$). Median OS among pts with BM MRDneg at 1 mo was 34 mo (95% CI: 24, NR) vs 22 mo (95%CI: 7, NA) for BM MRDpos ($p<0.01$). At month 1, 112 pts had both BM and PET/CT assessments available, 64/112(57%) were both BM MRDneg/PET MRDneg, 38/112 (34%) were MRDneg for either BM or PET and 10/112 (9%) were positive for both BM and PET (MRDpos/PET MRDpos). Baseline demographics except age were comparable between the 2 groups (Table). Rate of conversion from MRDpos to MRDneg was low. Rate of sustained BM and PET MRDneg at mo 12 was 44% (8/18). The median PFS and OS for BM MRDneg/PET MRDneg was significantly longer as compared to others (Table). **Conclusions:** Achieving FLC below normal, BM MRDneg and PET MRDneg at 1 month, regardless of IMWG response at that time, is prognostic for both PFS and OS in MM pts receiving CAR-T. Failure to achieve any of these confers poor prognosis. Research Sponsor: None.

Pt characteristics.

	BMneg/PETneg (N=64)	BMpos/PETpos (N=10)	BMneg/PETpos OR BMpos/PETneg (N=38)	Total (N=112)	p value
Age, yrs, median (Range)	65 (45, 82)	55 (43, 67)	64 (33, 81)	64 (33, 82)	**0.02**
Cilta-cel, n(%)	14 (22)	0 (0)	6 (16)	20 (18)	0.12
Ide-cel, n(%)	31 (48)	4 (40)	13 (34)	48 (43)	
Trial (≥Phase II), n(%)	19 (30)	6 (60)	19 (50)	44 (39)	
sFLC <normal, n(%)	64 (100)	3 (30)	31 (82)	98 (87)	**< 0.001**
Best response, CR/sCR, n(%)	27 (42)	0 (0)	13 (34)	40 (36)	**<0.001**
PFS, mo, median (95% CI)	13 (12, NR)	2 (12, NR)	9 (6, NR)	12 (12, 16)	**<0.0001**
OS, mo, median (95% CI)	NR (NR, NR)	7 (4, NR)	37.9 (22, NR)	29 (22, NR)	**<0.01**

8025 **Poster Session**

CT103A, a novel fully human BCMA-targeting CAR-T cells, in patients with relapsed/refractory multiple myeloma: Updated results of phase 1b/2 study (FUMANBA-1).

Chunrui Li, Di Wang, Yongping Song, He Huang, Jianyong Li, Bing Chen, Jing Liu, Yujun Dong, Kai Hu, Peng Liu, Xi Zhang, Jian-Qing Mi, Zhenyu Li, Kaiyang Ding, Ai-ning Xu, Song-bai Cai, Jing-jing Guo, Hong-yu Gui, Wen Wang, Lugui Qiu, Nanjing IASO Biotherapeutics Ltd; Department of Hematology, Tongji Hospital of Tongji Medical College, Huazhong University of Science, Wuhan, China; Department of Hematology, the Affiliated Cancer Hospital of Zhengzhou University and the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Hematology, The First Affliated Hospital, Zhejiang University;, Hangzhou, China; Jiangsu Province Hospital, Nanjing, China; Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China; Department of Hematology, Third Xiangya Hospital of Central South University, Changsha, China; Department of Hematology, Peking University First Hospital, Beijing, China; Department of Adult Lymphoma, Beijing GoBroad Boren Hospital, Beijing, China; Department of Hematology, Zhongshan Hospital, Fudan University, Shanghai, China; Medical Center of Hematology, Xinqiao Hospital, State Key Laboratory of Trauma, Burn and Combined Injury, Army Medical University, Chongqing, China; State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine, Shanghai Institute of Hematology, Ruijin Hospital Affiliated With Shanghai Jiao Tong University School of Medicine, Shanghai, China; The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; Department of Hematology, The First Aìliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China; Nanjing IASO Biotherapeutics Ltd, Shanghai, China; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Background: CT103A, which is designed with a fully human BCMA-specific CAR structure, has shown sustained efficacy and durable safety in heavily pretreated relapsed and refractory multiple myeloma patients. Here, we report updated efficacy and safety data of its phase 1b/2 study (FUMANBA-1) with longer duration of follow-up. **Methods:** FUMANBA-1 is conducted in 14 centers in China. This study enrolled RRMM patients who received ≥ 3 lines of prior therapies containing at least a proteasome inhibitor and an immunomodulatory agent and were refractory to their last line of treatment. Patients who have progressed on previous BCMA CAR-T cell therapy were also included. All patients received a single infusion of CT103A at the dose of 1.0×10^6 CAR-T cells/Kg. The objective is to evaluate the efficacy, safety and PK/PD of CT103A. **Results:** As of the September 9th, 2022, 103 patients [53.4% male; median age 58.0 years (range 39-70)] with RRMM received CT103A (17 in phase 1b; 86 in phase 2) with a median follow-up of 13.8 months (range 0.4 to 27.2). The treated patients had received a median of 4 (range 3-23) lines of prior therapy. 101 patients were evaluable for efficacy assessment. The median time to first response was 16 days (range 11-179). A 96% ORR was observed, with 74.3% ≥ CR. Median DOR and median PFS have still not reached. The 12-month PFS rate was 78.8% (95% CI: 68.6–85.97). For patients without prior BCMA CAR-T therapy (N = 89), ORR was 98.9% with 78.7% ≥ CR. For patients without prior BCMA CAR-T therapy and received CT103A for more than 6 months as of the cutoff date (N = 81), ORR was 98.8% with 80.2% ≥ CR. For patients with prior BCMA CAR-T cell therapy, 4/5 (80%) of those who achieved sCR still sustained sCR over 18 months post infusion. Of the 101 patients, 95% achieved MRD-negativity with a median time to MRD-negative of 14 days (range 13-185), and all patients with CR/sCR were MRD-negative. Furthermore, 82.4% (95%CI 70.90-89.72%) achieved sustained MRD negativity over 12 months. Since the previous publication in 64th ASH meeting, no new events of CRS and ICANS occurred. The most common ≥ grade 3 treatment-related AEs were still hematologic. The expansion of CT103A reached the median peak level of 87570.6 copies/μg gDNA at a median of 12 days. CT103A was still above lower limit of qualification (100 copies/μg gDNA) in 50.0% (28/56) patients at 12 months and 40.0% (4/10) patients at 24 months after infusion. In addition, only 20 of 103 patients (19.4%) with evaluable samples were detected to be positive for the anti-drug antibody. **Conclusions:** At a longer median follow-up of 13.8 months, CT103A achieved deep and long-lasting responses in heavily pre-treated patients with MM. Furthermore, patients with prior BCMA CAR-T cell therapy who achieved sCR had sustained sCR over 18 months. CT103A demonstrated a favorable safety profile with no new risk observed with longer follow-up. Clinical trial information: NCT05066646. Research Sponsor: None.

8026 **Poster Session**

Updated OS of patients with AL amyloidosis after CAEL-101.

Michael Sang Hughes, Samuel M Pan, Rajshekhar Chakraborty, Jayant Raikhelkar, Mathew Maurer, Markus Y. Mapara, Andrew Eisenberger, Suzanne Lentzsch, Divaya Bhutani; Columbia University Medical Center, New York, NY; Columbia University Irving Medical Center, New York, NY; Presbyterian Hospital and Vanderbilt Clinic, New York, NY

Background: Morbidity and mortality remain high in immunoglobulin light chain (AL) amyloidosis due to organ involvement despite hematologic remission. Few anti-amyloid fibril therapies for AL amyloidosis exist. We previously published the results of the phase 1a/1b study of CAEL-101 in AL amyloidosis showing significant improvement in organ response rates.[1] We report long-term outcomes. **Methods:** Patients enrolled in NCT02245867 with relapsed/refractory AL amyloidosis received in phase 1a, a one-time dose-finding CAEL-101 infusion and in phase 1b, 4 weekly CAEL-101 infusions with preplanned dose escalation. Patients were evaluated for organ response for 12 weeks after last infusion. We extracted clinical, laboratory, and pathology data regarding clinical course beyond 12 weeks after last treatment. We performed a review of all AL amyloidosis patients at our center not treated with CAEL-101 1/01/2012-12/30/19 as clinical comparisons. **Results:** 22 patients were enrolled in CAEL-101. 5 patients were treated in both phase 1a and phase 1b. With median follow-up of 81.3 months (IQR 60.4-87.7), long term follow-up data are available for 19/22 patients. 5 patients died during long term follow-up: 3 from progressive AL amyloidosis; 1 from organ transplantation complication; and 1 from venous thromboembolism sequelae. Among patients with organ data available, 10/17 had hematologic progression and received next line therapy. 5/17 patients had organ progression. All patients with organ PD had previous/concomitant hematologic PD. Median OS was not reached; median organ PFS was 93.3 months (38.9-NR). No delayed adverse events occurred. Comparison with historical control groups revealed trends toward improved OS: HR 0.42 (0.09-1.81 p=0.23) in all comers AL amyloid controls, and HR 0.20 (0.03-1.16 p=0.07) in cardiac controls. Kaplan-Meier analysis and Cox regression were performed. **Conclusions:** Patients with relapsed/refractory AL amyloidosis who received a low cumulative amount of the novel anti-amyloid CAEL-101 in a phase 1a/1b study had lengthy overall and progression-free survival compared to historical controls. Patterns of organ progression after initial response may reflect intrinsic differences in organ vulnerability. The CAEL101-301 and CAEL101-302 phase 3 clinical trials are underway to confirm these findings.
Reference: 1. Edwards CV, Rao N, Bhutani D, et al: Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood 138:2632-2641, 2021. Research Sponsor: None.

Baseline patient characteristics.

	CAEL-101 (N=22)	Control (N=86)	Cardiac control (N=62)
Age	66	63	62
Gender (M/F)	14/8	46/40	32/30
Cardiac involvement	54%	72%	100%
Renal involvement	45%	61%	51%
NT-proBNP	1377 (662-13131)	1040 (89-17000)	2289 (191-17000)
Creatinine	1.03 (0.8-1.3)	1.07 (0.53-5.4)	1.01 (0.59-5.4)
Light chain type (K/L)	11/11 (50%/50%)	19/67 (78%/22%)	14/48 (22%/78%)
24h urine protein (mg)	3062 (1200-7260)	2346 (600-23,000)	3700 (330-23,000)

8027 **Poster Session**

Population pharmacokinetic-pharmacodynamic model of nirogacestat effects on B-cell maturation antigen in healthy subjects.

Todd Shearer, Rex L. Williams, Mark Johnson, Ewa Cendrowicz, Cathrine Leonowens, Margaret Smith, Todd Baughman, Caroline J. Breitbach, L. Mary Smith, Shinta Cheng; SpringWorks Therapeutics, Inc., Stamford, CT; SpringWorksTherapeutics, Stamford, CT; SpringWorks Therapeutics, Stamford, CT; ICON BioAnalytical Laboratories, Assen, Netherlands; Nuventra Pharma Sciences, Durham, NC

Background: B-cell maturation antigen (BCMA) is expressed on the membrane of normal plasma cells (PCs) and multiple myeloma (MM) cells and is the target of several investigational agents and approved products for MM treatment. Mechanistically, BCMA is cleaved from the cell surface by the enzyme gamma secretase, resulting in reduced levels of membrane-bound BCMA (mbBCMA) and release of soluble BCMA. Gamma secretase inhibitors (GSIs) have been shown to increase BCMA receptor density and potentiate the activity of several BCMA-targeted therapies in both clinical trials and *in vitro* studies. Although the effect of GSIs on BCMA receptor density has been well characterized *in vitro*, their effect on BCMA dynamics is incompletely understood in humans. This study sought to evaluate the pharmacodynamics (PD) of the GSI nirogacestat on mbBCMA in healthy subjects. **Methods:** A total of 23 healthy subjects were administered single doses of 50, 150, or 300 mg nirogacestat or multiple doses of 100 mg every 12 hours. Density of mbBCMA on PCs isolated from whole blood and bone marrow was measured by flow cytometry at baseline and 1, 2, 4, 8, 24, and 48 hours after single doses and 24 and 48 hours after the first dose in subjects receiving multiple doses. Nirogacestat serum concentrations were also measured at multiple time points to fully characterize the pharmacokinetics (PK). A population PK-PD model of the effect of nirogacestat on BCMA dynamics in humans was developed and used to simulate various administration dose levels and schedules to find an optimal nirogacestat regimen that continually increases mbBCMA over the dosing interval. **Results:** A 2-compartment model with linear absorption and elimination described serum nirogacestat in healthy subjects. A sequential PK-PD model that included an effect compartment and drug effect on mbBCMA cleavage rate described mbBCMA values. Simulations indicated that a 100-mg dose administered twice daily sufficiently maintained elevated and clinically relevant mbBCMA levels. Exposure and efficacy benchmarks from *in vitro* experiments and published clinical studies were used to contextualize simulations and hypothesize various dose and schedule scenarios to minimize dose of the BCMA-targeting therapy while maximizing BCMA potentiation. **Conclusions:** These results suggest that nirogacestat dose and schedule may have direct implications on the potentiation of BCMA-targeting therapies. Simulations suggest that the 100-mg, twice-daily nirogacestat dose results in elevated mbBCMA levels that could even allow for use of lower doses of BCMA-targeted agents while maintaining or improving efficacy. Study results along with this PK-PD model will be used to support nirogacestat dose and schedule in ongoing and planned studies in patients with MM. Research Sponsor: SpringWorks Therapeutics.

8028 **Poster Session**

Measurable residual disease (MRD) and clonal diversity for multiple myeloma treatment monitoring.

Joaquin Martinez-Lopez, Sandy Wai Kuan Wong, Nieves Lopez-Muñoz, Natasha Bahri, Shagun Arora, Mikaela Kuan, Sara Dorado, Santiago Barrio, Alfred Chung, Thomas G. Martin, Jeffrey Lee Wolf; Departamento de Hematología, Hospital 12 de Octubre, Complutense University, CNIO, Madrid, Spain; Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA; Hospital Universitario 12 de Octubre, Madrid, Spain; University of California San Francisco Department of HeM/onc, San Francisco, CA; University of California San Francisco, San Francisco, CA; University of California, San Francisco, San Francisco, CA; Altum Sequencing, UC3M Computer Science and Engineering Department, Madrid, Spain; Hospital 12 de Octubre, Madrid, Spain; University of California San Francisco Medical Center, San Francisco, CA

Background: MRD assessment is a known surrogate marker for survival in multiple myeloma (MM). However, some patients with non-detectable MRD, do relapse, and some MRD-positive patients with an extensive follow-up, do not relapse. Clonal diversity is defined as the number of unique Immunoglobulin (H, K, or L) sequences in each sample. Here, we present a single institution experience assessing MRD by NGS of Ig genes and the long-term impact of depth of response as well as clonal diversity on the clinical outcome of a large population of MM patients. **Methods:** 482 MM patients at University of California, San Francisco (UCSF) diagnosed from 2008 to 2020. Of them, 304 were newly diagnosed and 178 in $\geq$ 2nd line. MRD was assessed in patients achieving VGPR or better by IMWG criteria. MRD assessment was performed by NGS (Adaptive Biotechnologies, Seattle, WA). PFS curves were plotted by the Kaplan-Meier method, and the log-rank test was used to estimate statistical significance. **Results:** 1098 MRD samples were analyzed. MRD was available at 3 time points for 118 patients. Median follow-up was 26m. Overall, 181 of 482 patients (38%) achieved MRD- ($< 10^{-6}$) on one or more samples. Clonal diversity was available in 87 of those patients. In the newly diagnosed group, 84 of 120 (39%), achieved MRD- at the level of 10^{-6} at least once. These patients had a prolonged PFS versus patients who were persistently MRD+ at different levels ($p > 0.0001$). Notably, patients achieving a MRD $< 10^{-5}$ have longer OS than those with MRD $> 10^{-5}$ ($p = 0.009$). Of the 178 patients who received therapy for relapsed disease, 64 achieved MRD- at 10^{-6} (36%) and PFS was also prolonged versus patients who remained MRD+ (44 m v NR, $p = 0.03$). Then, we analyzed the effect of repeated MRD monitoring on PFS. Three categories were defined: (A) patients with $\geq$3 MRD- samples, (B) patients with continuously declining detectable clones, and (C) patients with a stable number of clones. Groups A and B had a more prolonged PFS than group C (NR vs NR vs 38m, $p < 0.0001$). Finally, we analyzed clonal diversity at the moment of maximum response: patients MRD+ who have not relapsed have higher clonal diversity than MRD+ patients who relapsed. Moreover, patients who were MRD- who have not relapsed have higher clonal diversity than patients who were MRD- who did relapse. This was also observed independently for the 3 receptors analyzed (IgH $p = 0.026$; IgK $p = 0.036$ and IgL $p = 0.036$). Patients with more than 66000 IgH unique sequences at the moment of maximum response had a prolonged PFS ($p = 00.5$). **Conclusions:** MRD assessment in a real-world setting has the same predictive power as that seen in clinical trials even on OS. MRD dynamics can accurately predict disease evolution and drive clinical decision-making. Clonal Diversity could complement MRD assessment in the prediction of the outcome in MM. Research Sponsor: CRIS against cancer.

8029 **Poster Session**

Long-term outcomes with isatuximab-carfilzomib-dexamethasone (Isa-Kd) in relapsed multiple myeloma patients with 1q21+ status: Updated results from the phase 3 IKEMA study.

Thierry Facon, Philippe Moreau, Ivan Spicka, Kenshi Suzuki, Kwee Yong, Joseph Mikhael, Taro Fukao, Kamlesh Bisht, Nicole Armstrong, Sandrine Macé, Marie-Laure Risse, Thomas G. Martin; Department of Hematology, Lille University Hospital, Lille, France; Department of Hematology, University Hospital of Nantes, Nantes, France; General Faculty Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic; Myeloma/Amyloidosis Center, Japanese Red Cross Medical Center, Tokyo, Japan; Department of Haematology, University College Hospital, London, United Kingdom; Applied Cancer Research and Drug Discovery, Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ; Sanofi, Global Oncology, Cambridge, MA; Sanofi, Global Medical Affairs, Cambridge, MA; Sanofi, Research and Development, Chilly-Mazarin, France; Sanofi, Research and Development, Vitry-Sur-Seine, France; University of California San Francisco Medical Center, San Francisco, CA

Background: Gain or amplification of 1q21 (1q21+, ≥3 copies), a chromosomal abnormality frequently observed in multiple myeloma (MM), has a negative impact on prognosis due to its potential involvement in resistance to MM therapy and disease progression. In the prespecified, long-term analysis of the Phase 3 IKEMA trial in relapsed MM patients (pts), treatment with Isa-Kd showed continued, significant improvement in progression-free survival (PFS) vs Kd (HR 0.58; 95.4% CI 0.42–0.79), with meaningful increase in depth of response (complete response or better [≥CR] 44.1% vs 28.5%; minimal residual disease negativity [MRD-] 33.5% vs 15.4%, MRD- ≥CR 26.3% vs 12.2%), and a manageable safety profile. In this subgroup analysis of IKEMA, we evaluated efficacy of Isa-Kd in pts with 1q21+ status (with or without high-risk chromosomal abnormalities [HRCA]) and related subgroups – isolated 1q21+ (≥3 copies without HRCA), gain(1q21), amp(1q21) – at long-term follow-up (44.2 months). **Methods:** Pts with 1–3 prior lines of therapy were randomized to Isa-Kd (n=179) or Kd (n=123). Assessment was prespecified (at 30% cut-off by FISH) for 1q21+ status as ≥3 copies, gain(1q21) as 3 copies, and amp(1q21) as ≥4 copies. **Results:** In the Isa-Kd and Kd arms, 41.9% and 42.3% of pts had 1q21+ status, 26.3% and 25.2% isolated 1q21+, 24.0% and 30.1% gain(1q21), 17.9% and 12.2% amp(1q21) respectively. Greater PFS benefit was achieved with Isa-Kd vs Kd in pts with 1q21+ status (HR 0.58, 95% CI 0.37–0.92) and in pts with isolated 1q21+, gain(1q21), or amp(1q21) (Table). Responses deepened by adding Isa to Kd, with increased rates of very good partial response or better (≥VGPR), ≥CR, MRD-, and MRD- ≥CR (Table). **Conclusions:** 1q21 abnormalities affect PFS in MM pts. Our results at long-term follow-up of pts with 1q21+ status (with or without HRCA) in the IKEMA study continue to show greater PFS benefit and deeper responses with Isa-Kd than Kd, consistent with the overall population and earlier 1q21+ subgroup interim analyses. Thus, they support Isa-Kd as an effective treatment option also for difficult-to-treat, 1q21+ pts with relapsed MM. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	Standard risk		1q21+		Isolated 1q21+ (w/o HRCA)		Gain(1q21)		Amp(1q21)	
	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
n	65	43	75	52	47	31	43	37	32	15
%	36.3	35.0	41.9	42.3	26.3	25.2	24.0	30.1	17.9	12.2
mPFS, mo	42.4	20.3	25.8	16.2	38.2	16.2	30.2	18.2	18.4	14.5
(95% CI)	(26.3-NC)	(15.2-28.2)	(17.1-38.2)	(10.2-24.8)	(18.8-NC)	(10.2-25.1)	(20.8-NC)	(10.2-25.0)	(13.1-NC)	(2.8-NC)
PFS HR vs Kd (95% CI)	0.50 (0.29–0.84)		0.58 (0.37–0.92)		0.50 (0.27–0.92)		0.50 (0.28–0.90)		0.73 (0.33–1.63)	
ORR %	90.8	86.0	86.7	82.7	91.5	87.1	90.7	86.5	81.3	73.3
≥VGPR %	76.9	53.5	73.3	51.9	80.9	51.6	79.1	56.8	65.6	40.0
MRD- %	44.6	18.6	34.7	15.4	40.4	12.9	34.9	13.5	34.4	20.0
MRD- ≥CR %	33.8	11.6	29.3	15.4	36.2	12.9	27.9	13.5	31.3	20.0

8030 **Poster Session**

Phase 2 study of abatacept, ixazomib, and dexamethasone in patients with relapsed/refractory multiple myeloma.

