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ORAL ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Talquetamab + Pomalidomide in Patients with Relapsed/Refractory Multiple Myeloma: Safety and Preliminary Efficacy Results from the Phase 1b MonumenTAL-2 Study

Jeffrey Matous, MD[1], Noa Biran, MD[2], Aurore Perrot, MDPhD[3], Jésus G Berdeja, MD[4], Kathleen Dorritie, MD[5], Janine Van Elssen, MD PhD[6], Emma Searle, MD[7], Cyrille Touzeau, MD PhD[8], Sébastien Anguille[9], Deeksha Vishwamitra[10], Ashley Nguyen[10], Debopriya Ghosh[11], Elizabeth Shearin, PharmD[12], Katherine Thornton[10], Damiette Smit[13], Hang Quach, MDFRACP,FRCPA,MBBS[14]

[1] Colorado Blood Cancer Institute, Denver, CO
[2] Multiple Myeloma Division, John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ
[3] Service Hematologie, Institut Universitaire du cancer de Toulouse-Oncopole, Toulouse, France
[4] Sarah Cannon Research Institute, Nashville, TN
[5] UPMC Hillman Cancer Center, Pittsburgh, PA
[6] Maastricht University Medical Center, Maastricht, Netherlands
[7] The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom
[8] Centre Hospitalier Universitaire de Nantes, Nantes, France
[9] Antwerp University Hospital, Edegem, Belgium
[10] Janssen Research & Development, Spring House, PA
[11] Janssen Research & Development, Bridgewater, NJ
[12] Janssen Research and Development, Spring House, PA
[13] Janssen Biologics Europe, Leiden, Netherlands
[14] St. Vincent's Hospital Melbourne, University of Melbourne, Melbourne, Australia

Introduction: Talquetamab (tal) is a T-cell redirecting bispecific antibody (BsAb) targeting GPRC5D and CD3. GPRC5D is a novel antigen that is highly expressed on malignant plasma cells but has low expression on B cells and normal plasma cells. Tal has demonstrated deep and durable responses, including in high-risk populations, and a clinically manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in the MonumenTAL-1 study (NCT03399799/NCT04634552). Pomalidomide (pom) is an established immunomodulatory drug (IMiD) that has direct on-tumor apoptotic activity and enhances immune activity. Combining pom with T-cell redirection therapy may lead to synergistic antimyeloma effects. We report initial efficacy and safety results of tal + pom from the MonumenTAL-2 study.
Methods: MonumenTAL-2 (NCT05050097) is a multi-arm, phase 1b study of tal in combination with antimyeloma agents in pts with MM. Pts received the recommended phase 2 doses of subcutaneous tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W), with step-up dosing, + oral pom 2 mg daily (dose escalation to 4 mg daily permitted) starting in cycle 2. Pts received ≥2 prior lines of therapy (LOT) including a proteasome inhibitor and an IMiD; prior T-cell redirection therapies including BsAbs and chimeric antigen receptor (CAR)-T along with prior pom exposure were permitted. CRS and ICANS were graded by ASTCT criteria; all other adverse events (AEs) were graded by CTCAE v5.0. Response was assessed by IMWG criteria. Efficacy endpoints are presented as individual cohorts (QW and Q2W); safety is presented across both cohorts.
Results: As of June 5, 2023, 35 patients were enrolled with a median follow-up of 11.4 months (range, 1.2-14.9) in the QW cohort (N=16) and 7.7 months (range, 1.6-10.8) in the Q2W cohort (N=19). Median ages were 69.5 years (range, 49-78) and 63.0 years (range, 43-76), respectively; 41.7% and 33.3% of pts had high-risk cytogenetics (del[17p], t[4;14], or t[14;16]) and 12.5% and 10.5% of pts had extramedullary disease, respectively. Median prior LOT were 3 in both cohorts; 25.0% and 21.1% were triple-class refractory, respectively, and 6.3% were penta-drug refractory (all in QW cohort). Prior treatments included CAR-T (18.8% and 0%), BsAb (6.3% and 0% [0% refractory]), and anti-CD38 Ab (75.0% and 73.7% [56.3% and 36.8% refractory]) in the QW and Q2W cohorts, respectively; 31.3% and 15.8% had prior pom exposure (18.8% and 5.3% refractory). All pts had ≥1 AE; most common were dysgeusia (77.1%), CRS (74.3%; most grade 1/2, 2.9% grade ≥3), and neutropenia (60.0%). Grade 3/4 AEs occurred in 88.6% of pts; most common were neutropenia (48.6%), anemia (25.7%), and thrombocytopenia (20.0%). Nail, skin, and rash toxicities occurred in 65.7%, 40.0%, and 20.0% of pts (majority grade 1/2 with no discontinuations), respectively.

