Abstract: PB2132

Title: EXCALIBER-RRMM: A PHASE 3, TWO-STAGE STUDY OF IBERDOMIDE, DARATUMUMAB, AND DEXAMETHASONE VERSUS DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Background:

New treatments (Txs) are needed to achieve deep and durable responses in relapsed/refractory multiple myeloma (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, IBER plus DARA and DEX (IberDd) demonstrated efficacy with a manageable safety profile in patients (pts) with RRMM (Lonial S, et al. *HemaSphere* 2021;5(S2):S187).

Aims:

The EXCALIBER-RRMM phase 3 trial (NCT04975997) will compare the efficacy and safety of IberDd with that of DARA plus BORT and DEX (DVd) in pts with early RRMM.

Methods:

This multicenter, open-label study will be conducted in 2 stages: in Stage 1, ≥ 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, ≈ 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 (≤ 70 vs > 70 years), 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 $\alpha = 0.025$) and adjusted for 3 interim analyses, 458 PFS events will have ≈ 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 ≈ 138 (30%) and ≈ 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 ≥ C7; and 40 mg oral DEX (20 mg in pts > 75 years 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 ≥ C9; 1800 mg SC DARA on D1, 8, and 15 for C1–3, D1 for ≥ 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 years 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 ≥ 18 years, 1–2 prior lines of antimyeloma Tx, partial response or better to ≥ 1 prior Tx, and documented PD during or after the last regimen. Prior anti-CD38 Tx is allowed only in Stage 2 (≤ 10% of pts).

Results:

Enrollment began in June 2022 and is currently ongoing.

Summary/Conclusion:

This phase 3 study will provide valuable insight into the efficacy and safety of IberDd as a potential treatment for patients with RRMM.

Keywords: Clinical trial, Multiple myeloma, Immunomodulation