Khalid Shalaby, Louise Carlson, Kimberly Celotto, Colin Chavel, Ian Lund, Kristina McCaffrey, Megan Schaefer, Megan Dupuis, Jens Hillengass, Kelvin Lee; Roswell Park Comprehensive Cancer Center, Buffalo, NY; IU Simon Comprehensive Cancer Center, Indianapolis, IN; Vanderbilt-Ingram Cancer Center, Lebanon, TN

Background: Multiple myeloma (MM) usually responds to induction therapy but relapses with therapy-resistant disease. CD28 expressed on MM cells is correlated with worse outcomes. Bone marrow stromal cells expressing CD28 ligands CD80 and/or CD86 are cellular partners in the MM niche transducing a pro-survival signal to MM cells contributing to therapy resistance in relapsed disease. We have previously shown in in vitro and in vivo preclinical studies that blocking the pro-survival CD28 activation on MM cells with abatacept (CTLA4 IgG binding to CD80/CD86 and blocking engagement to CD28) reverses chemotherapy resistance and re-sensitizes MM cells to drugs they previously were resistant to. **Methods:** We tested efficacy and safety of combining Abatacept with the proteasome inhibitor (PI) Ixazomib (Ixa) and Dexamethasone (Dex) in patients with MM who had relapsed (or primary refractory) disease following treatment with first line PI Bortezomib based regimen. Previous studies found that Ixa/Dex alone only had an 11% overall response rate (ORR) and 11% Clinical Benefit Rate (CBR) in patients with prior Bortezomib exposure. In our trial, patients with MM cells positive for CD28 or CD86 by flow cytometry or immunohistochemistry in any proportion were eligible. From September 11, 2018 to August 5, 2021, 15 patients received Abatacept loading dose cycle 1 day 1 followed by 125 mg subcutaneously on day 2 and then weekly. Patients received Ixa 4 mg on days 1, 8, and 15 and Dexamethasone 40 mg weekly of a 28-day cycle. The primary endpoint was ORR (partial response (PR) or better) according to International Myeloma Working Group criteria. Secondary end points were toxicity profile, progression-free (PFS), and overall survival (OS). **Results:** Median age was 62.8 years (range 50-83.9). Ten (66.6%) patients received prior autologous stem cell transplant. The ORR was 33.33% (90% CI 16.58%-54.46%) (one-sided Binomial exact test 0.4845). Complete remission (CR) was achieved in 6.7%, and 26.7% achieved PR with 53.3% of patients having stable disease (SD). Median time to best response among patients with CR and PR was 8.9 weeks (95% CI 4–21). Median time on treatment was 23 weeks (95% CI 12.143-48.143) for all patients and 52.5 weeks (95% CI 39.286-68) for patients with response. One-year PFS was 45% (90% CI 21%-66%), median PFS 12 months (90% CI 5.7-25.9) and 1-year OS 100%, median OS not reached. Two grade 3 treatment emergent adverse events (TEAE) (diarrhea and low platelets) occurred requiring hospitalization. Grade 1/2 GI TEAEs were most common. No grade 3/4 treatment related infections were observed and 2 grade 3 infections occurred. **Conclusions:** Despite prior exposure to Bortezomib, one third of patients had response to Ixa with Abatacept and Dex. Patients with response stayed on treatment for almost 1 year on average with limited AEs. Most patients on trial gained benefit with a clinical benefit rate (CR+PR+SD) of 86.66%. Clinical trial information: NCT03457142. Research Sponsor: Bristol-Myers Squibb.

8031 **Poster Session**

Baseline and early post-infusion biomarkers associated with optimal response to ide-cabtagene vicleucel (ide-cel) in the KarMMa-3 study of triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM).

Julia Piasecki, Keyur Desai, Carolyn Courtney, Ethan Thompson, Jim Pratt, Noopur S. Raje, Krina K. Patel, Marc S. Raab, Mark Cook, Katy L. Simonsen, Mihaela Popa McKiver, Shari Kaiser, Nathan Martin; Bristol Myers Squibb, Princeton, NJ; Massachusetts General Hospital, Boston, MA; MD Anderson Cancer Center, Houston, TX; Heidelberg University Hospital, Heidelberg, Germany; Bristol Myers Squibb, Boudry, Switzerland

Background: Ide-cel, a B-cell maturation antigen (BCMA) chimeric antigen receptor T cell therapy, significantly improved median progression-free survival (mPFS) and overall response rate (ORR) vs standard regimens (SRs) in patients (pts) with TCE RRMM in the KarMMa-3 study (NCT03651128; Rodríguez-Otero et al. *NEJM* 2023). Previous analyses in KarMMa (Munshi et al. *NEJM* 2021) of pts with later-line (4L+) TCE RRMM identified low baseline (BL) levels and complete clearance of soluble BCMA (sBCMA, a measure of tumor burden) and early minimal residual disease (MRD) negativity as correlates of durable response to ide-cel. The current analysis explored the association between biomarkers and efficacy or severity of inflammatory adverse events of ide-cel in KarMMa-3. **Methods:** sBCMA levels were measured in blood samples collected from pts in KarMMa-3 at BL and regular intervals from treatment (tx) initiation until confirmed progression. MRD status was assessed in bone marrow aspirate (clonoSeq; 10^{-5} sensitivity) at 6 and 12 mo post infusion and reported in all pts, regardless of response. Biomarker analyses were based on pts who received ide-cel or $\geq$1 dose of SR. Post hoc analyses assessed correlations between biomarkers and efficacy endpoints or cytokine release syndrome (CRS) and investigator-identified neurotoxicity (iiNT); associations of interest were identified using a ranked sum test and nominal *P* value < 0.05. **Results:** Lower BL sBCMA levels were associated with higher ORR ($<$ partial response [PR] vs $\geq$PR) in both tx arms (ide-cel, $P = 0.0223$; SR, $P = 0.0395$), indicating this may be agnostic of the BCMA-directed modality. Lower BL sBCMA was also associated with higher complete response (CR) rate ($<$ CR vs $\geq$CR) in the ide-cel arm ($P = 0.0038$). Additionally, lower BL sBCMA levels in the ide-cel arm were associated with lower grade (gr) of CRS (gr 0–1 vs 2 vs $\geq$3; $P = 0.0022$) and iiNT (gr 0–1 vs $\geq$2; $P = 0.0113$); however, overlapping ranges may limit predictive utility. Further analyses will be presented. In the ide-cel arm, landmark mPFS was longer in pts with undetectable versus detectable sBCMA at 2 mo post infusion (16.3 vs 5.2 mo; HR, 0.26) or at 6 mo (16.8 vs 9.6 mo; HR, 0.62). Furthermore, landmark mPFS was also longer in pts with MRD negativity versus pts with positive/indeterminate MRD status at 6 mo (17.2 vs 5.8 mo; HR, 0.288) or at 12 mo (13.8 vs 4.6 mo; HR, 0.121). **Conclusions:** BL sBCMA levels correlated with response and CRS and iiNT grade in the ide-cel arm of KarMMa-3, potentially reinforcing the importance of management of BL tumor burden for optimal response to ide-cel. Early clearance of sBCMA at 2 mo, sustained clearance of sBCMA at 6 mo, and MRD negativity at 6 or 12 mo, regardless of clinical response, may be useful biomarkers for identifying pts likely to achieve a complete and durable response to ide-cel. Clinical trial information: NCT03651128. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, and 2seventy bio.

8032 **Poster Session**

Health related quality of life (HRQoL) in patients with triple-class-exposed relapsed/refractory multiple myeloma (TCE RRMM) treated with idecabtagene vicleucel (ide-cel) versus standard regimens: Patient-reported outcomes (PROs) from KarMMa-3 phase 3 randomized controlled trial (RCT).

Michel Delforge, Krina K. Patel, Laurie Eliason, Devender Dhanda, Ling Shi, Shien Guo, Thomas Marshall, Bertrand Arnulf, Michele Cavo, Ajay K. Nooka, Salomon Manier, Natalie Scott Callander, Sergio Giralt, Hermann Einsele, Sikander Ailawadhi, Mihaela Popa McKiver, Mark Cook, Paula Rodríguez-Otero; University of Leuven, Leuven, Belgium; MD Anderson Cancer Center, Houston, TX; Bristol Myers Squibb, Princeton, NJ; Evidera, Bethesda, MD; Hôpital Saint-Louis, Paris, France; Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; Winship Cancer Center of Emory University, Atlanta, GA; Centre Hospitalier Universitaire de Lille, Lille, France; University of Wisconsin Health, Carbone Cancer Center, Madison, WI; Memorial Sloan Kettering Cancer Center, New York, NY; Medizinische Klinik und Poliklinik II, Uniklinikum Würzburg, Würzburg, Germany; Mayo Clinic, Jacksonville, FL; Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; Clínica Universidad de Navarra, Pamplona, Spain

Background: Patients (pts) with TCE RRMM have few treatment (Tx) options and poor HRQoL. Ide-cel, the first in class CAR T cell Tx for pts with TCE RRMM, improved PFS versus standard (std) regimens in the KarMMa-3 trial. We report the PRO results comparing the Tx arms. PROs provide further understanding of Tx benefit of ide-cel from the pts' perspective. **Methods:** KarMMa-3 (NCT03651128) is an open-label phase 3 RCT comparing the efficacy and safety of ide-cel with std regimens in pts with TCE RRMM, who had received 2–4 prior regimens. In addition to clinical endpoints, we evaluated the impact of ide-cel compared with std regimens on the changes in HRQoL, measured by the EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L questionnaires. PROs were collected at baseline (screening), day of infusion and monthly from 2–24 months (mo) and thereafter every 3 mo. This interim analysis reports PROs through 20 mo. Comparisons were performed on least squares mean (LSM) changes from baseline over time between arms using constrained longitudinal data analysis (cLDA). **Results:** In total, 386 pts were randomized (ide-cel, 254; std regimens, 132). PRO compliance was high over time ($>$ 80%). At baseline, PROs were similar between arms. LSM changes from baseline to 20 mo showed significant differences ($P < 0.05$), with effect sizes of 0.3–0.7, in favor of ide-cel for most domains, including global health status/QoL, cognitive functioning, fatigue, and pain (EORTC QLQ-C30); side effects of Tx (EORTC QLQ-MY20); and the EQ-5D-5L VAS. The difference in overall LSM change reached or exceeded the pre-specified between-groups minimal importance difference (MID) for improvement in most domains in favor of ide-cel (Table). **Conclusions:** Ide-cel showed statistically significant and clinically meaningful improvements in HRQoL, including key MM symptoms and functioning, for pts with TCE RRMM compared with std regimens. The PRO data for ide-cel expands upon the clinical outcomes observed in the KarMMa-3 trial. Clinical trial information: NCT03651128. Research Sponsor: Bristol Myers Squibb.

Differences in cLDA overall LSM changes from baseline to 20 mo in ide-cel versus std regimen arm.

Instrument/Domain	Diff Between Arms LSM (95% CI) Ide-cel versus Std Regimens	MID	Hedges' g (95% CI)
EORTC QLQ-C30			
Global health status/QoL	6.17* (3.35, 8.99)	4	0.46 (0.25, 0.68)
Physical functioning	4.32* (1.66, 6.98)	5	0.34 (0.13, 0.56)
Cognitive functioning	5.64* (3.02, 8.27)	3	0.46 (0.24, 0.67)
Fatigue	−6.24* (−9.52, −2.96)	−5	−0.40 (−0.62, −0.19)
Pain	−5.68* (−9.36, −1.99)	−6	−0.33 (−0.54, −0.11)
EORTC QLQ-MY20			
Side effects of Tx	−6.08* (−7.89, −4.26)	−10	−0.71 (−0.93, −0.49)
EQ- 5D-5L VAS	7.26* (4.70, 9.83)	7	0.60 (0.39, 0.82)

*P value < 0.05.; Results favor ide-cel with - values for symptoms (fatigue, pain) and side effects and + values for functioning/health.

8033 **Poster Session**

Evaluation of prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) to inform the management of patients (pts) treated with teclistamab in MajesTEC-1.

Niels W.C.J. van de Donk, Alfred L. Garfall, Lotfi Benboubker, Katarina Uttervall, Kaz Groen, Laura Rosiñol, Caroline Hodin, Tara Stephenson, Danielle Trancucci, Alfredo Perales-Puchalt, Rachel Kobos, Arnob Banerjee, Maria-Victoria Mateos; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Hopital Bretonneau, Centre Hospitalier Régional Universitaire, Tours, France; Karolinska University Hospital, Stockholm, Sweden; Amsterdam UMC, Amsterdam, Netherlands; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; Janssen Research & Development BE, Antwerp, Belgium; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Springhouse, PA; University Hospital of Salamanca, Salamanca, Spain

Background: Teclistamab is the first BCMA × CD3 bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM). In MajesTEC-1, CRS occurred in 72.1% of pts treated at the recommended phase 2 dose (RP2D) of weekly teclistamab 1.5 mg/kg (50.3% grade [gr] 1; 21.2% gr 2; 0.6% gr 3), and was successfully managed using toci in 36.4% of pts (± other interventions) without affecting response to teclistamab. Emerging data show that prophylactic administration of toci prior to first dose of bispecific antibodies reduces CRS incidence and severity, which may facilitate outpatient initiation of therapy. The current analysis includes the first prospective study of effects of prophylactic toci on incidence and severity of CRS with teclistamab. **Methods:** Eligible pts were aged ≥18 y with RRMM and had previously received a PI, IMiD, and anti-CD38 antibody. Pts received subcutaneous teclistamab (following 2 step-up doses) in a prospective exploratory cohort at the RP2D or in a fixed-dose cohort. Toci (single 8 mg/kg IV dose) was given ≤4 hours before the first teclistamab step-up dose. CRS was graded per Lee et al 2014 and managed per institutional guidelines. **Results:** 14 pts were included: median age 64 y (range 50–82); all pts had ECOG score ≤1 and ISS I/II; 91% had standard cytogenetic risk; 21% had extramedullary plasmacytomas; 31% had ≥30% BMPCs; median 4 prior lines of therapy (range 2–7); 64% triple-class refractory. Median follow-up was 1.2 mo (range 0.2–4.6). CRS occurred in 4 pts (29%; no gr ≥3 CRS); 1 had a subsequent CRS event (table). Median time to onset was 2 d (range 1–3); median duration was 2 d (range 2–4); all events were managed with toci and resolved without teclistamab discontinuation. 7 of 14 pts had gr 3/4 neutropenia (consistent with the overall MajesTEC-1 population). 2/14 had a gr 3/4 infection. 2/14 had a neurotoxicity AE. Of the response evaluable patients, 4/7 responded. Cytokine and PK data in additional pts with longer follow-up will be presented to further inform pt management. **Conclusions:** A single dose of toci before teclistamab treatment appeared to reduce the incidence of CRS relative to the overall MajesTEC-1 study population with no new safety signals and no evidence of impact on response to teclistamab considering the short follow-up. Prophylactic toci has the potential to reduce CRS risk in pts with disease profiles suitable for outpatient dosing, reducing the burden of hospitalization during teclistamab step-up dosing. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

Pt	CRS grade	Dose after which CRS occurred	Disease characteristics in pts with CRS
1	1	Step-up dose 1	40% BMPCs (biopsy); 0 plasmacytomas
2	2	Step-up dose 2	30% BMPCs (aspirate); 2 plasmacytomas
3	1	Step-up dose 2	70% BMPCs (biopsy); 0 plasmacytomas; 11.6% circu-
	2	Cycle 1 Day 1	lating plasma cells at baseline
4	2	Step-up dose 1	80% BMPCs (biopsy); 0 plasmacytomas

8034 **Poster Session**

Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study.

Saad Zafar Usmani, Lionel Karlin, Lotfi Benboubker, Hareth Nahi, Jesús San-Miguel, Danielle Trancucci, Keqin Qi, Tara Stephenson, Alfredo Perales-Puchalt, Katherine Chastain, Ajai Chari; Memorial Sloan Kettering Cancer Center, New York, NY; Centre Hospitalier Lyon Sud, Lyon, France; Hopital Bretonneau, Centre Hospitalier Régional Universitaire, Tours, France; Karolinska University Hospital at Huddinge, Stockholm, Sweden; University of Navarra, Pamplona, Spain; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Titusville, NJ; Janssen Research & Development, Spring House, PA; Mount Sinai School of Medicine, New York, NY

Background: Teclistamab is the first B-cell maturation antigen (BCMA) bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM) at a dose of 1.5 mg/kg weekly (QW) given subcutaneously. A less frequent dosing schedule offers added convenience and flexibility to patients, physicians, and caregivers. We evaluated the ability of patients to maintain their responses after transitioning from QW to every other week (Q2W) dosing schedules in the pivotal phase 1/2 MajesTEC-1 trial (NCT03145181/NCT04557098). **Methods:** Eligible patients had RRMM and received ≥3 prior lines of therapy including a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. Patients received the recommended phase 2 dose (RP2D) of 1.5 mg/kg teclistamab QW, with the option to switch to Q2W dosing if patients achieved a confirmed partial response or better after ≥4 cycles of treatment (phase 1) or a confirmed complete response (CR) or better for ≥6 months (phase 2). Response was assessed per IMWG 2016 criteria. **Results:** As of Dec 9, 2022, 165 patients in the pivotal cohort had received teclistamab at the RP2D. Of 104 responders, 60 patients switched to Q2W dosing; 50 met the protocol-defined criteria for switching, and 10 switched who did not meet the criteria (4 due to adverse events [AEs]; 6 due to other reasons). Patients who switched had a median age of 64 years, 58% were male, 25% had high-risk cytogenetics, 7% had extramedullary plasmacytomas, and 3% had International Staging System stage III disease at baseline. Patients received a median of 4 prior lines of therapy, and 75% were triple-class refractory. At the time of switch, 49 (82%) patients achieved ≥CR, and 11 (18%) had a very good partial response. Median time to switch from QW to Q2W dosing was 11.1 months (range, 3–20). At median 11.1-month (range, 2–24) follow-up since switching, the median duration of response from the date of switch was 20.5 months (range, 1–23), with 40/60 patients still in response and ongoing treatment. Of the remaining patients, 13/60 have progressed (median time from switch to progression not estimable), 2 discontinued due to AEs, 1 discontinued for other reason, and 4 died. Additional results will be presented. **Conclusions:** Overall, patients from the MajesTEC-1 study who transitioned from QW to less frequent Q2W dosing of teclistamab had sustained remission, with a median duration of response of 20.5 months from the date of switch. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

8035 **Poster Session**

Tumor-intrinsic features associated with progression-free survival (PFS) in patients (pts) with relapsed and refractory multiple myeloma (RRMM) treated with idecabtagene vicleucel (ide-cel).

Nicholas Stong, Ethan Thompson, Amy Xu, Julie Rytlewski, Arnaud Amzallag, Timothy Brandon Campbell, Sundar Jagannath, Nikhil C. Munshi, Julia Piasecki, Debashree Basudhar, Maria Ortiz Estevez, Shari Kaiser, Erin Flynt, Nathan Martin; Bristol Myers Squibb, Princeton, NJ; Mount Sinai Medical Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: Ide-cel, a B-cell maturation antigen chimeric antigen receptor T cell therapy, has demonstrated frequent, deep, and durable responses in pts with RRMM in the KarMMa (NCT03361748), KarMMa-2 (NCT03601078), and KarMMa-3 (NCT03651128) trials. A previous analysis of KarMMa showed comparable efficacy of ide-cel across molecular high-risk/resistance (HR/R) features such as biallelic *p53* inactivation, 1q amplification, t(4;14), and *CRBN* dysregulation, and identified a baseline gene expression pattern (PC4) associated with PFS (Martin N, et al. *Hemasphere* 2022;6:(S6):1452). We aim to identify additional genomic features associated with ide-cel efficacy in KarMMa and KarMMa-2, and evaluate samples from KarMMa-3 pts as an independent validation cohort. **Methods:** Transcriptional and genomic profiles were assessed at baseline in CD138+ cells from bone marrow from pts in KarMMa, KarMMa-2 cohort 1, and KarMMa-3. Gene copy number aberrations were evaluated for associations with response. Analyses were post hoc and exploratory, and a *P*-value, or false discovery rate (FDR), of < 0.05 was used to identify associations of interest. **Results:** In evaluable pts in KarMMa (n = 70), single copy number loss was observed at 2 loci that associated with PFS, a broad region across 14q (n = 16) and deletion at 1p31.2 (n = 6). These were generally independent and collectively represented 30% (21/70) of pts. Both were associated with shorter median PFS (mPFS) in KarMMa (cohort mPFS, 8.8 mo, n = 128; Munshi et al. *N Engl J Med* 2021;384:705-16) after FDR correction (del 14q, mPFS, 4.0 mo; del 1p31.2, mPFS, 2.3 mo). No pt with 1p loss achieved a best overall response (BOR) better than partial response. Pts with loss vs non-loss of 14q had similar BOR distribution, but poorer mPFS within each BOR (10.4 vs 29.7 mo for loss vs non-loss in pts with complete response/stringent complete response). Due to small sample size in KarMMa-2 cohort 1 (n = 18), these data were aggregated with those from KarMMa. When combined, previously described associations with HR/R features were maintained except for biallelic p53 inactivation, which showed a stronger association with shorter PFS in the aggregate dataset (n = 83, $P = 0.04$) than in KarMMa (n = 65, $P = 0.09$). KarMMa-3 (n = 210) analysis is ongoing and will be used as a validation cohort for these findings. Consistent trends for the association of the PC4 gene signature with PFS were observed in KarMMa-2 but were not statistically significant and limited by sample size. **Conclusions:** Two novel genomic HR/R features associated with PFS were identified using samples from KarMMa; validation is ongoing using samples from KarMMa-3. The PC4 gene signature was consistent in 2 RRMM cohorts. A modest association between biallelic p53 disruption and PFS emerged with increased sample size and will be studied in KarMMa-3. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, and 2seventy bio.

