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POSTER ABSTRACTS

653.MYELOMA AND PLASMA CELL DYSCRASIAS: PROSPECTIVE THERAPEUTIC TRIALS

Isatuximab in Combination with Lenalidomide and Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma: Updated Safety Run-in Results from the Randomized Phase 3 Ithaca Study

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Abstract Background: Results from a randomized, Phase 3 study by the Spanish Myeloma Group (PETHEMA/GEM) previously showed that treatment with lenalidomide plus dexamethasone (Rd) may delay progression to active disease in patients (pts) with high-risk smoldering multiple myeloma (SMM), compared with observation. To further improve outcomes, addition of the anti-CD38 antibody isatuximab (Isa) to lenalidomide and dexamethasone (Isa-Rd) for the treatment of pts with high-risk SMM is being evaluated in the ongoing, randomized, multi-center, Phase 3 ITHACA study (NCT04270409). Initial findings from the safety run-in analysis of this trial have shown a manageable safety profile and encouraging, preliminary anti-myeloma activity. We now report updated safety and efficacy results from the safety run-in part of ITHACA at a median follow-up of 19.4 months.

Methods: Pts were included in the study if they had been diagnosed within 5 years with SMM (per the International Myeloma Working Group [IMWG] criteria) and had high-risk SMM according to the Mayo '20-2-20' and/or updated PETHEMA model criteria. Pts who had received prior anti-myeloma treatment were not eligible. Enrolled pts received Isa 10 mg/kg IV on day (D) 1, 8, 15, and 22 in cycle (C) 1, D1 and D15 C2-12, D1 C13-36; plus R D1-21 (25 mg C1-9; 10 mg C10-24) and d weekly (40 mg, 20 mg for ≥75 yr-old pts C1-9; 20 mg C10-24). Cycle duration was 28 days. Safety evaluations included treatment-emergent AEs (TEAEs)/serious AEs and laboratory parameters, graded by NCI-CTCAE v5.0. Response was determined by IMWG criteria (2016). Mandatory imaging by MRI and/or low-dose whole-body CT/PET-CT, and assessments of minimal residual disease (MRD, by next-generation sequencing in pts with very good partial response [VGPR] or better), were performed at protocol-defined time points. The primary study objective for the safety run-in was to confirm the recommended dose of Isa in combination with Rd. Overall response rate (ORR) and MRD negativity rate at 10^{-5} sensitivity were included as secondary endpoints.

Results: At data cut-off (May 9, 2022), 23 pts (median age, 63 [range, 28-85] years) had received Isa 10 mg/kg once weekly then biweekly (QW-Q2W), in combination with Rd. Two (9%) pts met the Mayo clinical model criteria, 13 (57%) pts the updated PETHEMA model criteria and 8 (35%) pts both models' criteria for high-risk SMM. No pt had a focal lesion on MRI. The median duration of treatment exposure was 19.7 (range, 3.7-22.1) months with a median of 20 (range, 4-24) cycles. Grade ≥3 TEAEs were reported in 11 (47.8%) pts: Covid-19 pneumonia (n=3), insomnia (n=3), and pneumonia, hyperglycemia, agitation, lethargy, gastroesophageal reflux disease, retinal detachment, papular rash, and muscle spasms (n=1 each). No pt died or definitively discontinued treatment due to a TEAE. Serious TEAEs were Covid-19 pneumonia (n=3, grade ≥3), pneumonia (n=1, grade ≥3), and radicular pain, musculoskeletal chest pain, reactive arthritis, pyrexia, and amyloidosis (disease progression) (n=1 each, grade <3). The most common TEAEs (generally of grade 1-2) were insomnia (44%), constipation (30%), peripheral edema (30%), and headache (26%). Infusion reactions occurred in 2 pts (8.7%) (grade 2, infusion day 1, cycle 1). Grade ≥3 treatment-related TEAEs were reported in 9 (39.1%) pts and serious treatment-related TEAEs in 2 (8.7%) pts. Grade 3-4 neutropenia occurred in 7 (30%) pts (grade 4 in 1 [4%] pt) and grade 3 thrombocytopenia in 1 (4%) pt (no grade 4), with no treatment discontinuations due to neutropenia or thrombocytopenia. Responses deepened over time versus the initial analysis, with an ORR of 100% at a median follow-up of 19.4 (range, 18.5-19.5) months: 13.0% of pts reached a stringent complete response (sCR), 30.4% a CR, and 30.4% a VGPR. Results of the MRD assessments will be presented depending on data availability.

Conclusions: Updated results from the safety run-in part of the ITHACA trial continue to show a manageable safety profile for Isa-Rd in pts with high-risk SMM, with no definitive treatment discontinuations due to a TEAE. At a median follow-up of 19.4 months, treatment with Isa-Rd has shown promising efficacy (sCR/CR in 43.5% and ≥VGPR in 73.9% of pts), thus further confirming the recommended dose of Isa (10 mg/kg QW-Q2W) for the randomized part of the study, currently evaluating efficacy and safety of Isa-Rd vs Rd in pts with high-risk SMM.

Clinical trial registration: NCT04270409. **Funding:** Sanofi.

Table: Efficacy

	Isa-Rd N=23
Best overall response	n (%)
ORR	23 (100)
sCR	3 (13.0)
CR	7 (30.4)
VGPR	7 (30.4)
PR	6 (26.1)

CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Figure 1.

Disclosures Mateos: *Bristol Myers Squibb/Celgene:* 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; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen Cilag:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *GSK:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Oncopeptides:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Rodriguez Otero:** *Oncopeptides:* Other: Advisory board participation ; *Pfizer:* Other: Advisory board participation ; *Kite Pharma:* Other: Advisory board participation ; *AbbVie:* Other: Advisory board participation ; *Regeneron:* Honoraria; *Sanofi:* Honoraria, Other: Advisory board participation; *GSK:* Honoraria, Other: Advisory board participation ; *Amgen:* Honoraria; *Janssen:* Honoraria, Other: Advisory board participation ; *BMS-Celgene:* Honoraria, Other: Advisory board participation ; *Consultant in Hematology Clínica Universidad de Navarra:* Current Employment; *Janssen, BMS, Sanofi, Pfizer, GSK:* Consultancy; *Amgen, Sanofi, GSK, Janssen, BMS-Celgene, Regeneron:* Speakers Bureau.

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OffLabel Disclosure: Investigational use of isatuximab in patients with high-risk smoldering multiple myeloma

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