(S100) PHASE 3, RANDOMIZED STUDY OF TALQUETAMAB (TAL) PLUS DARATUMUMAB (DARA) ± POMALIDOMIDE (POM) VS DARA PLUS POM AND DEXAMETHASONE (DPD) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): MONUMENTAL-3

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

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Background

Tal (anti-GPRC5D bispecific antibody) has shown deep responses and durable efficacy in late line RRMM with a favorable infection profile. Its B-cell sparing mechanism facilitates combination with Dara and Pom, enabling potential synergistic efficacy in earlier lines where durable remissions are needed.

Aims

To report efficacy and safety of Tal+Dara+Pom (Tal-DP) and Tal+Dara (Tal-D) vs DPd in pts with RRMM and ≥1 prior line of therapy (LOT) from the pre-planned interim analysis of MonumenTAL-3 (NCT05455320).

Methods

Phase 3 study randomizing pts with RRMM and ≥1 prior LOT including lenalidomide (Len) and a proteasome inhibitor 1:1:1 to Tal-DP, Tal-D or DPd (**Figure A**). Primary endpoint was progression-free survival (PFS) by IRC for Tal-DP vs DPd and Tal-D vs DPd. Secondary endpoints included overall response, complete response or better (≥CR), minimal residual disease (MRD)-negative ≥CR (10^{-5}, NGS), overall survival (OS) and safety.

Results

Overall, 864 pts were randomized (Tal-DP, N=287; Tal-D, N=287; DPd, N=290). Baseline characteristics were balanced across arms. Median age was 64.0 yrs (range 30–88), median prior LOT was 2 (range 1–8); 11.8% were anti-CD38 (nearly all Dara) exposed; 85.1% and 93.4% were refractory to Len or last LOT, respectively; 30.9% had high risk cytogenetics. At 24.6 mo median follow-up, Tal-DP and Tal-D significantly improved PFS vs DPd (HRs [95% CI]: 0.28 [0.20–0.40], P<0.0001 and 0.33 [0.24–0.46], P<0.0001; **Figure B+C**). 24-mo PFS rates (95% CI) favored Tal-DP (81.3% [75.8–85.7]) and Tal-D (77.6% [71.7–82.5]) vs DPd (51.2% [44.8–57.1]). PFS benefit was consistent across clinically relevant subgroups. ORRs (88.2%, 88.5%, 77.6%), ≥CR rates (71.1%, 69.0%, 34.5%) and MRD-negative ≥CR rates (52.3%, 46.3%, 15.9%) were significantly higher for Tal-DP and Tal-D vs DPd, respectively. OS HRs (95% CI) vs DPd were 0.47 (0.30–0.73; P=0.0006) for Tal-DP and 0.51 (0.33–0.78; P=0.0015) for Tal-D. At data cutoff, 70.3% (Tal-DP), 69.7% (Tal-D) and 47.3% (DPd) of pts remained on study tx. AEs were manageable and consistent with expectations for each agent; overall AE rates (gr 3-4, gr 5): Tal-DP (96.7%, 1.8%), Tal-D (78.8%, 4.0%), DPd (95.8%, 4.6%). AEs leading to discontinuation (d/c) of all study tx occurred in 10.5% (Tal-DP), 8.0% (Tal-D), and 6.7% (DPd). Rates of cytopenias (any gr, gr 3-4) were: Tal-DP (91.7%, 87.7%), Tal-D (68.2%, 51.8%), and DPd (91.9%, 89.0%). Infection rates (any gr, gr 3-4, gr 5) were: Tal-DP (87.3%, 37.0%, 0.7%), Tal-D (84.3%, 27.7%, 1.5%), and DPd (83.0%, 41.0%, 1.8%). With Tal-DP and Tal-D, respectively, CRS (any gr: 67.8%; 58.4%) and ICANS (any gr: 2.9%; 1.8%) were mostly gr 1-2. Any gr GPRC5D-related AEs with Tal-DP, Tal-D and DPd, respectively, included taste changes (72.8%; 74.8%; 3.9%) and decreased weight (45.7%; 38.3%; 7.4%); most events were gr 1-2 and did not lead to Tal d/c. Ataxia/balance disorders (gr 1-2, gr 3) with Tal-DP (11.6%, 2.9%), Tal-D (10.2%, 2.2%) and DPd (0.4%, 0%) were primarily low gr (none gr ≥4); events led to Tal d/c in 4.7% (Tal-DP) and 2.2% (Tal-D).

Summary/Conclusion

Tal-DP and Tal-D demonstrated a significant and profound PFS benefit vs DPd, clinically meaningful OS improvements and gr ≥3 infection rates similar to or lower than DPd. Tal was combinable, with low rates of tx d/c. Efficacy appeared numerically better with Tal-DP vs Tal-D but with a higher gr 3-4 cytopenia rate, as expected with Pom. Tal-D with or without Pom represents a new standard of care for RRMM as early as 2L across all practice settings.