8036 **Poster Session**

Pivotal phase 2 MonumenTAL-1 results of talquetamab (tal), a GPRC5DxCD3 bispecific antibody (BsAb), for relapsed/refractory multiple myeloma (RRMM).

Carolina D. Schinke, Cyrille Touzeau, Monique C. Minnema, Niels W.C.J. van de Donk, Paula Rodríguez-Otero, Maria-Victoria Mateos, Leo Rasche, Jing Christine Ye, Deeksha Vishwamitra, Xuewen Ma, Xiang Qin, Michela Campagna, Tara J. Masterson, Brandi Hilder, Jaszianne A. Tolbert, Thomas Renaud, Jenna Goldberg, Christoph Heuck, Ajai Chari; Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR; Centre Hospitalier Universitaire de Nantes, Nantes, France; University Medical Center of Utrecht, Utrecht, Netherlands; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; University Hospital of Würzburg, Würzburg, Germany; University of Michigan, Rogel Cancer Center at the time that the work was performed, Ann Arbor, MI; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Madrid, Spain; Janssen Research & Development, Raritan, NJ; Janssen Research & Development at the time that the work was performed, Raritan, NJ; Mount Sinai School of Medicine, New York, NY

Background: Tal is a first-in-class BsAb targeting the novel antigen G protein–coupled receptor family C group 5 member D. In MonumenTAL-1 (NCT03399799/NCT04634552), tal showed promising efficacy and clinically manageable safety in patients (pts) with RRMM. We report pivotal phase 2 results in pts with and without prior T-cell redirection therapy. **Methods:** Eligible pts were intolerant to or progressed on established therapies (phase 1) or had ≥3 prior lines of therapy (LOT), including ≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 antibody (phase 2). Pts received RP2Ds of SC tal 0.4 mg/kg QW or 0.8 mg/kg Q2W with step-up doses. CRS and ICANS were graded by ASTCT criteria; all other AEs were graded by CTCAE v4.03. Response was assessed by IMWG criteria. Data cut-off was Sep 12, 2022 for efficacy and Oct 19, 2022 for safety. Data will be updated for the meeting. **Results:** From the pivotal cohorts, 288 pts received tal 0.4 mg/kg QW (n = 143) or 0.8 mg/kg Q2W (n = 145), and 51 pts with prior T-cell redirection therapy received either dose. In the QW, Q2W, and prior T-cell redirection cohorts, respectively, median prior LOT was 5–6; 74%, 69%, and 84% were triple-class refractory and 29%, 23%, and 41% were penta-drug refractory; 15%, 11%, and 12% received prior belantamab. In the prior T-cell redirection cohort, 71% received CAR-T therapy, 35% received a BsAb, and 6% received both. In the pivotal cohorts, ORR was 74% (QW, 14.9 mo median follow-up [mF/U]) and 73% (Q2W, 8.6 mo mF/U), with very good partial response or better (≥VGPR) in 59% (QW) and 57% (Q2W). ORR was consistent across subgroups, including baseline ISS stage III disease, cytogenetic risk, number of prior LOT, and belantamab exposure. In pts with baseline plasmacytomas, ORR was 49% in both pivotal cohorts. In the prior T-cell redirection cohort, ORR was 63% (53% ≥VGPR) at 11.8 mo mF/U. Median PFS was 7.5, 11.9 (61% censored), and 5.1 mo in the QW, Q2W, and prior T-cell redirection cohorts, respectively. Common AEs included CRS (79%, 75%, 77%), skin-related AEs (56%, 71%, 69%), nail-related AEs (54%, 53%, 61%), and dysgeusia (50%, 48%, 61%); most were grade 1/2 and clinically manageable. ICANS occurred in 11%, 11%, and 3% of pts. Infections occurred in 58%, 65%, and 71% (grade 3/4: 22%, 16%, 26%) of pts, with low rates of opportunistic infections. AEs resulted in dose reductions in 15%, 8%, and 10% of pts and discontinuation in 5%, 8%, and 6%. There were no tal-related deaths. Responders to tal had higher T cell counts and lower frequencies of exhausted T cells and CD38+ Tregs vs non-responders. **Conclusions:** Pivotal phase 2 tal data showed > 70% ORR in heavily pretreated pts with RRMM. High response rates were also seen in pts with prior T-cell redirection therapy. The safety profile was clinically manageable with low rates of high-grade infections and tal discontinuations. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

8037 **Poster Session**

Adjusted indirect treatment comparison of progression-free survival (PFS) associated with DRd and VRd based on MAIA and SWOG S0777 individual patient-level data.

Brian G. Durie, Shaji Kumar, Eric M. Ammann, Alex Z. Fu, Shuchita Kaila, Annette Lam, Saad Zafar Usmani, Thierry Facon; Samuel Oschin Comprehensive Cancer Center, Los Angeles, CA; Department of Hematology, Mayo Clinic Rochester, Rochester, MN; Janssen Global Market Access, Raritan, NJ; Janssen Scientific Affairs, Horsham, PA and Georgetown University Medical Center, Washington, DC; Janssen Scientific Affairs, Horsham, PA; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; University of Lille, CHU Lille, Lille, France

Background: Both daratumumab in combination with lenalidomide and dexamethasone (DRd) and bortezomib in combination with lenalidomide and dexamethasone (VRd) are endorsed by NCCN guidelines as preferred regimens for the treatment of transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM). DRd and VRd have each demonstrated superior efficacy relative to lenalidomide and dexamethasone (Rd) alone in the MAIA and SWOG S0777 trials, respectively, but have not been compared directly in a head-to-head trial. Naive comparisons of efficacy across the 2 trials may be biased because MAIA enrolled only TIE patients (median age 73 years), whereas S0777 enrolled a mixed transplant-not-intended (TNI) population, which included both TIE patients and patients choosing to defer/refuse frontline stem cell transplantation (median age 63 years). **Methods:** The present study leveraged individual patient-level data (IPD) from both trials to perform an anchored indirect treatment comparison of DRd vs VRd, adjusting for differences in trial eligibility criteria and baseline patient characteristics. Harmonized inclusion criteria (NDMM, age $\geq$65 years, ECOG performance status $\leq$2) were applied to both trial populations. Age $\geq$65 years served as a proxy for TIE status since S0777 enrolled a mixed TNI population. Propensity score (PS) reweighting was used to balance the 2 trial populations on key baseline prognostic factors including age, sex, ISS stage, ECOG performance status, hemoglobin, eGFR, lactate dehydrogenase (LDH) level, and cytogenetic risk. Missing data were addressed with multiple imputation. After alignment of inclusion criteria and PS reweighting, an anchored indirect comparison was performed wherein within-trial progression-free survival (PFS) hazard ratios (HRs) for DRd vs Rd and VRd vs Rd were estimated and used to make indirect inference about PFS for DRd vs VRd. **Results:** 727 MAIA participants and 198 S0777 participants were eligible for inclusion. After PS reweighting, the trial populations were balanced on the key baseline prognostic factors identified above (standardized difference < 0.1 for each). The adjusted PFS HRs were 0.53 (95% CI: 0.41–0.68; $P< 0.0001$) for DRd vs Rd in MAIA and 0.88 (0.63–1.23; $P= 0.46$) for VRd vs Rd in S0777. In the adjusted Rd-anchored indirect comparison, the PFS HR for DRd vs VRd was 0.60 (0.39–0.90; $P= 0.02$). **Conclusions:** In this adjusted indirect treatment comparison based on IPD from the MAIA and S0777 trials, PFS was significantly longer for DRd relative to VRd. In the absence of a head-to-head trial comparing DRd and VRd, the present study may help to inform treatment selection in TIE patients with NDMM. Research Sponsor: Janssen.

8038 **Poster Session**

Results from a first-in-human phase I study of F182112, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma.

Mingyuan Sun, Lugui Qiu, Yongqiang Wei, Jie Jin, Xin Li, Xue Liu, Shaohong Yin, Junyuan Qi; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Hematological Disorders, Institute of Hematology and Blood Diseases Hospital, Tianjing, China; State Key Laboratory of Experimental Hematology, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical Co, Tianjin, China; Nanfang Hospital, Southern Medical University, Guangzhou, China; The First Affiliated Hospital of College of Medicine, Zhejiang University, Zhejiang, China; Department of Hematology, The Third Xiangya Hospital, Central South University, Changsha, China; Lunan Pharmaceutical Group Co. LTD, Linyi, China; Blood Institute of the Chinese Academy of Medical Sciences, Tianjin, China

Background: F182112 is a BCMA x CD3 bispecific antibody that redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells.NTP-F182112-001 is a First-in-human, Open-label, Multiple center Phase 1 Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetic, Immunogenicity, and Preliminary Efficacy of F182112 in Patients with Relapsed or Refractory Multiple Myeloma. Clinical trial information: NCT04984434. **Methods:** Eligible patients aged ≥ 18 years had received at least 2 prior multiple myeloma treatment regimens (not including autologous stem cell transplant) including a proteasome inhibitor, an immunomodulatory agent. Three dose cohorts (0.01, 0.1, and 0.3μg/kg) were planned for accelerated titration phase and the following dose cohorts (3, 10,20, and 30 μg/kg) were planed for the i3+3 dose escalation phase. F182112 were administered as QW or Q2W IV infusion. The primary endpoint was safety and tolerability assessed throughout the study by monitoring AEs per the CTCAE 5.0, except CRS per ASTCT 2018. **Results:** As of Feb 2,2023, 16 pts in the first 7 cohorts received F182112 (0.01-20 μg/kg). Median follow-up was 3.1 mo (range 0.9–11.7; median age 64 y [range 52–74]; 68% female). 9 (56%) pts had received ≥4 prior lines of therapy and 12 (75%) pts were refractory to last lines of therapy. The ORR was 43.8% (95% CI 19.8-70.1) among all enrolled patients (7/16). Of the 9 pts treated with ≥ 10 μg/kg F182112, 6 pts achieved a partial response (PR) or better (overall response rate; 66.7%), including 2 (22.2%) with a very good partial response or better.The most common treatment-related AEs were CRS (81%), lymphopenia (75%; grade 3/4: 69%), neutropenia (63%; grade 3/4: 44%), leukopenia (56%; grade 3/4: 50%), and anemia (31%). CRS and anemia events were all grade 1–2 and median duration time to CRS was 2 days (1-5). One dose-limiting toxicities (transient ALT elevation, grade 3) occurred at the dose group of 10 μg/kg. No pts required a F182112 dose reduction due to AEs. **Conclusions:** F182112 provides a novel immunotherapy approach for the treatment of Relapsed/ Refractory Multiple Myeloma that may yield improved clinical efficacy in heavily pretreated pts. Clinical trial information: NCT04984434. Research Sponsor: Shan Dong New Time Pharmaceutical Co. Ltd.

8039 **Poster Session**

Elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, for patients (pts) with relapsed/refractory multiple myeloma (RRMM): Extended follow up and biweekly administration from the MagnetisMM-3 study.

Mohamad Mohty, Michael H. Tomasson, Bertrand Arnulf, Nizar J. Bahlis, H. Miles Prince, Ruben Niesvizky, Paula Rodríguez-Otero, Joaquin Martinez-Lopez, Guenther Koehne, Yogesh Jethava, A. Eli Gabayan, Don A. Stevens, Ajay K. Nooka, Noopur S. Raje, Shinsuke Iida, Eric Leip, Umberto Conte, Akos Gabor Czibere, Andrea Viqueira, Alexander M. Lesokhin; Sorbonne University, Hôpital Saint-Antoine, and INSERM UMRs938, Paris, France; Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; Hôpital Saint-Louis, Paris, France; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; Epworth Healthcare, Melbourne, Australia; Weill Cornell Medical College - New York Presbyterian Hospital, New York, NY; Clinica Universidad de Navarra, Madrid, Spain; Hospital Universitario 12 DE OCTUBRE, Madrid, Spain; Miami Cancer Institute, Miami, FL; Indiana Blood & Marrow Transplant, Indianapolis, IN; Beverly Hills Cancer Center, Beverly Hills, CA; Norton Cancer Institute, Louisville, KY; Winship Cancer Institute, Emory University Hospital, Atlanta, GA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Department of Hematology & Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; Pfizer Inc., Cambridge, MA; Pfizer Inc., New York, NY; Pfizer, Inc., Cambridge, MA; Pfizer SLU, Madrid, Spain; Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY

Background: MagnetisMM-3 (NCT04649359) is an open-label, multicenter, registrational phase 2 study evaluating the efficacy and safety of elranatamab monotherapy in pts with RRMM; pts naïve to BCMA-directed therapies were enrolled in Cohort A. **Methods:** Eligible pts were refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody. Pts received SC elranatamab in 28-d cycles with step-up doses of 12 mg on C1D1 and 32 mg on C1D4 followed by 76 mg QW beginning C1D8. Pts treated for 6 cycles and achieving partial response (PR) or better with response persisting ≥2 mo were switched to 76 mg Q2W, 46 and 58 pts are included in the Q2W efficacy and safety analyses, respectively. **Results:** Overall, 123 pts received elranatamab. Median pt age was 68.0 y (range, 36−89), 63.4% of pts had an ECOG PS ≥1 and median prior lines of therapy was 5.0 (2−22); 96.7% and 42.3% of pts were triple-class- and penta-drug refractory, respectively. At data cutoff (~12 mo after last pt initial dose), the median follow up was 12.8 mo (0.2−22.7); 34.1% of pts remained on treatment. Most common reasons for permanent treatment discontinuation were progressive disease (39.0%) and adverse events (AE; 13.8%). Objective response rate per blinded independent central review (BICR) was 61% (95% CI 51.8−69.6), with 39 (31.7%) pts with complete response (CR) or stringent CR (sCR); very good partial response (VGPR) and PR were achieved in 29 (23.6%) and 7 (5.7%) pts, respectively. MRD-negativity (threshold 10^{-5}) was achieved by 92.0% (n = 23/25) of evaluable pts. Median duration of response (mDOR) has not been reached (95% CI 12.9−NE) and DOR at 12 mo was 74.1% (95% CI 60.5−83.6). In pts with CR/sCR or VGPR, mDOR was not reached by 12 mo; in pts with PR, mDOR was 5.2 mo (95% CI 1.6−NE). There were 46 responders by BICR who switched to Q2W dosing ≥24 wk prior to the data cut-off; among these pts, 80.4% maintained/improved their response ≥24 wk after the switch. Median progression-free and overall survival have not been reached by 12 mo, and the respective rates (95% CI) at 12 mo were 57.1% (47.2−65.9) and 62.0% (52.8−70.0). Most common Grade 3/4 treatment emergent AEs were hematologic; Grade 3/4 non-hematologic events reported in ≥5% of pts were COVID-pneumonia (10.6%), hypokalemia (9.8%), pneumonia (7.3%), sepsis (6.5%), hypertension (6.5%), ALT increased (5.7%), and SARS-COV-2 test positive (5.7%). Among pts who switched to Q2W dosing, the incidence of Grade 3/4 AEs decreased by > 10% after the switch. **Conclusions:** Elranatamab remains efficacious and well tolerated in pts with RRMM after > 1 y of follow-up. Updated analysis with a median follow up of ~15 mo, the longest of all phase 2 BCMA-CD3 bispecific antibody studies, including the outcome of pts who switched to the Q2W dosing, will be presented. These results support continued elranatamab development for pts with MM. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

8040 **Poster Session**

Efficacy and safety of elranatamab by age and frailty in patients (pts) with relapsed/refractory multiple (RRMM): A subgroup analysis from MagnetisMM-3.

Noopur S. Raje, Xavier P Leleu, Alexander M. Lesokhin, Mohamad Mohty, Ajay K. Nooka, Eric Leip, Umberto Conte, Andrea Viqueira, Salomon Manier; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; CHU de Poitiers, Hôpital de la Milétrie, Pôle Régional de Cancérologie, Poitiers, France; Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY; Sorbonne University, Hôpital Saint-Antoine, and INSERM UMRs938, Paris, France; Winship Cancer Institute, Emory University Hospital, Atlanta, GA; Pfizer Inc., Cambridge, MA; Pfizer Inc., New York, NY; Pfizer SLU, Madrid, Spain; CHU de Lille, Lille, France

Background: Multiple myeloma is predominantly a disease of elderly and frail pts, who are often ineligible for intensive therapies. Data from the ongoing Phase 2 MagnetisMM-3 (NCT04649359) study demonstrated the efficacy and safety of elranatamab in pts with RRMM and no prior BCMA-directed therapy (Cohort A). Here we report results for subgroups of pts by age and frailty. **Methods:** Eligibility criteria, dosing and administration were previously reported (Bahlis, ASH 2022). Subgroups of pts within Cohort A (n = 123) were analyzed by age: <65 (n = 43) vs ≥ 65 years n = 80), and frailty: non-frail (n = 84) vs frail (n = 39). A simplified frailty scale was used (Facon et al, Leukemia 2020). Results include data up through ~12 months after last pt initial dose. **Results:** The median treatment duration was 8.2 vs 5.5 mo in the <65 vs ≥ 65 years, and 6.4 vs 5.6 mo in the non-frail and frail subgroups, respectively. Discontinuation occurred in 62.8% vs 67.5% of pts aged <65 vs ≥ 65 years and in 63.1% vs 71.8% of the non-frail vs frail groups, respectively. The most common reason for discontinuation in all subgroups was progressive disease, 51.2%, 32.5%, 42.9%, and 30.8% of <65, ≥ 65 years, non-frail, and frail subgroups, respectively. The objective response rate (ORR) (95% CI) was 58.1% (42.1%, 73.0%) vs 62.5% (51.0%, 73.1%) for pts aged <65 vs ≥ 65 years. Median duration of response was not reached in either age subgroup. The probability of maintaining response (95% CI) at 12 mo was 74.1% (51.0%, 87.5%) vs 73.8% (55.7%, 85.4%) for pts aged <65 vs ≥ 65 years. The ORR (95% CI) for non-frail pts was 63.1% (51.9%, 73.4%) vs 56.4% (39.6%, 72.2%) for frail pts. Median duration of response was not reached in either frailty subgroup. The probability of maintaining response at 12 mo (95% CI) was 76.0% (60.2%, 86.2%) vs 70.5% (41.9%, 86.9%) for non-frail vs frail pts. Any Grade treatment-emergent adverse events (TEAEs) were reported in 100% of pts in the study. Grade 3/4 TEAEs were reported in 74.4%, 68.8%, 73.8% and 64.1% of pts in <65, ≥ 65, non-frail and frail subgroups, respectively. Infections (Any Grade; Grade 3/4; Grade 5) were reported in 72.1%, 32.6% and 4.7% vs 68.8%, 40.0% and 6.3% in <65 and ≥ 65 pts, respectively, and in 70.2%, 38.1% and 4.8% vs 69.2%, 35.9% and 7.7% in non-frail and frail pts, respectively. The rate of cytokine release syndrome was similar in patients with respect to age (<65, 58.1%; ≥ 65 years, 57.5%) and frailty groups (non-frail, 57.1%; frail, 59.0%). Immune effector cell-associated neurotoxicity syndrome was reported in 2.3%, 6.3%, 6.0% and 2.6% of pts in <65, ≥ 65, non-frail and frail subgroups, respectively. **Conclusions:** Elranatamab is efficacious and has a manageable safety profile in elderly or frail pts with RRMM and may be a treatment option for those ineligible for more intensive myeloma therapies. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

8041 **Poster Session**

Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) support for talquetamab (tal) QW and Q2W dosing in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Analyses from MonumenTAL-1.

