2. NEWLY DIAGNOSED MULTIPLE MYELOMA

ISATUXIMAB WITH BORTEZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE FOLLOWED BY ISATUXIMAB AND LENALIDOMIDE MAINTENANCE IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS WITH SEVERE RENAL IMPAIRMENT: FINAL ANALYSIS OF A PHASE 2 STUDY BY GREEK MYELOMA STUDY GROUP

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Introduction. Isatuximab (Isa), an anti-CD38 monoclonal antibody, has shown efficacy and improved renal recovery in combination with pomalidomide/dexamethasone in relapsed/refractory (RR) Multiple myeloma (MM). Isa with bortezomib (V), lenalidomide (R), and dexamethasone (d) (Isa-VRd) is approved for the treatment of newly diagnosed MM (NDMM) in both transplant-eligible (TE) and transplant-ineligible (TI) patients (pts), including those not eligible for ASCT. We evaluated the renal/hematologic efficacy and safety of Isa with V, cyclophosphamide(C), and d (Isa-VCd) followed by Isa and R maintenance in NDMM pts with severe RI.

Methods. EAE116 (NCT05147493) is a phase 2, prospective, open-label, multicenter study of previously untreated NDMM pts with severe RI (eGFR <30 mL/min/1.73m2 or requiring dialysis). Pts received six 28-day cycles of IsaVCd as induction treatment (Isa 10 mg/kg IV [C1: QW; C2-6: Q2W]; V 1.3 mg/m2 SC [C1: D1, 4, 8, 11; C2–6: QW]; C 300 mg/m2 IV [C1: D1, 8, 15; C2-6: QW]; d 40 mg [or 20 mg for pts ≥75 years old] PO/IV [C1: D1-4 and D 9-12; C2–6: QW]). In the maintenance phase (C7 onwards), pts received Isa 10 mg/kg IV Q4W and daily R 10 mg PO (or per renal function). Endpoints included renal response rate (RRR), ORR (≥PR), PFS, OS, time to response and safety.

Results. To-date 51 pts entered the study (median age: 70.0 years; male: 62.7%; ECOG PS ≤1: 88.2%; median involved FLC: 1791 mg/L); 92.2% pts had ISS stage III and 47.1% pts had R-ISS stage III disease; 62.7% pts were still on treatment and 37.3% discontinued (death: 21.6%; PD: 7.8%; consent withdrawal: 3.9%; physician decision: 3.9%). Overall, 13.7% pts had high-risk cytogenetics and 11.8% had soft tissue plasmacytomas. At a median follow-up of 19.7 months, all pts received a median of 16.0 treatment cycles and 78.4% pts had completed 6 months of treatment. During the induction phase, the median Isa exposure was 22.5 mg/kg/28 days, while during maintenance it was 9.6 mg/kg/28 days. AE-related dose skips occurred in 9/51 pts (17.6%) during induction and in 2/40 pts (5.0%) during maintenance. The median dose administered was 100% during both induction and maintenance phases. Among renal-response-evaluable pts (N=50), 72.0% achieved ≥MRR in a median time of 1.1 months. RRR (≥ renal PR) was observed in 36.0%; CRR: 30.0%; PRR: 6.0%, with a median time to first response of 2.3 months. Among 11 pts (21.6%) dialysis-dependent at baseline, 6(54.5%) became dialysis independent. Hematologic ORR was 84.3% (sCR: 21.6%, CR: 13.7%, VGPR: 37.3%, PR: 11.8%), with a median time to first response of 1 month. PFS was 77.6% at 12 months (95% CI: 63.2–86.9) and 60.3% at 24 months (95% CI: 42.7–74.0). Overall median PFS and time to progression were not reached, with 17 PFS events: 4 PD and 13 deaths. OS was 84% at 12 months (95% CI: 70.4-91.6) and 63.9% at 24 months (95% CI: 46.0-77.2). TEAEs occurred in 86.3% pts overall; Grade ≥3 TEAEs in 39.2%, Grade 5 events in 21.6%, ≥1 serious TEAEs in 35.3%.

Conclusions. IsaVCd induction treatment followed by IsaR maintenance elicits notable renal and hematologic responses in NDMM pts with severe RI and advanced risk features. Responses were rapid, including high rates of dialysis independence, with a favorable safety profile consistent with known toxicities of the individual agents. These findings support IsaVCd as a promising frontline option for patients with MM and severe RI.*Funding by Sanofi; no role in study design, analysis/interpretation*