Abstract Submission

14. Myeloma and other monoclonal gammopathies - Clinical

EHA-2692

ANCHOR (OP-104): A PHASE 1 STUDY UPDATE OF MELFLUFEN AND DEXAMETHASONE PLUS BORTEZOMIB OR DARATUMUMAB IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS REFRACTORY TO AN IMID OR A PROTEASOME INHIBITOR

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Does the study abide by applicable national and international regulations and guidelines, including but not limited to ethical committees, data protection and privacy regulations, informed consent and off-label use of drugs?: Yes

Background: Despite recent advances in therapy, multiple myeloma (MM) remains incurable, showing the need for novel therapies. Melflufen is a novel peptide-conjugated alkylator potentiated by intracellular aminopeptidases, which are markedly overexpressed in MM.

In the phase 1/2 study O-12-M1, melflufen + dexamethasone (dex) had promising activity in relapsed/refractory MM (RRMM; overall response rate [ORR], 31%; median overall survival, 20.7 mo), with acceptable safety (Richardson et al. *Blood.* 2017). Melflufen is now being explored in triplet regimens.

Aims: To assess the safety and efficacy of melflufen + dex in a triplet regimen with bortezomib (BTZ) or daratumumab (dara) in patients (pts) with RRMM (ANCHOR, NCT03481556).

Methods: Pts must have RRMM and be refractory (or intolerant) to an IMiD and/or proteasome inhibitor (PI) with 1-4 prior lines of therapy. Pts who receive BTZ or dara cannot be refractory to a PI or have had prior anti-CD38 therapy, respectively. Melflufen (30, 40 or 20 mg intravenously [IV]) is administered on d 1 of each 28-d cycle in 1 of 2 regimens selected based on prior therapy and investigator choice. Regimen A: BTZ 1.3 mg/m^2 subcutaneous + dex 20 mg on d 1, 4, 8 and 11 and dex 40 mg on d 15 and 22. Regimen B: dara 16 mg/kg IV qw (8 doses), every 2 w (8 doses), then every 4 w + dex 40 mg qw. Pts are treated until disease progression (PD)/unacceptable toxicity. The phase 1 primary objective is to determine the optimal melflufen dose in the combination.

Results: As of 6 Feb 2019, 15 pts were treated: 5 in the BTZ combination with melflufen 30 mg (n=3) or 40 mg (n=2) and 10 in the dara combination with melflufen 30 mg (n= 4) or 40 mg (n= 6).

Regimen A (BTZ combination): Median age was 70 y (63-82). Median no. of prior lines was 2 (2-4); 2 pts were refractory to last therapy. Median time since diagnosis was 5.8 y (1.2-7.4). No dose-limiting toxicities (DLTs) were observed in the melflufen 30 mg cohort. The 40 mg cohort is recruiting. After 27 cycles, 3 pts (60%) experienced grade 3/4 treatment-related adverse events (TRAEs), most commonly thrombocytopenia (60%) and neutropenia (40%). One pt experienced treatment-related serious AEs (TRSAEs; grade 3 neutropenia and grade 3 pneumonia). All pts were ongoing on treatment. ORR was 100% for the melflufen 30 mg cohort (median 9 cycles [6-9]) and 0% for the 40 mg cohort (median, 1.5 cycles [1-2]).

Regimen B (dara combination): Median age was 63 y (35-78). Median no. of prior lines was 2.5 (1-3); 6 pts were refractory to last therapy. Median time since diagnosis was 5.0 y (1.9-8.2). No DLTs were observed in the melflufen 30 mg and 40 mg cohorts. After 59 cycles, 6 pts experienced grade 3/4 TRAEs, most commonly neutropenia (40%) and thrombocytopenia (30%). No pts experienced TRSAEs. Nine pts were ongoing on treatment; 1 pt discontinued after 2 cycles due to PD (best response, stable disease). ORR was

100% for the melflufen 30 mg cohort (median, 8 cycles [6-10]) and 50% for the 40 mg cohort (median, 3 cycles [2-8]). The non-responders (n=3) completed a median of 2 cycles. Phase 2 was initiated with melflufen 40 mg.

Summary/Conclusion: Melflufen + dex is feasible as a triplet regimen with BTZ or dara, with promising tolerability and efficacy in pts with RRMM. All pts were ongoing except 1 (dara combination). The longest treatment duration was 10 and 9 cycles for the combination with dara and BTZ, respectively; ORR in pts with ≥ 2 cycles was 78% and 100%, respectively. The study is actively recruiting. Phase 2 has been initiated for the dara combination with melflufen 40 mg.

Keywords: Bortezomib, Clinical trial, Multiple myeloma, Phase I