Xuewen Ma, Jue Gong, Jie Zhou, Dongfen Yuan, Deeksha Vishwamitra, Brandi Hilder, Tara J. Masterson, Jaszianne A. Tolbert, Thomas Renaud, Christoph Heuck, Colleen Kane, Mahesh N. Samtani, Suzette Girgis, Jesus G. Berdeja, Amrita Y. Krishnan, Daniele Ouellet; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Raritan, NJ; Janssen Research & Development at the time that the work was performed, Spring House, PA; Sarah Cannon Research Institute, Nashville, TN; City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Tal is a first-in-class bispecific antibody targeting the novel antigen G protein–coupled receptor family C group 5 member D. In MonumenTAL-1 (NCT03399799/NCT04634552), tal demonstrated an overall response rate (ORR) of $>$ 70%, with clinically manageable safety in pts with RRMM. We summarize efficacy, safety, PD, and PK results supporting the recommended phase 2 doses (RP2Ds) of tal: 0.4 mg/kg QW and 0.8 mg/kg Q2W SC. **Methods:** In MonumenTAL-1, pts received IV (0.5–180 μg/kg) or SC (5–1600 μg/kg) tal doses in phase 1 and at the RP2Ds in phase 2, preceded by step-up doses. Blood samples were collected for the measurement of tal serum concentration and anti-tal antibodies (ADAs). Covariate effects on PK and efficacy were characterized. Efficacy and safety exposure–relationships (E–R) were evaluated using predicted PK metrics, ORR, and key treatment-emergent adverse events (TEAEs), including neurotoxicity, infections, cytopenia, ageusia, dysgeusia, weight loss, and cytokine release syndrome (CRS). **Results:** PK exposure was approximately dose proportional across IV and SC doses, with a SC bioavailability of 61.9%. At the RP2Ds, the mean concentration–time profiles were comparable and maintained at or above the concentration associated with the 90% maximal drug effect identified in an ex vivo cytotoxicity assay. The incidence of ADAs was 29% (QW) and 20% (Q2W). Presence of ADAs had no apparent impact on PK, safety (CRS, systemic administration–related reaction, or injection site reaction), or efficacy (ORR). At the RP2Ds, PD changes indicative of the proposed mechanism of action, such as T-cell activation, induction of cytokines, and T-cell redistribution, were comparable. Body weight, myeloma subtype, and International Staging System stage were identified as covariates for tal PK; however, there was no clinically relevant impact of age, sex, race, or mild/moderate hepatic or renal impairment on PK. Across SC doses in phase 1, ORR increased with exposure and reached a plateau at or above the RP2Ds, supporting the selected RP2Ds. Baseline myeloma subtype and extramedullary plasmacytoma status were identified as prognostic factors for ORR at the RP2Ds. There were no observed E–R for key TEAEs, including grade $\geq$3 infections or cytopenia, grade $\geq$2 weight loss, or grade 2 ageusia. No E–R for grade $\geq$1/$\geq$2 CRS and peak tal exposure for any step-up doses, irrespective of tocilizumab administration, was observed. Dysgeusia rates were comparable between the 2 RP2Ds. **Conclusions:** Efficacy, safety, PK, and PD analyses support the selection of tal 0.4 mg/kg QW and 0.8 mg/kg Q2W SC regimens as RP2Ds. The RP2Ds provided comparable PK, PD, efficacy, and safety profiles. Covariates for PK exposure had no impact on E–R, and dose adjustment was not warranted. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

8042 **Poster Session**

Phase 1 study of tasquinimod, an S100A9 inhibitor, alone and in combination with IRd for relapsed and refractory multiple myeloma (RRMM).

Dan T. Vogl, Yulia Nefedova, E. Paul Wileyto, Chau T. Nguyen, Cynthia Diaczynsky, Abigail Etzweiler, Inna Strakovsky, Cindy Lin, Eva Bondesson, Helen Tuvesson, Erik Vahtola, Adam D. Cohen, Sandra P. Susanibar-Adaniya, Adam J. Waxman, Alfred L. Garfall, Edward Allen Stadtmauer; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; The Wistar Institute, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; Active Biotech, Lund, Sweden

Background: S100A9, a protein produced by myeloid-derived suppressor cells (MDSCs) in the bone marrow microenvironment, promotes multiple myeloma (MM) progression and confers therapeutic resistance. Tasquinimod (tasq), an oral S100A9 inhibitor, has pre-clinical anti-myeloma effects alone and combined with proteasome inhibitor (PI) and immunomodulator (Imid) therapy (Lin C, EHA 2020: EP896). Tasq previously improved PFS in prostate cancer patients (pts) (JCO 2016;34(22):2636-43). We are conducting a phase 1 trial (NCT04405167) of tasq as a single agent and in combination with ixazomib (ixa), lenalidomide (len), and dexamethasone (dex) (IRd) in pts with RRMM. **Methods:** We enrolled pts with RRMM refractory to, intolerant of, or with contraindication to len, pomalidomide (pom), bortezomib, carfilzomib (cfz), and a CD38 monoclonal antibody. Tasq was given in 28-day cycles as shown below, with a 3+3 dose escalation scheme. For combination therapy, pts received ixa (4 mg days 1/8/15), len (25 mg days 1-21, with adjustments for renal dysfunction), and dex (40 mg qwk). **Results:** Of 15 pts, median age was 70y (range 56-84); 53% were male; 27% were African American and 73% Caucasian. Pts had received a median of 8 prior lines of therapy (range 4-17), and all were refractory to $\geq$1 Imid, 87% to $\geq$1 PI, and 100% to a CD38 mAb, with 87% triple class refractory and penta-exposed. 10 pts received single-agent tasq at dose levels 1 (3 pts), 2 (3 pts), and 3 (4 pts). The most common treatment-emergent adverse events (TEAEs) were fatigue (all grade [gr] 1/2), anemia (5 pts, gr 3 in 2), anorexia (5 pts, gr 3 in 2), pain (5 pts, all gr 1/2), nausea/vomiting (4 pts, all gr 1/2), and neuropathy (3 pts, all gr 1/2). No dose-limiting toxicities (DLTs) were observed, but at dose level 3, 2 pts stopped for intolerable toxicities, and we identified dose level 2 as the single-agent MTD. 5 pts have received tasq with IRd at dose levels 1 (3 pts) and 2 (2 pts). Gr $>$ = 3 TEAEs were gr 4 thrombocytopenia in 1 pt (improved with dose reductions of ixa and len), gr 3 insomnia in 1 pt, and gr 5 COVID pneumonia in 1 pt. No tasq-related DLTs were observed. On single-agent tasq, 3 pts with progressive disease at study entry had stabilization of serum markers while on study. Of 5 pts on the IRd combination, 1 has had a partial response that is ongoing after 10 months, despite being previously refractory to ixa/pom and cfz/pom combinations. **Conclusions:** Tasquinimod, an S100A9 inhibitor, is well tolerated in pts with RRMM as a single-agent and in combination with IRd, with a single-agent MTD of 1 mg daily after a 1-week dose escalation. Tasq has anti-myeloma activity in combination with IRd, as evidenced by a partial response in a patient previously refractory to Imid/PI combination therapy. Enrollment continues to tasq with IRd at dose level 2. Clinical trial information: NCT04405167. Research Sponsor: The Leukemia & Lymphoma Society; Active Biotech.

Dose level	Tasquinimod dose
1	0.25 mg qd x1 wk, 0.5 mg qd x1 wk, then 1 mg qd
2	0.5 mg qd x1 wk, then 1 mg qd
3	1 mg qd
4	1.25 mg qd
5	1.5 mg qd

8043 **Poster Session**

Clinical characteristics, markers of adverse prognosis, and predictors of development of extramedullary multiple myeloma.

Saurabh Zanwar, Matthew Ho, Prashant Kapoor, Moritz Binder, Francis Buadi, Angela Dispenzieri, David Dingli, Amie L. Fonder, Morie A. Gertz, Wilson I. Gonsalves, Suzanne R. Hayman, Yi Lisa Hwa, Miriam A. Hobbs, Taxiarchis Kourelis, Martha Lacy, Nelson Leung, Eli Muchtar, Rahma M. Warsame, S. Vincent Rajkumar, Shaji Kumar; Mayo Clinic, Rochester, MN; Mayo Clinic (Rochester, MN), Rochester, MN; Mayo Clinic Department of Pediatric and Adolescent Medicine, Rochester, MN; Division of Hematology, Mayo Clinic, Rochester, MN

Background: Extramedullary Multiple Myeloma (EMM) has an aggressive clinical course and can present at diagnosis [primary EMM, (pEMM)] or relapse [secondary EMM, (sEMM)]. Here, we report clinical characteristics and outcomes of EMM, and predictive factors for the development of sEMM. **Methods:** We identified 299 patients with biopsy-proven EMM between 01/01/2000 and 12/31/2021. Patients with solitary plasmacytomas, paraskeletal MM and primary plasma cell leukemia were excluded. A 1:1 matched pair analysis (matched for year of diagnosis of MM for comparable follow-up and treatment eras) was performed to compare clinical characteristics and outcomes for patients with and without sEMM. **Results:** The median follow-up from the diagnosis of MM was 11.5 years (95%CI: 9.3-14.8). Of 299 patients, 204 (68%) patients had sEMM and 95 (32%) had pEMM, with largely comparable baseline characteristics (Table). The median overall survival (OS) from the diagnosis of sEMM was 0.7 (95% CI: 0.6-0.9) years compared to 3.6 (95%CI: 2.4-5.6) years for pEMM ($p<0.0001$). For sEMM, mutlvariable analysis (MVA) for OS identified visceral organ involvement (eg. liver, lung/pleura, brain, pancreas, etc.) to be associated with inferior OS [HR 1.6 (95% CI: 1.1-2.4), p=0.01]; high-risk cytogenetics (HR-CTG), ISS-3 stage, and age did not impact OS from sEMM. For pEMM, HR-CTG [HR 2.3 (95% CI 1.1 -4.8), p=0.03] and ISS-3 stage [HR 3.1 (95% CI 1.5-6.7), p=0.003] were associated with inferior OS on MVA whereas visceral EMM or age did not impact OS from pEMM. On univariate analysis, patients with sEMM were younger (median age 58.7 vs 61 years, p=0.006), had a higher proportion of 1q duplication (32% vs 17%, p=0.001), t(4;14) [16% vs 9%, p=0.047] and elevated LDH (30% vs 19%, p=0.04), compared to the matched cohort of patients without sEMM. On MVA, younger age at diagnosis, t(4;14) and 1q duplication at diagnosis of MM were independent predictors of development of sEMM. The median OS from diagnosis of MM was 5.4 years (95%CI: 4.1-6.2) for patients with sEMM versus 7.5 years (95% CI: 6.4-10.1; $p<0.001$) for the matched cohort. Secondary EMM was an independent poor prognostic marker for OS from the diagnosis of MM [HR 1.6 (95%CI: 1.2-2.1); p=0.004] in addition to age, ISS3 disease and HR-CTG. **Conclusions:** Outcomes of patients with EMM, especially sEMM, remain dismal. Patients with sEMM have higher rates of 1q duplication and t(4;14) at diagnosis of MM and carried an independent adverse prognosis in a matched cohort. Research Sponsor: None.

Parameter at Diagnosis of MM	Primary EMM (n=95)	Secondary EMM (n=204)	p-value
Median age, years, (range)	61 (18-83)	58.7 (35-89)	0.09
ISS Stage 3, %	21	32	0.22
High-risk cytogenetics, %	53	54	0.89
17p deletion	18	16	0.7
1q duplication	26	31	0.44
t(4;14)	15	16	0.84
MAF translocations	15	8	0.15
Visceral site of disease, %	52	52	0.9
LDH > ULN at MM diagnosis, %	33	30	0.7
Marrow plasma cell infitrate, median, %	30	50	**0.005**

8044 **Poster Session**

Identification of cytokines associated with response and cytokine release syndrome: Analysis of MagnetisMM-3 cohort A.

Hang Quach, Nizar J. Bahlis, Paula Rodríguez-Otero, Andrea Viqueira, Shen-Wu Wang, Sangeetha Sathaiah, Douglas M Robinson, Thomas O'Brien, Katja Weisel; St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; Clinica Universidad de Navarra, Madrid, Spain; Pfizer SLU, Madrid, Spain; Pfizer Oncology, Pfizer Inc, San Diego, CA; Translational Biomarker Statistics, Pfizer Healthcare India Private Ltd, Chennai, India; Translational Biomarker Statistics, Pfizer Inc, Cambridge, MA; University Medical Center of Hamburg-Eppendorf, Hamburg, Germany

Background: MagnetisMM-3 (NCT04649359) is a phase 2 study of elranatamab monotherapy in patients with multiple myeloma refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody. Promising efficacy and safety have been observed in patients who were naïve to B-cell maturation antigen (BCMA)-directed therapy (Cohort A) in MagnetisMM-3 (Bahlis et al., ASH 2022). **Methods:** In MagnetisMM-3, patients received subcutaneous elranatamab in 28-day cycles with step-up doses of 12 mg on C1D1 and 32 mg on C1D4 followed by 76 mg QW beginning C1D8. Serum samples were collected on C1D1 prior to first priming dose, and on C1D2, pre-dose C1D4, C1D5, pre-dose C1D8, C1D15, and C1D22. Levels of 45 peripheral cytokines were analyzed by proximity extension assay and a longitudinal mixed effects model was applied to each cytokine separately. Cytokines with a significant 2-fold differential expression (responders [defined as patients with best overall response of very good partial response or better] vs non-responders [defined as patients with best overall response of partial response or worse]; cytokine release syndrome [CRS] vs no CRS) at any timepoint are reported. Clinical data cutoff was in Oct 2022 with median follow up of 10.4 months. **Results:** Baseline levels of IL-6 (2.6-fold), IL-17C (2.0-fold), and MIP-1α (2.1-fold) were lower in patients who achieved a response. After the first priming dose, 13 cytokines in the panel, including CCL8, IFN-γ, IL-2, and IL-27, were differentially expressed in responders vs non-responders. At baseline, no cytokines were found to predict CRS. After the first priming dose, 18 cytokines in the panel, including CCL8, IFN-γ, IL-10, IL-2, IL-27, IL-6, and IL-17A, were differentially expressed in patients with CRS vs no CRS. The maximal differential expression for 17/18 cytokines occurred at C1D2, ~24 hours post the first priming dose. **Conclusions:** Lower baseline levels of IL-6, IL-17C, and MIP-1α correlated with a response of VGPR or better in BCMA-naïve patients from MagnetisMM-3, suggesting that lower levels of these cytokines might reflect a favorable immune environment. Many cytokines were differentially expressed at higher levels in patients who experienced CRS vs those who did not; the most prominent cytokines included CCL-8, IFN-γ, and IL-10. The timing of induction of CCL-8, IFN-γ, and IL-10 occurred by C1D2 suggesting a potential contribution of these cytokines in driving CRS. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

8045 **Poster Session**

Genomic analysis to identify determinants of inherent response and resistance to elranatamab in MagnetisMM-3 cohort A.

Nizar J. Bahlis, Hang Quach, Katja Weisel, Andrea Viqueira, Shen-Wu Wang, Phineas T. Hamilton, Tao Xie, Thomas O'Brien, Paula Rodríguez-Otero; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia; University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; Pfizer SLU, Madrid, Spain; Pfizer Oncology, Pfizer Inc, San Diego, CA; Oncology Research and Development, Pfizer, La Jolla, CA; Clinica Universidad de Navarra, Madrid, Spain

Background: MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized phase 2 study of elranatamab monotherapy in patients (pts) with multiple myeloma refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug and 1 anti-CD38 antibody. This analysis examined molecular correlates of elranatamab response and resistance in pts naïve to B-cell maturation antigen (BCMA)-directed therapy (Cohort A). **Methods:** Bone marrow aspirate (BMA) samples collected at screening were analyzed by whole exome and whole transcriptome sequencing. To investigate the contribution of the tumor microenvironment (TME) in elranatamab response, the abundance of cell types in the BMA samples collected at screening was estimated using single sample gene set enrichment analysis (ssGSEA) of LM22 cell type signatures. Response was defined as a best overall response of very good partial response or better (partial response was considered non-response for this analysis). **Results:** *TNFRSF17* (BCMA encoding gene) expression correlated with markers of disease burden: levels increased with disease stage (with progressively higher levels in R-ISS stages I, II, and III; $p = 0.014$), were higher in pts with high-risk cytogenetics ($p = 0.002$) and correlated with plasma cell content in BMA samples ($\rho = 0.80$; $p < 10^{-10}$). *TNFRSF17* expression trended higher in non-responders ($p = 0.08$), but this trend was diminished when adjusting for disease burden. These findings suggest *TNFRSF17* expression in bulk BM samples is associated with higher disease burden and likely poorer response. According to ssGSEA of LM22 cell types, plasma cells in BMA were associated with non-responders ($p = 0.03$). Further multivariable modeling (controlling for plasma cell content) revealed additional cell types associated with response, including macrophages and monocytes, which were associated with poor outcome. Pts with both low plasma and low myeloid cells were most likely to respond. Genome wide copy number analysis showed that *TNFRSF17* locus amplification was associated with non-response ($p = 0.008$). Chromosomal alterations associated with non-response were identified, including genomic loci known to define high-risk MM (eg, 1q21+) and loci not known to be associated with high-risk MM (eg, 17q21+ and 6p21+). **Conclusions:** Genomic analysis of BMA samples from MagnetisMM-3 identified an association between higher *TNFRSF17* expression in the TME and unfavorable outcomes, likely due to its surrogacy with increased tumor burden. Features of high-risk disease were also associated with lack of response to elranatamab. Adjusting for tumor cell content revealed additional aspects of the TME associated with poor response, including increased myeloid cell populations. Lastly, alterations in specific genomic loci were also associated with response, consistent with tumor intrinsic features influencing elranatamab response. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

8046 **Poster Session**

ISAMAR: Multicenter phase II single arm trial of isatuximab (ISA) with/without lenalidomide (LEN) in pts with high risk smoldering multiple myeloma (HRSMM).

Elisabet Esteve Manasanch, Neha Korde, Hans C. Lee, Krina K. Patel, Melody Becnel, David Berrios, Sheeba K. Thomas, Swaminathan Padmanabhan Iyer, Sham Mailankody, Behrang Amini, Pei Lin, Zuzana Berkova, Donna M. Weber, Lei Feng, Sattva Swarup Neelapu, Sundar Jagannath, Michelle Ann Theobald Hildebrandt, Robert Z. Orlowski, Ola Landgren; Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Myeloma, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Statistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Myeloma, Mount Sinai Hospital, New York, NY; Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX; Myeloma Program and Experimental Therapeutics Program, University of Miami, Miami, FL

Background: HRSMM patients (pts) have a median time to progression of < 2 years. ISA is a monoclonal antibody that binds to highly expressed CD38 on myeloma cells and is approved in RRMM. We designed a phase II study to test the efficacy of ISA +/- LEN in HRSMM (NCT02960555). **Methods:** The primary endpoint of the study was the overall response rate (ORR) after 6 months of ISA 20 mg/kg IV days 1, 8, 15, 22 cycle 1; days 1, 15 cycles 2-6; day 1 cycles 7-30 monotherapy (stage 1, n = 25) or with LEN 25 mg po daily on days 1-21 every 28 days, cycles 1-6 (stage 2, n = 36). Secondary endpoints are progression free survival (PFS), overall survival (OS) while exploratory endpoints included quality of life (QoL), flow and sequencing. **Results:** 61 HRSMM pts (+immunoparesis and $\geq$95%abnormal plasma cells in bone marrow) (stage 1 n = 25; stage 2 n = 36) were accrued 02/2017-10/2022. The study met its primary endpoint of ORR $\geq$ 70% after 6 cycles of therapy [Stage 2 ORR (89%) = VGPR 9 (25%), PR 23 (64%), MR 3(8%), PD 1(3%)]. Median time to response was 1 cycle. In stage 2, 17/36 (47%) patients had grade 3 treatment related adverse events (AEs): 1 pt related to ISA (myalgia, 3%) and 16 pts related to LEN (44%) [ANC decrease (36%), skin rash (8%), ALC decrease (11%), WBC decrease (8%), fatigue (6%)] and 1/36 pts a grade 4 (related to LEN) [ANC decrease 3%]. Most common grade 1-2 AEs: WBC decrease (53%), ANC decrease (56%), skin rash (28%), fatigue (39%), ALC decrease (42%), thrombocytopenia (28%), diarrhea (39%), constipation (28%). There were no grade 5 AEs. No patients discontinued treatment due to AEs. There were 3 deaths in stage 1 unrelated to therapy: 1 patient progressed to and died while on systemic AL amyloidosis therapy, one patient (with COPD) died of COVID19 while in sustained PR, one heavy smoker died of squamous cell cancer of the tongue. Pre- and post-treatment BM flow showed that ISA/LEN increased CD4+/CD8+ and effector memory cytotoxic T cells. QoL measures (n = 32; 15 in stage 1, 17 in stage 2 and 21 with both BL/after 6 months data) showed that ISA+/- LEN resulted in decreased cancer worry/anxiety and improved future perspective at 6 months compared to BL in both stages. QoL was favorable and conserved throughout treatment, suggesting minimal effects of treatment on patient assessment of well-being. For stage 1, median PFS was 49.3 months (95% CI:40.8~NA months); median OS not reached at a median f/u of 49 months (range 6.3-68 months). Stage 2 median PFS/OS is not reached. **Conclusions:** ISA/LEN results in high ORR without decrease in patient well-being. ISA monotherapy also results in prolonged PFS when compared to historical data. ISA/LEN therapy remodels the BM TME with increase in memory cytotoxic T cells. The results of this study give rationale for the ongoing phase 3 ITHACA evaluating ISA +/- LEN/DEX with the potential to change the standard of care in HRSMM (NCT04270409). RO and OL have equal contribution. Clinical trial information: NCT02960555. Research Sponsor: High-risk Multiple Myeloma Moon Shot Program at UT MD Anderson Cancer Center; SANOFI; Miriam and Sheldon Adelson Medical Research Foundation; The Paula and Rodger Riney Foundation.