ICANS occurred in 2 pts (both grade 1). Infections occurred in 71.4% of pts (22.9% grade 3/4); most common were pneumonia (20.0%) and COVID-19 (14.3%). AEs led to dose reduction or schedule change of tal in 34.3% of pts and dose reduction of pom in 31.4% of pts. Two pts (5.7%) in the Q2W cohort had AEs, myocardial infarction and pulmonary embolism (PE), that led to treatment discontinuation (not drug related). One death due to PE occurred (same pt who discontinued treatment). ORR was 86.7% and 83.3% in the QW and Q2W cohorts, respectively, with ≥CR in 60.0% and 44.4% and ≥VGPR in 86.7% and 77.8%, respectively. ORRs were consistent across pt subgroups (>80% independent of prior pom or CAR-T exposure). Median time to first response was 1.0 month (range, 0.9-2.1) in the QW cohort and 1.3 months (range, 0-4.8) in the Q2W cohort. At 6 months, 100% of responders were still responding in both cohorts. Median DOR and PFS were not reached, with 6-month PFS rates of 93.3% (QW) and 88.9% (Q2W).

Conclusions: In this first reported combination of a GPRC5D-targeted therapy and an IMiD, tal + pom showed rapid, deep responses in pts with RRMM and ≥2 prior LOT. The safety profile of the combination, including grade 3/4 hematologic toxicity, was consistent with the individual agents, with no evidence of additive hematologic toxicities; additionally, there were low rates of treatment discontinuation due to AEs. The promising efficacy and manageable safety profile of this combination further supports tal as a versatile combination partner and warrants further evaluation of this regimen.

Disclosures Matous: *BeiGene and Pharrmacyclics:* Membership on an entity's Board of Directors or advisory committees, Other: WM advisory Boards for both companies. **Biran:** *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Boehringer Ingelheim:* Other: spouse of employee; *Abbvie:* Honoraria; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Genomic Testing Cooperative:* Divested equity in a private or publicly-traded company in the past 24 months; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Merck:* Research Funding; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Karyopharm:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Perrot:** *Abbvie, Adaptive, Amgen, BMS, Janssen, Pfizer, Sanofi, Takeda:* Honoraria. **Berdeja:** *2seventy bio:* Consultancy, Research Funding; *Amgen:* Research Funding; *Teva:* Research Funding; *Lilly:* Research Funding; *Incyte:* Research Funding; *Janssen:* Consultancy, Research Funding, Speakers Bureau; *Karyopharm:* Research Funding; *Kite Pharma:* Consultancy; *Celularity:* Research Funding; *Cartesian:* Research Funding; *CARsgen:* Research Funding; *AbbVie:* Research Funding; *Acetylon:* Research Funding; *Celgene:* Consultancy, Research Funding; *C4 Therapeutics:* Research Funding; *Bristol Myers Squibb:* Consultancy, Research Funding; *CRISPR Therapeutics:* Consultancy, Research Funding; *Legend Biotech:* Consultancy; *Novartis:* Research Funding; *Poseida:* Research Funding; *Sanofi:* Research Funding; *Takeda:* Consultancy, Research Funding; *Roche:* Consultancy; *EMD Serono:* Research Funding; *Fate Therapeutics:* Research Funding; *Genentech:* Research Funding; *GSK:* Research Funding; *Ichnos Sciences:* Research Funding. **Dorritie:** *Hoffman-LaRoche:* Research Funding; *Genmab:* Research Funding; *Kite, a Gilead Company:* Research Funding; *Genentech:* Research Funding; *BMS:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Curio and Dava Oncology:* Honoraria; *Janssen:* Research Funding. **Searle:** *Shattuck Labs:* Consultancy; *Sanofi:* Consultancy; *Abbvie:* Honoraria, Other: Conference travel; *Janssen:* Honoraria, Other: Conference travel. **Touzeau:** *Bristol Myers Squibb:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Vishwamitra:** *Johnson & Johnson:* Current Employment, Current holder of *stock options* in a privately-held company. **Nguyen:** *Janssen:* Current Employment. **Ghosh:** *Janssen:* Current Employment. **Shearin:** *Janssen R&D:* Current Employment. **Thornton:** *Janssen:* Current Employment, Current holder of *stock options* in a privately-held company. **Smit:** *Janssen Biologics:* Current Employment, Current equity holder in publicly-traded company. **Quach:** *Sanofi:* Consultancy, Other: receipt of study materials; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Leadership or fiduciary role; *Karyopharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: receipt of study materials, Research Funding; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: receipt of study materials; Leadership or fiduciary role, Research Funding.

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