8047 **Poster Session**

Patient-derived MicroOrganoSpheres (MOS) and precision clinical decision-making for patients with multiple myeloma.

Rui Xi, Xiaobei Wang, Nicholas Baro, Renuka Raman, Shaun Steele, Elena Helman, Shengli Ding, Yubin Kang, Xiling Shen; Xilis.Inc, Durham, NC; Duke University, Durham, NC; Xilis, Inc., Durham, NC; Xilis Inc., Durham, NC; Duke University Trent Center for Bioethics Humanities and History of Medicine, Durham, NC

Background: There are many multiple myeloma (MM) treatments and nearly all patients undergo continual cycles of treatment, response, and resistance. Selecting an effective therapeutic strategy is of critical importance; but there is currently a lack of patient-derived MM models that can enable functional precision medicine to help real-time clinical decision-making to guide individual patient treatment. **Methods:** We show a method to rapidly establish MM patient-derived MicroOrganoSheres (MOS), which are microscale, droplet-sized patient avatars that sustain the native tumor niche, including both stromal and immune compartments. We generated first-of-its-kind data showing that MM MOS predicted patient treatment outcomes and have the potential to guide clinical treatment decisions. We further developed high-throughput drug screen to demonstrate MM MOS response to FDA-approved single and combination therapies and developed MOS assays to predict patient responses to immunotherapies including bispecific and phagocytosis-inducing antibodies. **Results:** MM MOS established from patient bone marrow (BM) biopsies preserved CD138/CD38 tumor cells, stromal (e.g., osteoblast) cells, and all major immune cell populations (T, NK, B, macrophage, dendritic, and myeloid-derived suppressor cells) for 11 days in culture. We performed single and combo drug testing on MOS derived from 7 MM patients within 10 days of biopsy collection. Patients went on receiving treatments and their responses were assessed using International Myeloma Working Group response criteria. The MOS assay predicted responses of both treatment-naïve and refractory patient to standard-of-care regimens, including combinations of proteasome inhibitors (bortezomib, carfilzomib), immunomodulatory agents (lenalidomide) and DCEP. Moreover, the BM biopsy-derived MOS enabled high-throughput drug testing of single agents and combinations in 9-dose titrations, providing clinicians the ability to evaluate alternative treatment options. Furthermore, because MOS retain the immune compartments of the original tumor niche, we were able to evaluate patients' response to bispecific T cell engagers and developed a phagocytosis assay to measure anti-tumor phagocytosis activity, which showed efficacy in both single-agent and combo settings. Multi-modal profiling and an AI image analysis pipeline provided robust measurements that confirmed the unique phenotypic profile of each patient sample, highlighting the critical unmet need to guide each patient to the optimal treatment. **Conclusions:** Based on this groundbreaking feasibility study, a subsequent clinical trial of 40 patients is current under IRB review to further validate the clinical power of MM MOS to predict patient outcome and to demonstrate utility as a viable functional precision medicine approach to inform treatment decisions in the clinic. Research Sponsor: None.

8048 **Poster Session**

Retrospective analysis of the relationship between time to anti-resorptive therapy and incidence of skeletal related events in patients with multiple myeloma.

Adam F Binder, Kelly Hughes, Abdullateef Abdulkareem, Adam Barsouk, Niketa Raj, Tingting Zhan, Sai Gundepalli, Srinivas S. Devarakonda; Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University Hospital, Philadelphia, PA; Sidney Kimmel Medical College, Philadelphia, PA; Department of Pharmacology, Physiology, & Cell Biology at Thomas Jefferson University, Philadelphia, PA; Ohio State University, Columbus, OH; Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Patients with multiple myeloma (MM) often have bone disease at diagnosis and are at risk of developing skeletal related events (SRE) (pathological fractures, spinal cord compression, and/or need for radiotherapy or surgery to bone). It is well established that for patients with lytic bone lesions at diagnosis, the use of anti-resorptive agents lead to a lower incidence of SREs. However, it is common for initiation of anti-resorptive therapy to be delayed. Recent studies have demonstrated that anti-resorptive therapy is underutilized in patients with MM. However, the effect of time to initiation of anti-resorptive agent after diagnosis of MM on SREs has not been well studied. Herein, we conducted a multi-center retrospective analysis to determine if time to anti-resorptive agent has an adverse impact on the risk of SREs. **Methods:** We performed a retrospective cohort study using our Electronic Health Record system to identify patients with newly diagnosed MM between July 1st, 2016 and June 30th, 2019 at two large academic centers. Patients previously treated or patients not treated with anti-resorptive therapy were excluded. The study's primary endpoint was hazard ratio of developing a SRE based on time to anti-resorptive therapy. The relationship between incidence of SREs and time to anti-resorptive therapy, gender, age, International Staging System (ISS) stage at diagnosis, and prior SRE present at diagnosis was analyzed by using a multivariable Cox proportional hazards model. The cutoff point of anti-resorptive therapy delay was based on the recursive partitioning of univariable Cox model. **Results:** 759 patients were included in the study (Thomas Jefferson University: n = 232; The Ohio State University: n = 527). Median age at diagnosis is 60.2 years (IQR: 12.4 years). 57% of patients were male. 77.9% and 20.3% of patients identified as white and black respectively. 210 patients (27.7%) were noted to have osteopenia, 45 (5.9%) had osteoporosis, 229 (30.2%) were vitamin D deficient, and 319 (42%) were obese at diagnosis. A skeletal related event was present at diagnosis in 338 (45.1%) of patients. 180 (34%) patients received anti-resorptive agents within 31 days. A delay in initiating anti-resorptive agents of greater than 31 days from diagnosis had an increased risk for SRE with a hazard ratio 1.654 (1.054~2.598; p-value: 0.029). **Conclusions:** This large multicenter retrospective study demonstrated that time to anti-resorptive therapy MM patients has a significant impact on the risk of SRE. Given many of the challenges in starting anti-resorptive therapy in a timely manner, this study emphasizes the need for inter-professional, multi-disciplinary collaborations to streamline the workflow and start therapy within the first month of diagnosis. Ongoing efforts are underway to develop quality improvement processes to achieve this goal.
Research Sponsor: None.

8049 **Poster Session**

Evaluating the efficacy of commercial teclistamab in relapsed refractory multiple myeloma patients with prior exposure to anti-BCMA therapies.

Ross Firestone, Tala Shekarkhand, Dhwani Patel, Carlyn Rose Co Tan, Malin Hultcrantz, Alexander M. Lesokhin, Sham Mailankody, Hani Hassoun, Urvi A Shah, Neha Korde, Kylee Maclachlan, Heather Jolie Landau, Michael Scordo, David J. Chung, Gunjan L. Shah, Oscar Boutros Lahoud, Sergio Giralt, Saad Zafar Usmani; Memorial Sloan Kettering Cancer Center, New York, NY; MSKCC, New York, NY; Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Teclistamab (Tec) is the first CD3 x BCMA bispecific antibody (BsAb) receiving accelerated FDA approval for treatment of relapsed or refractory multiple myeloma (RRMM) in patients who have received ≥4 prior lines of therapy, including a PI, IMiD and an anti-CD38 monoclonal antibody. The approval was based on the results of the MajesTec-1 study (Usmani S et al Lancet 2021, Moreau P et al NEJM 2022), demonstrating a 63% overall response rate in a heavily pretreated RRMM population. Patients with prior exposure to anti-BCMA therapies, such as BCMA targeted ADCs, CAR T-cell products and BsAbs were excluded from this study. Herein, we present our institutional experience with commercial Tec for RRMM including patients with prior BCMA and GPRC5D directed therapies. **Methods:** We have performed an IRB-approved, retrospective analysis of clinical outcomes of all patients who have received commercial Tec at MSKCC since its approval on 10/26/2022 using the PCD research database. Descriptive analyses were performed for baseline characteristics. The IMWG criteria (Kumar S et al, Lancet Oncol 2016) were used to assess response and define prior therapy refractoriness. Immune profile was assessed via high-dimensional flow cytometry using lineage, exhaustion, and activation markers. Serum soluble BCMA levels were assessed using an immunoassay. **Results:** As of 2/4/2023, 24 patients have received commercial Tec and 15 are response evaluable with ≥1 month of clinical follow-up. Median age was 66 (51-80), prior lines of therapy was 7 (4-13), time from diagnosis was 7 years (1.5-16), 53% had high-risk cytogenetics, and 40% had EMD. All patients were triple class refractory and 80% were penta-drug refractory. Ten had prior anti-BCMA therapy (7 Belamaf, 8 BCMA CART, 1 BCMA BsAb, 5 with ≥2 anti-BCMA therapies). With a median follow-up time of 1.3 months, the median time to response was 16 days. ORR was 60% (9/15) in all patients and 50% (5/10) in the prior anti-BCMA therapy group. Pts with ≥2 anti-BCMA therapies had a 40% (2/5) response rate to Tec. Clinical benefit rate (CBR) in all patients was 73% (11/15). None of the responders have progressed at this short follow-up time. Cytokine release syndrome was observed in 7/15 patients (41%) during step-up dosing (5/7 with g1 and 2/7 with g2 CRS) and CBR was 100% in patients with CRS (71% ORR). Other notable toxicities include 2 patients with grade 2 neurotoxicity that improved with therapy discontinuation. **Conclusions:** To our knowledge, this is the first report of commercial Tec in RRMM. Tec remains effective in RRMM despite prior exposure to anti-BCMA therapies, though exposure to multiple prior anti-BCMA therapies may be predictive of diminished efficacy. Clinical data on additional patients will be presented at the meeting. Ongoing translational investigations on soluble BCMA levels and patient-specific immune phenotype will also be presented at the meeting. Research Sponsor: MSKCC.

8050 **Poster Session**

Safety and clinical activity of belantamab mafodotin plus lenalidomide and dexamethasone in transplant ineligible patients with newly diagnosed multiple myeloma: The phase 1/2, prospective, open-label, BelaRd study.

Evangelos Terpos, Maria Gavriatopoulou, Ioannis Ntanasis-Stathopoulos, Panagiotis Malandrakis, Despina Fotiou, Magdalini Migkou, Foteini Theodorakakou, Vasiliki Spiliopoulou, Rodanthi Syrigou, Evangelos Eleutherakis Papaiakovou, Stavros Gkolfinopoulos, Kyriaki Manousou, Efstathios Kastritis, Meletios A. Dimopoulos; Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Attica, Greece; Health Data Specialists, Dublin, Ireland, Dublin, Ireland; Alexandra Hospital, Athens, Greece

Background: We present the updated safety and efficacy of upfront belantamab mafodotin (belamaf) plus lenalidomide and dexamethasone (Rd) in transplant ineligible (TI) pts with newly diagnosed multiple myeloma (NDMM). **Methods:** The ongoing, prospective, open-label, phase 1/2 BelaRd study (NCT04808037) aims to enroll 66 pts with TI NDMM, with ECOG PS < 2 and adequate organ function. In Part 1, 36 pts are randomized (1:1:1) to receive belamaf 2.5, 1.9, or 1.4 mg/kg Q8W plus Rd. Eye exams include Snellen best corrected visual acuity (BCVA) and corneal exam (slit lamp examination). Ocular adverse evets (OAEs) are classified by CTCAE v5.0. This descriptive analysis presents the updated safety and efficacy findings for all Part 1 pts (cutoff date 15/12/22). **Results:** The analysis included 36 pts [median age: 73 years (64–86); male: 19 (53%)], of whom 31 (86%) were still on treatment and 5 (14%) had discontinued [4 pts due to belamaf-unrelated adverse events (AEs); 1 pt withdrew consent]. At baseline, 32 (89%) pts were intermediate fit as per International Myeloma Working Group frailty score and 34 (94%) had ECOG PS$\leq$1. Median follow up was 15 months (3–23); median belamaf administrations and number of cycles reached were 6 (2–10) and 15 (3–22). Thirty-four (94%) pts experienced $\geq$1 grade (Gr) $\geq$3 treatment-emergent AEs (TEAEs). Most common ($\geq$ 10% of pts) non ocular Gr $\geq$3 TEAEs were fatigue (21 pts, 58%), rash (6 pts, 17%), diarrhoea (5 pts, 14%) and COVID-19 infection (4 pts, 11%); no Gr $\geq$3 thrombocytopenias and any Gr infusion-related reactions were reported. Regarding pts visual acuity, out of a total of 499 BCVA assessments, 164 (33%) were Gr 2 and 54 (11%) were Gr 3. Notably, a meaningful BCVA decline (worse than 20/50 in better seeing eye) was observed in 38 (8%) assessments, with a median time to resolution of 1 month. Regarding clinically relevant Gr$\geq$2 ocular symptoms, blurred vision, dry eye and visual impairment were observed in 38 (8%), 96 (20%) and 98 (20%) assessments, with a median time to resolution of 2, 3 and 2 months. Slit lamp examinations by the ophthalmologist (N = 501) revealed a Gr 2 keratopathy in 55 (11%) assessments and Gr 4 keratopathy in 2 ($<$ 1%) assessments, with a median time to resolution of 4 months. Overall response rate [partial response (PR) or better] was 100.0% [36 pts; stringent complete response: 14% (5 pts); complete response: 19% (7 pts); very good partial response: 47% (17 pts); PR: 19% (7 pts)]. Median time to first response was 1 month. **Conclusions:** Part 1 of the BelaRd study showed that in TI pts with NDMM, the safety profile of belamaf plus Rd was manageable and a meaningful BCVA decline was noted in a minority ($<$ 10%) of assessments which resolved quickly (1 month). The combination induced rapid and deep responses, with all pts achieving $\geq$PR and first response observed at a median of 1 month. Clinical trial information: NCT04808037. Research Sponsor: GSK.

8051 **Poster Session**

Outcomes of patients with primary refractory multiple myeloma in the era of triplet and quadruplet induction therapy.

Charalampos Charalampous, Utkarsh Goel, Prashant Kapoor, Moritz Binder, Francis Buadi, Joselle Cook, David Dingli, Angela Dispenzieri, Morie A. Gertz, Wilson I. Gonsalves, Suzanne R. Hayman, Miriam A. Hobbs, Yi Lisa Hwa, Taxiarchis Kourelis, Martha Lacy, Nelson Leung, Yi Lin, Rahma M. Warsame, S. Vincent Rajkumar, Shaji Kumar; Mayo Clinic, Rochester, MN; Division of Hematology, Mayo Clinic, Rochester, MN; Mayo Clinic Department of Pediatric and Adolescent Medicine, Rochester, MN; Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

Background: Patients with multiple myeloma (MM) that do not respond to initial therapy have worse outcomes compared to primary responders, and effective treatments are lacking in this population. However, the outcomes of primary refractory disease in the modern treatment era have not been studied. **Methods:** From 2007-2019, we reviewed MM patients treated with triplet/quadruplet therapy in our institution to assess the incidence of primary refractory disease and the impact of salvage therapies in this population. Primary refractory disease was defined as either progressive disease or stable disease at 4-6 cycles. The Kaplan-Meier estimates were used for survival probabilities. PFS and OS were calculated from MM diagnosis to progression, escalation/change of treatment, or death, respectively. For the primary refractory group, the second PFS and second OS were measured from the start of second-line therapy. The Cox regression model was used for multivariable analysis with the following variables (age, ISS, induction therapy, FISH, and bone marrow plasma cells at diagnosis). **Results:** We identified 1127 patients, of which 1086 were evaluated for hematologic response after 4-6 cycles. Of these, 93.3% (1013) had evidence of response, while 6.7% (73) had primary refractory disease. With a median OS of 50.7 months, patients with primary refractory disease had an increased risk for shorter survival in univariable and multivariable analysis (HR: 3.6, 95% CI = 2.61 – 4.96, HR = 3.89, 95% CI = 2.68 – 5.65, respectively). In subgroup analysis of primary refractory patients, the median second PFS and second OS from the first relapse were 11.9 months (95% CI: 8.7 – 17.3 months) and 43.4 (95% CI: 31.4– 75.9 months), respectively. Patients that received 2nd line ASCT had increased second PFS (20.9 vs. 8.1 months, respectively, $p < 0.01$) and second OS (74.7 vs. 31.3 months, respectively, $p = 0.02$) compared to patients that did not. Patients that took daratumumab as the second line did not have any significant survival differences compared to those who did not, p = NS. **Conclusions:** We conclude that early progression remains a significant factor for shorter OS in the current era, and salvage ASCT could be the most beneficial option for this population. Research Sponsor: None.

	No salvage ASCT (N = 33)	Salvage ASCT (N = 34)	Total (N = 67)	p-value
Age (years)				0.051
Median (range)	67.2 (27.1 - 85.5)	60.9 (30.8 -71.6)	63.2 (27 - 85.5)	
ISS				0.778
1	9 (32.1%)	7 (25.9%)	16 (29.1%)	
2	8 (28.6%)	10 (37.0%)	18 (32.7%)	
3	11 (39.3%)	10 (37.0%)	21 (38.2%)	
R-ISS				0.666
1	7 (28.0%)	4 (17.4%)	11 (22.9%)	
2	12 (48.0%)	12 (52.2%)	24 (50.0%)	
3	6 (24.0%)	7 (30.4%)	13 (27.1%)	
Induction regimen				
VRd	32 (97.0%)	29 (85.3%)	61 (91.0%)	
KRd	0 (0.0%)	4 (11.8%)	4 (6.0%)	
Quadruplets	1 (3.0%)	1 (2.9%)	2 (3.0%)	
FISH (mSMART)				0.688
Standard-Risk	12 (42.9%)	14 (42.4%)	26 (42.6%)	
High-Risk	13 (46.4%)	13 (39.4%)	26 (42.6%)	
Double-Hit	3 (10.7%)	6 (18.2%)	9 (14.8%)	

8052 **Poster Session**

Determinants of overall survival of young adults with multiple myeloma: A National Cancer Database (NCDB) analysis of years 2004-2017.

Chakra Pani Chaulagain, Ludovic Saba, Hong Liang, Barbara Dominguez, Chieh Lin Fu; Cleveland Clinic Florida, Weston, FL

Background: There is paucity of real-world data on the outcomes of younger patients with multiple myeloma (MM). In this IRB approved retrospective analysis, the NCDB was used to evaluate the determinants of overall survival (OS) of young adults ≤ 50 years with MM who were treated at commission on cancer (CoC) accredited facilities across the USA. **Methods:** Using the NCDB, we identified N = 16,792 patients ≤ 50 years old diagnosed and treated for MM from 2004 to 2017. Multivariable cox regression analysis with backward elimination was utilized to identify the independent survival factors, using significance level of $p < 0.05$. Kaplan-Meier survival curves were generated and SAS version 9.4 was used to analyze the data. **Results:** Overall median survival time was 119 months; while survival rates of 1, 3, and 5-year were 90.6%, 78.0%, and 67.8%, respectively. Multivariable cox regression analysis with backward elimination method revealed that there were 13 significant independent survival factors: age, sex, race, ethnicity, Charlson-Deyo score, insurance status, facility type, median income, education level, distance to facility, year of diagnosis, hematopoietic stem-cell transplantation (HSCT), and treatment-regimen. Male patients were more likely to die compared to female patients (HR = 1.22, $p < 0.0001$). Black patients were predicted to have less death events compared to White patients (HR = 0.91, $p = 0.004$). In addition to that, Hispanic patients were more likely to die compared to non-Hispanics (HR = 1.2, $p = 0.0006$). Subjects who were treated in non-academic facilities were more likely to die compared to the ones who received care in academic centers (HR = 1.2, $p < 0.0001$). Moreover, patients with Medicare (HR = 1.65, $p < 0.0001$), Medicaid (HR = 1.49, $p < 0.0001$), and no insurance (HR = 1.63, $p < 0.0001$) had higher chance of death compared to those with private insurance. Patients with lower income < $38,000 were more likely to die compared to income ≥ $63,000 (HR = 1.19, $p = 0.0007$). Only 6.8% of patients underwent HSCT and 93.2% did not. Patients undergoing HSCT had worse OS compared to those treated without HSCT (HR = 0.36, $p < 0.0001$). Detailed analysis will be presented. **Conclusions:** In this large cohort of real-world data analysis of very young MM patients, we found that White and Hispanic patients age ≤ 50 years had significantly inferior survival compared to Black and non-Hispanic patients. Patients with lower income, lower education level, non-private insurance, and those without access to academic centers for MM care had worse survival outcomes. The findings can be useful for designing prospective studies addressing disparity and equitable access to MM care. Despite being a pivotal part of MM therapy, HSCT utilization in the real-world setting is minimal. The barriers to HSCT utilization and the reason why it is inferior to no-HSCT in real-world setting need to be identified and addressed.
Research Sponsor: Maroone Cancer Center, Cleveland Clinic Florida.

8054 **Poster Session**

Ixazomib and daratumumab without dexamethasone (I-Dara) in elderly frail patients with RRMM: Results of the multicenter phase 2 study (IFM 2018-02) of the Intergroupe Francophone du Myélome (IFM).

Cyrille Touzeau, Xavier P Leleu, Clara Mariette, Salomon Manier, Sabine Brechignac, Laure Vincent, Benjamin Hebraud, Olivier Decaux, Samantha Schulmann, Caroline Lenoir, Pascal Godmer, Agathe Farge, Laure Peyro Saint Paul, Jean-Jacques Parienti, Margaret Macro; University Hospital of Nantes, France, Nantes, France; Centre Hospitalier Universitaire de Poitiers, Poitiers, France; CHU Grenoble, Grenoble, France; Lille University Hospital, Lille, France; APHP Hôpital Avicenne, Bobigny, France; Montpellier University Hospital, Montpellier, France; Cancer University Institute of Toulouse - Oncopole, Toulouse, France; University Hospital, Rennes, France; CHU Nancy, Nancy, France; Polyclinique Bordeaux Nord Nord Acquitaine, Bordeaux, France; GHBA, Vannes, France; IHBN, CHU, Caen, France; CHU, Caen, France; CHU Caen, Caen, France; University of Caen Hospital Centre, Caen, France

Background: Frailty is associated with inferior outcome in older myeloma patients, especially in the relapse setting.[1,2] This adverse prognosis is mainly related to a high discontinuation rate for treatment (Tx) related adverse events (AE). Dexamethasone is responsible of a high rate of infections and metabolic AE. We present here the updated results from the phase 2 study I-Dara evaluating efficacy and tolerability of Ixazomib-Daratumumab without Dexamethasone in elderly frail patients with relapsed myeloma (RRMM) (NCT03757221). **Methods:** Ixa-Dara naïve RRMM patients received oral Ixazomib (4 mg: days 1, 8, 15), IV Daratumumab (16 mg/kg; days 1, 8, 15, 22, cycles 1-2; days 1, 15, cycles 3-6; days 1, cycles 7+) and IV Methylprednisolone before Daratumumab (100 mg at day 1, 8, cycle 1 and then 60 mg). They were enrolled after 1 or 2 prior therapy if their frailty score was ≥ 2 by IMWG score. The primary endpoint was ≥ very good partial response rate (VGPR) at one year. Secondary endpoints included ORR, PFS, OS & toxicity according to NCI-CTCAE version 5. **Results:** Sixty-three patients were screened and 55 enrolled between 03/2018 and 09/2021. Patient were at first (n = 36) or second relapse (n = 19). Thirty-five patients (64%) were previously exposed to bortezomib, 37 (67%) were previously exposed to lenalidomide (Len) and 23 (42 %) were refractory to Len. Median age was 82 (72-93). All patients had a frailty score ≥2 and 13 (24 %) had a 3 or 4 frailty score. In 41 patients ISS at diagnosis was stage I (n = 11), II (n = 18) or III (n = 12). Seventeen (36%) patients harbored high-risk (HR) cytogenetic, including t(4;14) (n = 8) or del17p (n = 10). The median duration of Tx (DOT) in 14 pts with ongoing Tx was 22 mos [min-max: 16-40] at data cutoff (January, 19)]. The median DOT in 41 pts who stopped Tx was 10 mos [min-max: 0-31]: 28 had progressive disease (PD). Fourteen patients died during the study: Daratumumab-related bronchospasm (D1C1); Ixazomib-related overdose (C2), sepsis (n = 3), pneumonia (n = 2), PD (n = 7). Regarding toxicity, 31 pts had a ≥grade 3 AE (55%). The most common grade 3-4 AE were thrombocytopenia (n = 10), other cytopenias (n = 5), anemia (n = 3), infection (n = 6), gastrointestinal disorders (n = 5) and hypertension (n = 3). The ≥VGPR rate is 32 % @ 1 year (34 % overall) with an ORR of 70% @ 1 year (74 % overall). In Len refractory patients the ≥VGPR rate is 40% @ 1 y and the ORR 70 %, in HR patients the ≥VGPR rate is 60 % and ORR 80%. With a median follow-up of 23.0 mos median PFS is 18.5 mos and median OS NR (75% OS estimated at 27.9 mos). **Conclusions:** In this elderly frail population Ixa-Dara is a feasible combination with favorable efficacy profile even in Len refractory and HR cytogenetic patients. Early toxicity remains a concern in this population eventhough more manageable with Dara SC. Late benefit is consistent with one third of patients still on treatment. Clinical trial information: NCT03757221. Research Sponsor: Takeda and Janssen.

8055 **Poster Session**

Lenalidomide-based monotherapy versus augmented therapy for maintenance in standard risk multiple myeloma patients with no complete response post autologous hematopoietic cell transplantation.

Hussein Awada, Adel Hajj Ali, Chadi Tabaja, Jack Khouri, Faiz Anwer; Department of Translational Hematology and Oncology Research, Lerner Research Institute, Cleveland Clinic, Cleveland, OH; Heart Vascular Thoracic Institute, Cleveland Clinic, Cleveland, OH; Cleveland Clinic Taussig Cancer Center, Cleveland, OH; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: Standard risk (SR) multiple myeloma (MM) is typically characterized by the absence of poor prognostic cytogenetic aberrations, and better outcomes. However, outcomes in SR MM remain far from homogeneous, especially in patients undergoing autologous hematopoietic cell transplant (AHCT). While many patients do well initially, relapse is inevitable. Here, we studied the role of lenalidomide (R) maintenance therapy in determining outcomes in SR MM with no complete response (non-CR) post-AHCT. **Methods:** We retrospectively reviewed all MM patients who underwent AHCT at the Cleveland Clinic between January 1, 2011 and January 15, 2021. Electronic medical charts were accessed to retrieve data on demographic characteristics, comorbidities, International Scoring System (ISS) staging, cytogenetic risk categorization, serum and bone marrow studies, as well as maintenance therapy. SR MM was considered in patients who did not have t(4;14), t(14;16), t(14;20), del(17p), or gain(1q). Remission status was determined by serum studies at 3 months post-AHCT. The primary endpoint was median time to either progression or death, reported as time to event (TTE) determined by Kaplan Meier analysis. **Results:** A total of 517 patients were reviewed, of whom 279 were determined as SR MM. Further stratification yielded 100 non-CR SR patients on lenalidomide-based maintenance, of whom 87 were on R monotherapy and 13 on R combination. Comparison between the R-monotherapy and combination groups showed similar age at AHCT (60.5 vs 56 years, P=0.07), time to transplant (23.5 vs 30.8%, P=0.7), albumin levels ($<$3.5 g/dL 25 vs 25%, P=1), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score ($\geq$3 43.5 vs 30.8%, P=0.5), Male preponderance (58.8 vs 69.2%, P=0.6), ethnicity (White 82.4 vs 76.9%, P=0.7), ISS stages (I 41 vs 45.5%, II 41 vs 36.4%, III 17.9 vs 18.2%, P=0.9), pre-AHCT lines of therapy ($\geq$2 31.8 vs 38.5%, P=0.8), and pre-AHCT bone marrow plasma cells ($\geq$10%:9.5 vs 7.7%, P=1), respectively. The only significant difference between the two groups was in the MM immunoglobulin subtype (IgG 80 vs 50%, P=0.02). Kaplan-Meier analysis for median TTE revealed that the R monotherapy group had a significantly shorter median TTE at 38.1 months versus 68.6 months (P=0.03) for the R combination group. **Conclusions:** SR MM patients who do not achieve a CR post-AHCT have better outcomes with R-combination rather than monotherapy. Research Sponsor: None.

8056 **Poster Session**

Three-dimensional telomere profiling to predict risk of progression in smoldering multiple myeloma.

Shaji Kumar, S. Vincent Rajkumar, Dragan Jevremovic, Robert A. Kyle, Sabine Mai, Sherif Louis; Division of Hematology, Mayo Clinic, Rochester, MN; Division of Hematopathology, Mayo Clinic, Rochester, MN; University of Manitoba, Winnipeg, MB, Canada; Telo Genomics, Toronto, ON, Canada

Background: Multiple myeloma (MM) is preceded by monoclonal gammopathy of undetermined significance (MGUS). A transitional stage of smoldering multiple myeloma (SMM) can be identified between MGUS and MM. While MGUS carries a steady risk of progression of 1% per year, SMM is more heterogenous with nearly 40% of patients progressing in the first 5 years, 15% in the next 5 years, reaching the same low risk as MGUS after 10 years. SMM with its high risk of progression in the initial years after diagnosis presents a viable opportunity for early intervention. For implementing early intervention, the ability to identify SMM patients at the highest risk of progression is critical. This has led to the development of several risk stratification systems. Using these systems high risk SMM patients studied in phase 3 trials demonstrated delayed progression to MM and improved overall survival with early initiation of therapy. However, these approaches showed limited specificity exposing patients at lower risk of progression to therapy. To date, identifying high risk SMM patients and confirming disease stability in low risk SMM patients remain an important clinical need. Genomic instability has been shown to be a sensitive indicator of disease progression in cancer. Telomere dysfunction is an early event in genomic instability. The 3-dimensional spatial profiling of telomeres using TeloView technology allows for quantification of telomere dysfunction, and was shown to be instrumental in risk stratification of cancer patients generally, but particularly in selected hematological malignancies. Importantly, in a previous SMM proof-of-concept study telomeric parameters measured by TeloView technology was found to be significantly different between SMM patients who progressed to active MM within 2 years and those who remained stable for over 5 years. **Methods:** We analyzed a total of 162 SMM patients using TeloView technology. 88 patients were employed as training dataset in Receiver Operating Curve (ROC) modeling to develop a scoring model that stratifies individual SMM patients based on risk of progression to full stage MM. An additional cohort of 74 SMM patients was used for blind validation of the developed scoring model. **Results:** We report area-under-the-curve (AUC) in the ROC analysis of 0.8 (accuracy 80%) achieved by the scoring model developed using the training dataset. Furthermore, the independent blind validation achieved positive predictive value of 83% and negative predictive value of 71%, with sensitivity and specificity of 80% and 76% respectively. **Conclusions:** The result of this study supports presenting TeloView as an accurate prognostic biomarker which appears able to stratify SMM patients into their respective risk groups with high sensitivity and specificity. This will potentially allow for evidence-based treatment decisions for high risk SMM patients and confident monitoring of stable patients. Research Sponsor: Telo Genomics Corp.

8057 **Poster Session**

A phase 2 evaluation of daratumumab-based induction therapy in patients with multiple myeloma with severe renal insufficiency.

R. Donald Harvey, Joseph Franz, Nisha S Joseph, Jonathan L. Kaufman, Elise Hitron, Hannah Collins, Catherine Braga, Kathryn T. Maples, Craig C. Hofmeister, Madhav V. Dhodapkar, Sagar Lonial, Ajay K. Nooka; Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA; UPMC Cancer Center, Pittsburgh, PA; Winship Cancer Institute of Emory University, Atlanta, GA

Background: Myeloma patients (pts) with renal insufficiency (RI) have inferior disease outcomes; up to 50% present with acute kidney injury (AKI). AKI results from light chain-induced cast nephropathy; physicochemical properties (self-association, aggregate formation) may determine severity. Daratumumab has extensive data in myeloma, reduces circulating light chains, preserves renal function in AL amyloidosis, and has non-renal clearance. We hypothesized early therapy with daratumumab and VRD normalize myeloma-induced AKI in a population rarely included in trials. **Methods:** We used a Simon's two-stage design in newly diagnosed pts with severe AKI (CrCl $<$30 mL/min) of 4 x 21-D cycles of daratumumab 16mg/kg IV QW x 3 (C1-3, C4D1 only), bortezomib 1.3 mg/m^2 SQ D1, 4, 8, and 11, and dexamethasone 40mg (reduced to 20mg at C2 for $\geq$75 yrs.) D1-4 (C1 only, D1 only C2-4), 8, and 15, with add-on lenalidomide at C2 (25mg if CrCl $\geq$30 mL/min). Standard antiviral, antithrombotic, premedications were used. Eligibility criteria were broad (CrCl $<$30 mL/min, PS 0-2, ANC$>$1000/mm^3, Hgb$>$7 g/dL, plt$>$75,000/mm^3) with liberal dose reductions for generalizability. Primary objective: determine proportion with renal recovery (CrCl $\geq$50 mL/min) after 2 cycles; secondary objectives: best response (IMWG), renal function at end of treatment, dose density/tolerability, adverse events (AE), renal function change by estimates [Cockcroft-Gault (C-G), MDRD, 24-hour urine, CKD-EPI], and daratumumab PK. If $\geq$7 responses seen in the first 11 pts, 14 more would be accrued. These data are the planned analysis of the initial cohort. **Results:** Thirteen pts enrolled: 8 male, 7 white/6 black, median age 69 yr (46-82), 11 treated/evaluable for the primary endpoint. Median baseline CrCl 13.8 mL/min (4.9-20.2), median serum creatinine (SCr) 4.92 mg/dL (3.53-9.93). One withdrew consent, 1 was inevaluable (rapid disease progression and death). Seven achieved CrCl of $\geq$50 mL/min (median C3D1 CrCl 61 mL/min, 22-151) after 2 cycles, all had SCr improvement at C3D1. Lenalidomide dose was 25 mg on C2D1 in 9/11 pts. Median (range) dose density (delivered/planned): daratumumab 100% (40-100), bortezomib 100% (25-100), dexamethasone 80% (67-100), lenalidomide 100% (0-100). The overall response rate was 100%, $\geq$VGPR rate 82%. Best responses were CR (3), VGPR (6), PR (2). Treatment-emergent grade $^3/_4$ hematologic AEs: anemia (90.9%), lymphopenia (81.8%), thrombocytopenia (36.4%), neutropenia (9.1%). **Conclusions:** Early, aggressive therapy with a daratumumab-based induction regimen in myeloma pts with severe AKI improves renal function, with the majority achieving CrCl $\geq$50 mL/min after 2 cycles; all responded. AEs seen were consistent with prior experience with the 4-drug regimen. Per protocol, 14 additional patients will be accrued in the second stage. Clinical trial information: NCT04352205. Research Sponsor: Janssen.

8058 **Poster Session**

Genomic landscape of multiple myeloma with extramedullary disease: Results from a large patient database.

Mateo Mejia Saldarriaga, David Jayabalan, Aubrie Sowa, Jorge Monge, Cara Rosenbaum, Roger Pearse, Ruben Niesvizky, Sajay Patel, Mark Bustoros; Weill Cornell Medicine, New York, NY; University College Dublin Medical School, Dublin, Ireland

Background: Extramedullary disease (EMD) is associated with poor outcomes and the biological mechanisms driving this phenotype are poorly understood. We used the CoMMpass registry data to explore the genomic characteristics of EMD. **Methods:** The CoMMpass study is a prospective, international registry of newly diagnosed MM. 1143 patients had clinical data. Patients were classified as EMD if they had EMD at any point. Genomic data from bone marrow (BM) samples at diagnosis (whole genome sequencing, whole exome sequencing (WES), and RNA sequencing (RNAseq)) were compared between EMD and non-EMD. A multivariable model was constructed based on univariable results. Differential expression (DEA) and gene set enrichment analysis (GSEA) were performed after normalization using Hallmark and MM transcriptomic subgroups. The top 24 most mutated genes in MM were selected. **Results:** The median overall survival (mOS) and progression free survival (PFS) was shorter for EMD. The presence of EMD, anemia at diagnosis, age >65 years at diagnosis, ISS stage, and use of ASCT at the first line were independently associated with worse mOS and PFS. EMD was associated with worse mOS (HR 1.7, 95% CI 1.3 - 2.2 p <0.01) and PFS (HR 1.5, 95% CI 1.23 - 1.8, p <0.01) in multivariable analysis and was not abrogated by ASCT, triplet induction or maintenance. Results did not vary when landmark analysis was used. *MYC* amplification, deletion 18q and 1q amplification were enriched in EMD cases. *TP53* mutations and *TP53* bi-allelic inactivation (mutation and deletion) were enriched in EMD (Table). DEA identified 1552 genes with increased and 3344 with decreased expression (2.7%, 5.4% of total genes respectively) in EMD when compared to non-EMD. On GSEA, EMD cases were enriched for the CD-1, PR, and CTA myeloma gene expression signatures, in addition to the Hallmark pathways MYC target, E2F targets, G2M checkpoint and unfolded protein response, while the adhesion molecules pathway and MM gene signatures LB, MS, and MF were downregulated in EMD. **Conclusions:** EMD cases were enriched for *TP53* mutations and bi-allelic *TP53* inactivation, both of which are prognostic. In addition, *MYC* amplification, 18q deletion and 1q gain were enriched in EMD which are novel CNA associated with EMD. EMD is also enriched for distinct molecular subgroup, including enrichment for CD-1, PR, and CTA signatures, the latter two are associated with poor outcomes, and the Hallmark pathways MYC, E2F and G2M checkpoints consistent with *MYC* amplification and PR molecular subgroup. WES and RNAseq of matching BM and EMD tissue samples from our institution is currently being performed. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	Status	EMD n=130	No EMD n=778	P value
Del 17p	Present	15 (11.9)	75 (10.0)	0.62
Gain 1q	Present	55 (43.7)	277 (36.9)	0.16
Amp 8q24 (*MYC*)	Present	35 (27.8)	116 (15.5	0.001
Del 18q	Present	29 (23.0)	106 (14.1)	0.015
***TP53* status and Deletion (%)**	Mutated	13 (9.6)	35 (4.4)	0.020
	CNA + Mutation	9 (7.3%)	21 (2.9%)	0.016

8059 **Poster Session**

Curability of multiple myeloma (MM) based on relative survival rate (RSR) in patients (pts) treated on earlier total therapy (TT) protocols.

Samer Al Hadidi, Obada Ehab Ababneh, Carolina D. Schinke, Sharmilan Thanendrarajan, Clyde Bailey, Maurizio Zangari, Guido Tricot, John D. Shaughnessy, Fenghuang Zhan, Jeffrey Sawyer, Frits van Rhee, Bart Barlogie; University of Arkansas for Medical Sciences, Little Rock, AR; Jordan University of Science and Technology, Irbid, Jordan; University of Arkansas for Medical Sciences Winthrop P. Rockefeller Institute, Little Rock, AZ; Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR; The University of Arkansas for Medical Sciences, Little Rock, AR

Background: Long term overall survival (OS) follow-up data in pts with MM treated on clinical trials is limited. TT approach uses all MM-active drugs upfront to target drug-resistant subclones during initial treatment to prevent later relapse. We report the longest follow up of MM trials (TT1 (NCT00580372), TT2 (NCT00083551), TT3a (NCT00081939) and TT3b (NCT00572169)) reported to date with RSRs to assess for curability. **Methods:** Pts treated on TT1, TT2, TT3a and TT3b were followed at the University of Arkansas for Medical Sciences after completion of therapy including multi-agent chemotherapy, high dose melphalan followed by tandem autologous stem cell transplantation (ASCT) and fixed duration maintenance therapy with introduction of thalidomide (thal) (TT2+thal vs TT2-thal), bortezomib (TT3a) and lenalidomide (TT3b). Expected survival rate was defined as probability of a population surviving from yr to yr. RSR was defined as ratio between observed survival of trials to expected survival in population adjusting for age and sex based on enrollment year. Data cut-off was October 10, 2022. **Results:** 1379 pts were enrolled (TT1:231, TT2:668, TT3a:303, TT3b:177) with median follow up duration of 16.6 years (yrs) (TT1:25 yrs, TT2:18.4 yrs, TT3a:16.2 yrs, TT3b:14.2 yrs). 10-yr PFS increased from 8.8% (TT1) to 15.5% (TT2-thal) to 25.1% (TT2+thal) to 32.9% (TT3a) to 42.4% (TT3b). Median OS improved over time (TT1:5.8 yrs, TT2:10.4 yrs, TT3a:11.9 yrs, TT3b:10.1 yrs). 15-yrs OS improved from 24.2% in TT1, 33% in TT2, 40% in TT3a and 37% in TT3b. 20-yr OS is 24.4% for pts treated on TT2 protocol. Outcomes were better for standard risk disease defined by low-risk gene expression profiling (GEP) with 20-yrs OS of 30% in TT2 and 15-yrs OS of 45% in TT3a. RSRs approach 1 at 10-15 yrs for TT1, but this occurs earlier, at 5-10 yrs, for TT2+Thal, TT3a and TT3b [Table]. No difference in RSR between TT3a and TT3b was noted. Relative excess risk (RER) showed an estimated 23%, 44% and 54% lower excess mortality when comparing TT2 (+ thal), TT2 (-thal) and TT3a with TT1, respectively. **Conclusions:** In the longest follow up duration of any MM clinical trial, a subset of MM pts are cured as evidenced by RSRs approaching 1. Approximately one third of pts treated on TT2 protocol and one-half pts treated on TT3a are alive at 20 year and 15 yrs from initial diagnosis, respectively. Incorporation of immunomodulatory drugs and proteasome inhibitors along with tandem ASCT resulted in cumulative improvement of OS as evidenced by lower RER of mortality. Clinical trial information: NCT00580372, NCT00083551, NCT00081939, NCT00572169. Research Sponsor: None.

RSRs.

No, of yrs from diagnosis	TT1	TT2+thal	TT2-thal	TT3a	TT3b
1	0.9214	0.9355	0.9347	0.9415	0.8965
5	0.9181	0.9602	0.9176	0.9751	0.9903
10	0.937	0.9507	0.9435	0.9582	0.9627
11	0.9316	0.9573	0.9205	0.9796	0.926
12	0.9252	0.9729	0.9744	0.9245	0.9478
13	0.9649	0.9605	0.9006	0.8959	0.9816
14	0.9637	0.9406	0.9266	0.9896	
15	0.9623	0.85	0.881	0.9744	
17	0.954	0.9371	0.9256		

8060 **Poster Session**

T cell exhaustion markers in multiple myeloma patients before and after physical activity intervention.

Janine Joseph, Michaela Hillengass, Joseph Tario, Kristopher Attwood, Adrienne Groman, Rikki A. Cannioto, Kirsten B. Moysich, Scott I Abrams, Jens Hillengass, Paul K Wallace; Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: There is substantial evidence that the immune system is dysfunctional in multiple myeloma (MM). Adaptive immune cells, such as $CD4^+$ and $CD8^+$ T cells, are ineffective at controlling MM progression, suggesting immunosuppression. Therefore, efforts to overcome immunosuppression are likely key to more effective tumor control. Recent evidence from pre-clinical models suggests that exercise represents a non-pharmaceutical means to reduce immune exhaustion, but few studies have examined the relationship between an exercise intervention and biomarkers of immune exhaustion in cancer patients, especially in MM – the objective of this study. **Methods:** In this feasibility trial, 24 MM patients participated in a six-month physical activity intervention. The strength training arm (n=12) performed twice weekly supervised resistance trainings. The walking arm (n=12) engaged in an unsupervised, home-based wearable activity tracker intervention. Subjects provided peripheral blood samples before the start and at the conclusion of the intervention. Comprehensive flow cytometry was utilized to assess the frequency of mononuclear cells of interest, including $CD4^+$ and $CD8^+$ T cells and subpopulations expressing the markers of exhaustion PD-1 and/or TIGIT, which are the two exhaustion markers with the highest expression in this study sample. Ratios of exhausted cells (expressing any, one, or both of those markers) to non-exhausted cells (expressing no exhaustion markers) were calculated. Changes in the median values of these ratios were compared using Wilcoxon signed-rank tests. **Results:** Results from the immune panels are shown for the combined sample (n=24). All ratios of exhausted to non-exhausted cells were lower at the end of the six-month intervention, compared to baseline. The ratio of $CD4^+$ $TIGIT^+$ to non-exhausted $CD4^+$ cells was significantly reduced, from 0.71 to 0.57 (p=0.04). The ratio of $CD8^+$ $PD\text{-}1^+$ to non-exhausted $CD8^+$ cells was borderline significantly reduced, from 1.81 to 1.48 (p=0.06). **Conclusions:** This pilot study suggests that physical activity induces changes in MM patients' immune systems, potentially rendering a less exhausted T cell state. Larger studies are warranted to examine how exercise alters activation vs exhaustion phenotypes within specific T cell subsets (naïve, central memory, effector memory, regulatory) and to elucidate the effects of strength-based vs aerobic exercise on T cell function. Research Sponsor: Roswell Park Comprehensive Cancer Center.

Ratio[1]	Baseline	Final	p-value
$CD4^+$ $PD\text{-}1^+$ or $TIGIT^+$	1.33 (1.18)	1.15 (1.04)	0.14
$CD4^+$ $PD\text{-}1^+$	1.18 (1.02)	0.92 (0.91)	0.17
$CD4^+$ $TIGIT^+$	**0.71 (0.58)**	**0.57 (0.39)**	**0.04**
$CD4^+$ $TIGIT^+$ and $PD\text{-}1^+$	0.48 (0.47)	0.41 (0.31)	0.10
$CD8^+$ $PD\text{-}1^+$ or $TIGIT^+$	2.36 (3.82)	2.13 (2.71)	0.09
$CD8^+$ $PD\text{-}1^+$	**1.81 (2.56)**	**1.48 (2.00)**	**0.06**
$CD8^+$ $TIGIT^+$	1.91 (3.36)	1.67 (2.67)	0.18
$CD8^+$ $TIGIT^+$ and $PD\text{-}1^+$	1.25 (2.16)	1.01 (1.38)	0.17

[1]Medians, interquartile ranges of ratios of exhausted CD4+ or CD8+ non-exhausted populations.

8061 **Poster Session**

Utilizing a two-step frailty assessment strategy in older adults with multiple myeloma (MM): A decision curve analysis.

Andrew Gahagan, Monica Sai Pasala, Clare Ubersax, Abigail Tucker, Christian Harmon, Susan Bal, Kelly Nicole Godby, Gayathri Ravi, Luciano J. Costa, Grant Richard Williams, Smith Giri; Department of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL; University of Alabama at Birmingham, Birmingham, AL; Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL; Department of Medicine, Division of Hematology/ Oncology, University of Alabama at Birmingham, Birmingham, AL

Background: The International Myeloma Working Group Frailty Index (IMWG-FI) has been shown to predict risk of toxicity and mortality in older adults with MM (Palumbo et al., *Blood* 2015). However, IMWG-FI requires a geriatric assessment (GA) that is not routinely done in clinical practice due to time constraints. A simplified frailty index (SFI; Facon et al., *Leukemia* 2020) has been proposed as an alternative using ECOG PS as a proxy to functional status. We previously reported a moderate concordance between these two frailty indices (Kappa statistic 0.50; Gahagan et al., *ASH* 2022). Here, we examined if SFI can be utilized as a screening tool to identify patients who would benefit from a formal GA and frailty assessment. We hypothesized that a two-step approach would minimize the need for unnecessary GAs, while saving time in clinical practice. **Methods:** For this analysis, we included patients $\geq$50yo with newly diagnosed (ND) or Relapsed/Refractory (RR)-MM at a single institution initiating a new treatment regimen (1^{st} to 6^{th} line) who are enrolled in a prospective registry (NCT05556928). All patients underwent a GA prior to a new line of therapy. ECOG PS and comorbidities were abstracted from medical records. We calculated IMWG-FI and SFI using published methods. Sensitivity, specificity along with their 95% CI were calculated for both SFI and IMWG-FI, using published SFI cutpoints. Lastly, we used decision curve analysis (DCA) as described by Vickers et al. to calculate the benefit of frailty screening using SFI for detection of non-frail patients and avoiding unnecessary GAs. We assumed that reasonable threshold probabilities were 0.25 and 0.33 respectively indicating that missing an unfit patient was 3 and 2 times worse than exposing a fit patient to an unnecessary GA (odds of 1:3 and 1:2 respectively). We quantified the net benefit (NB) of this two-step frailty assessment versus GA-for-all in terms of net reduction in unnecessary GAs. **Results:** A total of 146 adults with MM (49 ND-MM, 51 pre-transplant, and 46 RR-MM) starting a new line of therapy between 8/2020-1/2022 were included in this study. The median age was 62 (IQR 57-70) with 53% males and 36% blacks. The distribution by IWMG-FI was 43% fit, 32% intermediate-fit, and 25% frail. Using SFI, 32% of patients were frail. Using a cutpoint of $\geq$2, SFI as a screening tool had a sensitivity of 89.2% (95% CI 75-96%) and a specificity of 65% (95% CI 56% to 73%). DCA showed that selecting candidates for GA based on a two-step strategy (SFI followed by IMWG-FI) led to an absolute 40-45% reduction in the number of unnecessary GAs without missing any frail patients. **Conclusions:** Our results suggest that using a two-step frailty assessment strategy of SFI as a screening tool followed by confirmation with IMWG-FI reduces the need for unnecessary GAs by 40-45% and may be more suitable for integration in busy oncology practice. Research Sponsor: None.

8062 **Poster Session**

Presence of hyperdiploidy and history of tobacco use in African American patients with SMM.

Rujul H Parikh, Subir Goyal, Yuan Liu, Craig C. Hofmeister, Jonathan L. Kaufman, Leonard T. Heffner, Lawrence H Boise, Vikas Anand Gupta, Madhav V. Dhodapkar, Sagar Lonial, Ajay K. Nooka, Nisha S Joseph; Emory University, Winship Cancer Institute, Atlanta, GA; Emory University, Atlanta, GA; Emory University Hospital, Atlanta, GA; Winship Cancer Center of Emory University, Atlanta, GA

Background: Smoldering multiple myeloma (SMM) has a clinically variable course in progression to active myeloma (MM). Accurate risk stratification is essential in identifying which patients may benefit from early therapeutic intervention. Current models do not account for the potential impact of race on risk of progression to SMM. Here, we seek to identify independent risk factors for progression in African American (AA) versus white patients in a real-world single institutional database of SMM patients. **Methods:** We retrospectively identified 224 patients (pts) with untreated SMM from 2007 to 2021 treated at our institution. Patient demographics and disease characteristics were obtained from our IRB-approved myeloma database. TTP was defined as the time from diagnosis of SMM to diagnosis of active MM, estimated by Kaplan-Meier and compared by log-rank test. Univariate analyses were performed using Cox proportional hazard models for TTP. **Results:** A total of 224 pts (AA 35%, white 47%, other/unknown 17%) were identified with median age 62y (range 32-82). Median follow-up was 4.3y in Whites and 5y in AA pts. Notable characteristics include M/F 45%/54%, IgG/IgA/FLC 76%/17%/6%, 30% current/past smoker (median 15 pack-years), 12% alcohol use ($\geq$10 drinks/wk), 45% with BMI $>$ 30. Multiple cytogenetic abnormalities were defined as presence of $\geq$2 of the following: t(4;14), t(14;16), gain(1q21), del(1p), del(13), or del(17p). The median TTP (mTTP) was 6.8 [95% CI (3.7, 8.2)] years in whites and 5.6 [95% CI (4.6, 11.8)] years in AA. On univariate analysis, M-spike $>$ 1.5, involved K/L ratio $>$ 12, and bone marrow PC $>$ 20% were associated with increased risk of progression for both AA and whites (all $p < 0.05$). As expected, gain of 1q21 was associated with increased risk of progression for both groups, though more pronounced in AA (HR 2.94, $p = 0.025$) versus whites (HR 2.33, $p = 0.013$). Hyperdiploidy was associated with shorter mTTP in AA (HR 3.03, $p = 0.004$) compared to whites (HR 1.39, $p = 0.3$). Multiple cytogenetic abnormalities was associated with shorter mTTP in whites (HR 2.63, $p = 0.004$) but was not statistically significant in AA (HR 2.63, $p = 0.104$). Interestingly, tobacco use was associated with shorter mTTP in Blacks (HR 2.94, $p = 0.005$) but not in whites (HR 0.96, $p = 0.85$). **Conclusions:** Understanding the potential impact of racial background on progression from SMM to MM is critical in the appropriate management of all patients with SMM. In this database, with a large proportion of AA patients, hyperdiploidy and +1q portend high risk of progression in AA patients. Further study is needed to better classify these potential differences to ensure risk stratification models are applicable to all patients. Research Sponsor: None.

TPS8063 **Poster Session**

A first-in-human phase 1, multicenter, open-label study of CB-011, a next-generation CRISPR-genome edited allogeneic anti-BCMA immune-cloaked CAR-T cell therapy, in patients with relapsed/refractory multiple myeloma (CAMMOUFLAGE trial).

Jesus G. Berdeja, Thomas G. Martin, Adriana Rossi, James H. Essell, David Samuel DiCapua Siegel, Sham Mailankody, Neeraj Saini, Houston Holmes, Binod Dhakal, Cristina J. Gasparetto, Samir S. Parekh, Socorro Portella, Guy Ledergor, Ashley Hammad, Franco Davi, Justin Skoble, Elizabeth Garner, Steven Brian Kanner, Syed Rizvi, Sundar Jagannath; Sarah Cannon Research Institute, Nashville, TN; Department of Hematology, University of California San Francisco, San Francisco, CA; Icahn School of Medicine, Mount Sinai, New York, NY; Onc/Hem Care Inc, Cincinnati, OH; Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ; Memorial Sloan Kettering Cancer Center, New York, NY; University of Texas at MD Anderson Cancer Center, Houston, TX; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Medical College of Wisconsin, Milwaukee, WI; Department of Medicine, Duke University Cancer Institute, Durham, NC; Icahn School of Medicine at Mount Sinai, New York, NY; Caribou Biosciences, Berkeley, CA

Background: Autologous CAR-T cell therapies have shown significant benefit in the treatment of adults with relapsed/refractory multiple myeloma (r/r MM). However, these CAR-T cell therapies may have inherent challenges, including functional deficiencies in the patient's T cells, that could yield an inconsistent or impaired product, as well as require extended time and complexity in manufacturing, thereby limiting patient access and potentially requiring bridging therapy. CB-011 is an allogeneic, off-the-shelf anti-BCMA CAR-T cell therapy derived from healthy donor T cells. A next-generation CRISPR-Cas12a genome-editing technology using CRISPR hybrid RNA-DNA (chRDNA) guides, developed at Caribou to significantly reduce off-target editing, was implemented to generate 4 genome edits in the manufacture of CB-011: (i) the *TRAC* gene was knocked out to eliminate T cell receptor (TCR) expression and prevent graft versus host disease (GvHD), (ii) the BCMA-specific CAR was site-specifically inserted into the genome at the *TRAC* locus to eliminate random integration and serves to target the tumor antigen, (iii) the *B2M* gene was knocked out to eliminate expression of HLA class I molecules to mitigate host T cell cytotoxicity, and (iv) a B2M-HLA-E fusion transgene was site-specifically inserted into the genome at the *B2M* locus to overcome host NK cell-mediated killing following recognition of "missing self." This immune cloaking strategy has the potential to allow persistent antitumor activity of the CAR-T cells in the context of antigen engagement. Significant preclinical efficacy in vitro and in vivo supports the clinical evaluation of CB-011. **Methods:** CB-011 is being evaluated in a multicenter, Phase 1 clinical trial in patients with r/r MM. A 3+3 dose escalation design followed by expansion at the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) is being utilized. Primary objectives are to determine the safety and tolerability of CB-011, and the recommended Phase 2 dose (RP2D). Additional key objectives include preliminary antitumor activity and pharmacokinetics (PK). After concurrently receiving lymphodepletion therapy with cyclophosphamide (300 mg/m^2/d) and fludarabine (30 mg/m^2/d) for 3 days, patients receive a single dose infusion of CB-011 and are followed for safety and efficacy. Antitumor activity and disease response are measured by International Myeloma Working Group criteria. The CaMMouflage Phase 1 trial is actively enrolling patients and additional information is available on clinicaltrials.gov (NCT05722418). Clinical trial information: NCT05722418. Research Sponsor: Caribou Biosciences.

TPS8064 **Poster Session**

CAMMA 2: A phase I/II trial evaluating the efficacy and safety of cevostamab in patients with relapsed/refractory multiple myeloma (RRMM) who have triple-class refractory disease and have received a prior anti-B-cell maturation antigen (BCMA) agent.

Shaji Kumar, Carlos R. Bachier, Michele Cavo, Paolo Corradini, Michel Delforge, Wojt Janowski, Alexander M. Lesokhin, Roberto Mina, Laura Paris, Laura Rosiñol, Hang Quach, Grant R. Goodman, Rin Nakamura, Divya Samineni, Vallari Shah, Elisabeth Wassner Fritsch, Jesus G. Berdeja; Mayo Clinic, Rochester, MN; Sarah Cannon Transplant and Cellular Therapy, San Antonio, TX; Università di Bologna, Bologna, Italy; Università degli Studi di Milano Statale, Milan, Italy; Universitair Ziekenhuis (UZ) Leuven, Leuven, Belgium; Calvary Mater Newcastle, Waratah, NSW, Australia; Memorial Sloan Kettering Cancer Center, New York, NY; Università di Torino and Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, VC, Australia; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background: Multiple myeloma (MM) remains an incurable disease. Combinations of established agents, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 antibodies, are used in all lines of therapy, but re-exposure to previously received classes of therapy is associated with decreasing response rates and duration of response (Moreau et al. 2021). BCMA-targeted agents have recently been approved for the treatment of patients with RRMM whose disease has been exposed or become refractory to PIs, IMIDs and anti-CD38 antibodies (triple-class exposed or refractory MM). Although effective, the majority of patients who respond to anti-BCMA agents eventually relapse. Proven salvage therapies for these patients are currently lacking and represent a new unmet medical need. Cevostamab is an immunoglobulin G1-based T-cell-engaging bispecific antibody that targets Fc receptor-homolog 5 (FcRH5) on myeloma cells and CD3 on T cells. Dual binding results in T-cell activation and potent killing of MM cells. In an ongoing Phase I study (GO39775; NCT03275103), cevostamab monotherapy showed promising activity in heavily pre-treated patients with RRMM, including those with prior exposure to anti-BCMA agents (Trudel et al. 2021). **Methods:** CAMMA 2 (CO43476; NCT05535244) is an open-label, multicenter Phase I/II trial evaluating cevostamab monotherapy in patients with RRMM who are triple-class refractory and have previously received an anti-BCMA agent. Prior anti-BCMA antibody-drug conjugates or chimeric antigen receptor (CAR) T cells are permitted in Cohorts A1 and B1, while prior anti-BCMA bispecific antibodies are allowed in Cohorts A2 and B2. In A1 and A2, cevostamab is administered by intravenous infusion and is initiated with step dosing (0.3mg on Cycle [C] 1 Day [D] 1 and 3.3mg on C1D2, D3, or D4 depending on the emergence and resolution of cytokine release syndrome [CRS] after the initial administration), with the target dose of 160mg given on C1D8 and on D1 of each subsequent 21-day cycle. Patients are hospitalized for the C1 administrations only and treatment is continued until disease progression or unacceptable toxicity occurs. CRS is managed per protocol based on the clinical presentation and may involve corticosteroid and tocilizumab treatment. Primary objectives are evaluation of efficacy (primary endpoint: objective response rate by investigator assessment using IMWG criteria) and safety. Secondary objectives include assessment of quality of life, pharmacokinetics, pharmacodynamics, and immunogenicity. Cohorts B1 and B2 will evaluate the efficacy and safety of cevostamab at the recommended Phase II dose in this setting. As of February 2023, enrolment into Cohorts A1 and A2 is ongoing. Clinical trial information: NCT05535244. Research Sponsor: CAMMA 2 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Helen Cathro, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

TPS8065 **Poster Session**

MagnetisMM-6: An open-label, multicenter, randomized phase 3 study of elranatamab + daratumumab + lenalidomide (EDR) versus daratumumab + lenalidomide + dexamethasone (DRd) in transplant ineligible (TI) patients with newly diagnosed multiple myeloma (NDMM).

Sebastian Grosicki, Su-Peng Yeh, Jeffrey S.Y. Huang, Ja Min Byun, Christine DiRienzo, Andrea Viqueira; Department of Hematology and Cancer Prevention, Medical University of Silesia, Katowice, Poland; China Medical University Hospital, Taichung, Taiwan; Division of Hematology, National Taiwan University Hospital, Taipei, Taiwan; Seoul National University Hospital, Seoul, South Korea; Pfizer Inc., New York, NY; Pfizer SLU, Madrid, Spain

Background: Elranatamab, a humanized bispecific antibody targeting B cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells, has shown promising efficacy and acceptable safety in clinical studies, as monotherapy (MagnetisMM-3, NCT04649359) and in combination with daratumumab (MagnetisMM-5, NCT05020236), in the treatment of patients with relapsed/refractory multiple myeloma (RRMM). Despite recent advances in the treatment of NDMM, MM remains incurable and more effective treatment options are needed. The aim of the MagnetisMM-6 study (NCT05623020) is to evaluate EDR versus DRd for TI patients with NDMM. **Methods:** MagnetisMM-6 is an ongoing, open-label, 2-arm, multicenter, randomized phase 3 study estimated to enroll ~646 patients. There are 2 parts: Part 1 evaluates the safety and recommended phase 3 dose (RP3D) of EDR: Part 2 evaluates the efficacy and safety of EDR at RP3D vs DRd in TI patients with NDMM. TI is defined as age $\geq$65 or age $<$ 65 with comorbidities impacting the possibility of transplant. The primary endpoints of Part 2 are minimal residual disease (MRD) at 12 mo and progression-free survival. Secondary endpoints include overall and sustained MRD negativity rates, duration of MRD negativity, objective response rate, complete response (CR) rate, time to response, duration of response, duration of CR, overall survival, safety, quality of life, immunogenicity, and pharmacokinetics. Part 1 includes TI patients with NDMM as well as patients with RRMM who have received 1$-$2 prior lines of therapy including $\geq$1 immunomodulatory drug and $\geq$1 proteasome inhibitor. Part 2 includes only TI patients with NDMM. Key inclusion criteria are: $\geq$18 y; a diagnosis of MM (according to International Myeloma Working Group [IMWG] criteria); an ECOG performance status $\leq$2; and measurable disease based on IMWG criteria (serum M-protein $\geq$0.5 g/dL, urinary M-protein excretion $\geq$200 mg/24 hr, or involved serum free light chain [FLC] $\geq$100 mg/L and abnormal serum immunoglobulin κ:λ FLC ratio [$<$ 0.26 or $>$ 1.65]). Key exclusion criteria are: smoldering MM; monoclonal gammopathy; Waldenström's macroglobulinemia; plasma cell leukemia; active, uncontrolled bacterial, fungal, or viral infections; previous systemic treatment for MM (NDMM patients only); previous treatment with a BMCA-directed therapy or anti-CD38-directed therapy $\leq$6 mo of the first dose of study treatment (RRMM patients only); or stem cell transplant $\leq$3 mo of the first dose of study treatment or active graft versus host disease (RRMM patients only). As of February 2023, the study is open and enrolling at 9 sites in 5 countries. Clinical trial information: NCT05623020. Research Sponsor: Pfizer.

TPS8066 **Poster Session**

MagnetisMM-7: An open-label, multicenter, randomized phase 3 study of elranatamab versus lenalidomide in post-transplant patients with newly diagnosed multiple myeloma.

Maria Victoria Mateos Manteca, Sebastian Grosicki, Kihyun Kim, Eric Negre, Erik Vandendries; Salamanca University Hospital, Salamanca, Spain; Department of Hematology and Cancer Prevention, Medical University of Silesia, Katowice, Poland; Division of Hematology/Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Pfizer Inc., Paris, France; Pfizer Inc., Cambridge, MA

Background: Elranatamab is a humanized bispecific antibody targeting B cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells. Elranatamab has shown promising efficacy and acceptable safety in pts with relapsed and/or refractory multiple myeloma (MM). The aim of the MagnetisMM-7 study is to evaluate elranatamab monotherapy vs lenalidomide monotherapy in pts with newly diagnosed MM (NDMM) after undergoing autologous stem cell transplant (ASCT). **Methods:** MagnetisMM-7 is an ongoing, open-label, 2-arm, multicenter, randomized phase 3 study estimated to enroll ~700 pts. ClinicalTrials.gov ID: NCT05317416. Pts are randomized to receive either subcutaneous elranatamab or oral lenalidomide once daily. After initial step-up dosing, two alternative dosing regimens of elranatamab are examined. The primary endpoint is progression-free survival (PFS) assessed by blinded independent review per International Myeloma Working Group (IMWG) criteria (up to ~5 y). Secondary endpoints include overall survival, minimal residual disease (MRD) negativity rate at 12 mo after randomization per IMWG criteria as assessed via next-generation sequencing (NGS), sustained MRD negativity rate at 24 mo after randomization as assessed via NGS, PFS by investigator, duration of MRD negativity, complete response (CR) rate, duration of CR, safety, quality of life, immunogenicity, and pharmacokinetics. Key inclusion criteria are: ≥18 y; a diagnosis of MM with measurable disease according to IMWG criteria; history of induction therapy for NDMM, followed by high dose therapy and ASCT with or without consolidation; partial response or better according to IMWG criteria; identification of the dominant malignant clone; and Eastern Cooperative Oncology Group performance status ≤1. Randomization must occur ≤120 d from ASCT; for pts who receive consolidation therapy after ASCT, randomization must occur ≤60 d of consolidation and ≤7 mo of ASCT. Key exclusion criteria are: plasma cell leukemia; amyloidosis; Waldenström's macroglobulinemia; POEMS syndrome; known active CNS involvement or clinical signs of myelomatous meningeal involvement; previous MM maintenance treatment; prior treatment with BCMA-targeted therapy; any other active malignancy ≤3 y of enrollment; active, uncontrolled bacterial, fungal, or viral infection; and previous administration of an investigational drug or vaccine ≤30 d or 5 half-lives preceding the first dose of study treatment. As of February 2023, the study is open and enrolling at 29 sites in 13 countries. Clinical trial information: NCT05317416. Research Sponsor: Pfizer.

TPS8067 **Poster Session**

MajesTEC-9: A randomized phase 3 study of teclistamab versus pomalidomide, bortezomib, and dexamethasone or carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma.

Cyrille Touzeau, Vania TM Hungria, Divaya Bhutani, Ola Landgren, Diego Vieyra, Yue Guo, Raluca Verona, Xin Miao, Mia Qi, Latisha Watkins, Priya Shah, Katherine Chastain, Ming Qi, Hang Quach; Centre Hospitalier Universitaire de Nantes, Nantes, France; Clinica São Germano, São Paulo, Brazil; Columbia University Medical Center, New York, NY; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, High Wycombe, United Kingdom; University of Melbourne, St. Vincent's Hospital, Melbourne, Vic, Australia

Background: Despite the advance in therapeutic options for patients with relapsed/refractory multiple myeloma (RRMM) over recent years, there remains a significant unmet medical need for new, well-tolerated therapies in earlier lines for patients who have previously received an anti-CD38 monoclonal antibody and lenalidomide. Teclistamab is the first B-cell maturation antigen (BCMA)-directed bispecific antibody approved for the treatment of triple class-exposed RRMM. Teclistamab redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells. MajesTEC-9 (NCT05572515) is a phase 3, randomized, open-label, multicenter study comparing teclistamab with investigator's choice of pomalidomide, bortezomib, and dexamethasone (PVd) or carfilzomib and dexamethasone (Kd) in patients with RRMM. **Methods:** Patients aged ≥18 years with RRMM (International Myeloma Working Group [IMWG] criteria) must have evidence of progressive disease or failure to achieve a response to last line of therapy and an Eastern Cooperative Oncology Group performance status score of 0–2. All patients must have received 1–3 prior lines of therapy, including ≥2 consecutive cycles of an anti-CD38 monoclonal antibody and ≥2 consecutive cycles of lenalidomide. Those treated with prior BCMA-directed therapy will be excluded. Approximately 590 patients will be randomized 1:1 to receive either teclistamab (28-day cycles) or PVd (21-day cycles) or Kd (28-day cycles). Stratification factors include investigator's choice of PVd or Kd, stage of disease, number of prior lines of therapy, and anti-CD38 monoclonal antibody refractory status. Treatment will continue until disease progression, death, intolerance, withdrawal of consent, or end of study, whichever occurs first. The primary endpoint is progression-free survival (IMWG 2016 criteria); secondary endpoints include overall response rate, duration of response, and overall survival. Adverse events (AEs) will be graded by Common Terminology Criteria for AEs v5.0; cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome will be graded by American Society for Transplantation and Cellular Therapy criteria. The study opened in January 2023 and enrollment is ongoing. Clinical trial information: NCT05572515. Research Sponsor: Janssen Research & Development.

TPS8068 **Poster Session**

OMNIA-2: Phase I/II study of ANV419, an IL-2R-βγ targeted antibody-IL-2 fusion protein, in patients with relapsed or refractory multiple myeloma.

Dagmar Hess, Katrine Fladeland Iversen, Maria-Victoria Mateos, Thomas Pabst, Laura Rosiñol, Jana Kovacikova, Sangeeta Jethwa Schnetzler; Kantonsspital St. Gallen, St. Gallen, Switzerland; Department of Internal Medicine, Section of Hematology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark; University Hospital of Salamanca, Salamanca, Spain; Institute of Medical Oncology, Berne, Switzerland; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; ANAVEON AG, Basel, Switzerland; Anaveon, Basel, Switzerland

Background: ANV419 is a potent, selective IL-2Rβγ targeted antibody IL-2 fusion protein, designed to enable the delivery of high dose interleukin-2 (IL-2) to patients, in order to stimulate anti-tumour response and minimise toxicities. The ANV419-001 first-in-human study (NCT 04855929) demonstrated that ANV419 preferentially stimulates cytotoxic CD8+ T and natural killer (NK) cells over immunosuppressive regulatory T cells, with a significantly longer half-life than that of conventional IL-2. The safety and tolerability data from this study confirmed that ANV419 delivers high molar equivalents of IL-2 in a tolerable and convenient way. In patients with multiple myeloma, the critical role of NK cells has been well described. ANV419 is expected to promote antitumor response via the preferential stimulation of cytotoxic CD8+ T and NK cells. **Methods:** The OMNIA-2 study (ANV419-102; NCT 05641324) will evaluate safety and preliminary efficacy of ANV419 as monotherapy and in combination with daratumumab (dara), or lenalidomide with low dose dexamethasone (lena/dex), in patients with relapsed or refractory multiple myeloma. OMNIA-2 is a Phase I open-label, multi-center study in adult patients (n = 52) with symptomatic multiple myeloma who responded to previous treatment and received autologous stem cell transplant, or at least 2 lines of therapy including an immunomodulator, proteasome inhibitor, and/or dara. The study is conducted in 2 stages using a Bayesian Optimal Phase 2 approach. Stage 1 consists of a run-in phase with subsequent randomization to ANV419 243mcg/kg or ANV419 108mcg/kg for 8 weeks, followed by a second randomisation to ANV419 108mcg/kg in combination with lena/dex or dara for a further 8 weeks. Stage 2 follows a similar design as stage 1 and consists of a monotherapy run-in phase with either high or low dose ANV419, with a second randomisation to ANV419 108mcg/kg in combination with either lena/dex or dara, according to the safety and efficacy observed in Stage 1. ANV419 is administered intravenously over 15 to 20 minutes every two weeks. Lena, dex and dara are administered at their respective approved dosing regimens. Tumour response is determined using IMWG (2016) response criteria. AEs are assessed according to CTCAE V5.0. OMNIA-2 is being conducted in Denmark, France, Germany, Spain, Switzerland, UK and enrolment began in January 2023 and preliminary data are expected in Q1 2024. Clinical trial information: NCT05641324. Research Sponsor: ANAGEON AG.

TPS8069 **Poster Session**

EXCALIBER-RRMM: A phase 3, two-stage study of iberdomide, daratumumab, and dexamethasone (IberDd) versus daratumumab, bortezomib, and dexamethasone (DVd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).

Sagar Lonial, Hang Quach, Meletios A. Dimopoulos, Paula Rodríguez-Otero, Jesus G. Berdeja, Paul G. Richardson, Margee Kyada, Shuyu Chu, Min Chen, Patricia C. Abad, Juliane Morando, Niels W.C.J. van de Donk; Winship Cancer Center of Emory University, Atlanta, GA; St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia; National and Kapodistrian University of Athens, Athens, Greece; Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; Sarah Cannon Research Institute, Nashville, TN; Dana-Farber Cancer Institute, Boston, MA; Bristol Myers Squibb, Princeton, NJ; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands

Background: New treatments (Txs) are needed to achieve deep and durable responses in RRMM. Iberdomide (IBER) is a novel, potent oral cereblon E3 ligase modulator (CELMoD) with enhanced tumoricidal and immune-stimulatory effects compared with immunomodulatory drugs (IMiDs). IBER has synergy with dexamethasone (DEX), daratumumab (DARA), and bortezomib (BORT) in vitro. In a phase 1/2 trial, IberDd demonstrated efficacy with a manageable safety profile in pts with RRMM (Lonial S, et al. *HemaSphere* 2021;5(S2):S187). The EXCALIBER-RRMM phase 3 trial (NCT04975997) will compare the efficacy and safety of IberDd with that of DVd in pts with early RRMM. **Methods:** This multicenter, open-label study will be conducted in 2 stages: in Stage 1, $\geq$ 200 pts will be randomized 1:1:1:1 to 1 of 3 IBER doses (1.0, 1.3, or 1.6 mg) + DARA and DEX or to the DVd arm to identify optimal IBER dose when combined with DARA + DEX; in Stage 2, $\approx$ 664 additional pts will be randomized 1:1 to IberDd at the selected IBER dose or to DVd, for efficacy and safety analyses (Stage 1 pts in IBER selected dose cohort and DVd arm to be also included). Pts will be stratified by number of prior Tx lines (1 vs 2), age ($\leq$ 70 vs $>$ 70 y), and ISS stage at study entry (I–II vs III). Primary efficacy endpoint is progression-free survival (PFS), which is defined as the time from randomization to progressive disease (PD) or death. Assuming a decrease in PFS risk by 25% (HR = 0.75) with IberDd, under exponential distribution assumption of PFS (1-sided α = 0.025) and adjusted for 3 interim analyses, 458 PFS events will have $\approx$ 84% power to detect an improvement in Tx effect. The 3 planned interim analyses are: for IBER dose selection at end of Stage 1; and to examine PFS futility and superiority when $\approx$ 138 (30%) and $\approx$ 344 (75%) events, respectively, have been accumulated. Secondary endpoints include overall survival, duration of response, time to progression, overall response rate, measurable residual disease negativity rate, safety, and quality of life. Tx in the IberDd arm will consist of 28-day (D) cycles (C) with IBER on D1–21; 1800 mg subcutaneous (SC) DARA on D1, 8, 15, and 22 of C1–2, D1 and 15 of C3–6, and D1 of $\geq$ C7; and 40 mg oral DEX (20 mg in pts $>$ 75 y of age) on D1, 8, 15, and 22. Tx in the DVd arm will consist of 21-D cycles for C1–8 and 28-D cycles for $\geq$ C9; 1800 mg SC DARA on D1, 8, and 15 for C1–3, D1 for $\geq$ C4; 1.3 mg/m^2 SC BORT on D1, 4, 8, and 11 for C1–8; and 20 mg oral DEX (10 mg in pts $>$ 75 y of age) on D1, 2, 4, 5, 8, 9, 11, and 12 for C1–8. Tx will continue until confirmed PD, unacceptable toxicity, or consent withdrawal. Key eligibility criteria include age $\geq$ 18 y, 1–2 prior lines of antimyeloma Tx, partial response or better to $\geq$ 1 prior Tx, and documented PD during or after the last regimen. Prior anti-CD38 Tx is allowed only in Stage 2 ($\leq$ 10% of pts). Enrollment began in June 2022 and is currently ongoing. Clinical trial information: NCT04975997. Research Sponsor: Bristol Myers Squibb.

TPS8070 **Poster Session**

A phase 3, two-stage, randomized study of mezigdomide, carfilzomib, and dexamethasone (MeziKd) versus carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-2.

Paul G. Richardson, Michael Amatangelo, James R. Berenson, Claudio Cerchione, Meletios A. Dimopoulos, Charlotte Toftmann Hansen, Soo Jeong Hwang, Phillip Koo, Junya Kuroda, Albert Oriol, Robert Z. Orlowski, Hang Quach, Marc S. Raab, Alberto Rocci, Yue Wang, Darrell White, Brian Yu, Zehua Zhou, Jessica Katz; Dana-Farber Cancer Institute, Boston, MA; Bristol Myers Squibb, Princeton, NJ; Institute for Myeloma and Bone Cancer Research, West Hollywood, CA; Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; National and Kapodistrian University of Athens, Athens, Greece; Odense University Hospital, Odense, Denmark; Department of Hematology and Oncology, Kyoto Prefectural University of Medicine, Kyoto, Japan; Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Department of Lymphoma & Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, VIC, Australia; Universitätsklinikum Heidelberg, Heidelberg, Germany; Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Background: Mezigdomide (MEZI), a novel oral cereblon E3 ligase modulator (CELMoD), induces maximal degradation of Ikaros/Aiolos leading to increased MM cell apoptosis and immune-stimulatory effects. MeziKd has shown potent synergistic antiproliferative activity in MM cell lines resistant to lenalidomide (LEN), and in a phase 1/2 study showed promising preliminary efficacy and safety in RRMM. The SUCCESSOR-2 phase 3 trial (NCT05552976) will compare the efficacy and safety of MeziKd vs Kd in patients (pts) with RRMM. **Methods:** This multicenter, open-label study comprises 2 stages. In Stage 1, $\geq$ 128 pts will be randomized 3:3:3:2 to 1 of 3 MEZI doses (1.0, 0.6, or 0.3 mg) + Kd, or to the Kd arm to select the optimal MEZI dose in combination with Kd for Stage 2. In Stage 2, $\approx$ 397 additional pts will be randomized 3:2 to MeziKd at the selected MEZI dose or to Kd, for efficacy and safety analyses (Stage 1 pts in the selected MeziKd dose cohort and Kd arm will also be included in these analyses). Pts will be stratified by age ($\leq$ 70 vs $>$ 70 y), number of prior lines of treatment (Tx; $\leq$ 2 vs $>$ 2), and ISS stage at screening (I vs II vs III). MEZI dose selection will be based on Stage 1 efficacy, safety, pharmacokinetic and pharmacodynamic data, and exposure–response analyses. Primary efficacy endpoint is progression-free survival (PFS). Assuming a decrease in PFS risk by 33.3% (HR = 0.667) with MeziKd, under exponential distribution assumption of PFS (1-sided α = 0.025) and adjusted for 3 interim analyses, $\geq$ 273 PFS events will have $\approx$ 89% power to detect improvement in Tx effect. The planned interim analyses are for: MEZI dose selection at end of Stage 1, and to examine PFS futility and superiority when $\approx$ 82 (30%) and $\approx$ 205 (75%) events, respectively, have been accumulated. Secondary endpoints include determination of the recommended MEZI dose plus Kd (Stage 1 only), and assessment of overall survival, overall response rate, time to response, duration of response, time to progression, safety, and quality of life. MeziKd arm Tx consists of 28-day (D) cycles (C) with MEZI on D1–21; 20 mg/m^2 intravenous (IV) carfilzomib (CFZ) on D1 of C1, then 56 mg/m^2 on D8 and 15 of C1, on D1, 8, and 15 of C2–12, and on D1 and 15 of $\geq$ C13; and 40 mg oral/IV DEX (20 mg optional in certain pt groups) on D1, 8, 15, and 22. Tx in the Kd arm consists of 28-D cycles with 20 mg/m^2 IV CFZ on D1 and 2 of C1, then 56 mg/m^2 on D8, 9, 15, and 16 of C1, and on D1, 2, 8, 9, 15, and 16 of $\geq$ C2; and 20 mg oral/IV DEX (10 mg optional in certain pt groups) on D1, 2, 8, 9, 15, 16, 22, and 23. Tx will continue until progressive disease (PD) or unacceptable toxicity. Key eligibility criteria include age $\geq$ 18 y, $\geq$ 1 prior line of anti-MM Tx including LEN and an anti-CD38 monoclonal antibody, minimal response or better to $\geq$ 1 prior Tx, documented PD during or after last regimen, and no prior CFZ Tx. Enrollment began in October 2022 and is ongoing. Clinical trial information: NCT05552976. Research Sponsor: Bristol Myers Squibb.

TPS8071 **Poster Session**

Enrolling patients in Cardiac Amyloid Reaching for Extended Survival (CARES) trials: Two placebo-controlled, double-blind, randomized, international phase 3 trials assessing CAEL-101 in patients with Mayo stage IIIa or stage IIIb AL amyloidosis.

Michaela Liedtke, Giovanni Palladini, Maria Angelica Molina, Efstathios Kastritis, Juliana Ianus, Julia Catini, Candida Cristina Quarta, Ashutosh D. Wechalekar, on behalf of the 301 and 302 Investigators; Stanford Cancer Center, Stanford, CA; University of Pavia, Pavia, Italy; IQVIA, Durham, NC; Department of Clinical Therapeutics, Alexandra Hospital, Medical School, National & Kapodistrian University of Athens, Athens, Greece; Alexion, AstraZeneca Rare Disease, Boston, MA; Royal Free Hospital School of Medicine, University College London Medical School, London, United Kingdom

Background: Light-chain (AL) amyloidosis is a rare, progressive, systemic disorder caused by plasma cell dyscrasia (PCD). Amyloid fibrils deposit in organs leading to progressive organ damage and death. Prognosis is poor for patients with cardiac involvement. Median survival is 24 and 4 months for patients in Mayo Stages IIIa and IIIb (based on the 2013 European Modification of the Mayo 2004 staging criteria), respectively. The standard of care (SoC) is anti-PCD therapy to suppress amyloid fibril generation. As yet, there are no therapies that remove deposited fibrils. CAEL-101 is a monoclonal antibody that binds to amyloid fibrils and may facilitate their systemic removal, improve organ function, and patient survival. These ongoing trials will evaluate the efficacy and safety of CAEL-101 as first-in-class treatment to reduce amyloid burden in patients with cardiac AL amyloidosis. Notably, 301 (Mayo Stage IIIb) is the first randomized, placebo-controlled efficacy clinical trial to formally assess the effects of a pharmacological in this severely ill population. Because the median expected survival for Mayo Stage IIIb patients is far shorter than for Mayo Stage IIIa patients, the resulting sample size required for the Mayo Stage IIIb study is less than for the Mayo Stage IIIa study. The objective of these trials is to evaluate the efficacy and safety of CAEL-101 when administered concurrently with SoC anti-PCD therapy in treatment-naïve patients with cardiac AL amyloidosis in Mayo Stages IIIb (NCT04504825; 301) or IIIa (NCT04512235; 302). **Methods:** These international, multicenter, double-blind, randomized, phase 3 trials, initiated in 2020, are enrolling patients at $>$ 100 sites in $>$ 20 countries. Newly diagnosed adults with AL amyloidosis stage IIIb or IIIa measurable hematologic disease, and histopathological diagnosis of amyloidosis with cardiac involvement are eligible. Patients with other forms of amyloidosis, symptomatic orthostatic hypotension, or supine systolic blood pressure $<$ 90 mm Hg are ineligible. Patients in Mayo Stages IIIb (N = 124) and IIIa (N = 267) are being randomized 2:1 to receive once-weekly IV infusions of CAEL-101 (1000 mg/m^2) or placebo for 4 weeks, followed by maintenance dosing every 2 weeks. In these event-driven studies, treatment will continue to a minimum of 101 and 79 events for 301 and 302, respectively. Patients will receive concurrent institutional SoC anti-PCD therapy at the discretion of the investigator. Overall survival (primary endpoint) will be analyzed via time-to-event log-rank statistics. Secondary endpoints include functional outcomes, quality of life, and echocardiography. Clinical trial information: NCT04504825, NCT04512235. Research Sponsor: Alexion, AstraZeneca Rare Disease.