The OP-104 ANCHOR study: A phase 1/2 study of safety and efficacy of melflufen and dexamethasone in combination with either bortezomib or daratumumab in patients with RRMM; first report on phase 1 data

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Background: Recent improvements in the treatment of relapsed-refractory multiple myeloma (RRMM) have significantly increased the survival of patients. Despite the availability of new therapies, only 20-30% of the RRMM patients respond to any particular treatment and new approaches are clearly needed.

Melflufen is an alkylating peptide belonging to Peptidase Enhanced Compounds (PEnCs) targeting the multiple myeloma (MM) transformation process through aminopeptidase potentiation of the compound; aminopeptidases are heavily over-expressed in MM cells and involved in tumor migration, cell proliferation and angiogenesis. Melflufen selectively targets MM cells through aminopeptidase-driven accumulation, leading to a 50-fold enrichment of alkylating metabolites. The enrichment results in selective cytotoxicity (increased on-target cell potency and decreased off-target cell toxicity), overcomes resistance pathways of existing myeloma treatments (including alkylators) and demonstrates strong anti-angiogenic properties.

Melflufen in combination with dexamethasone (dex) has shown promising activity with an acceptable safety profile. The OP-104 ANCHOR phase 1/2 study was designed to evaluate melflufen and dex in triplet-combination, with either bortezomib or daratumumab in RRMM patients. Preliminary results of the phase I part are reported below.

Methods:
Patients must have RRMM as defined by refractory (or intolerant) to an immunomodulatory agent (IMiD) or a proteasome inhibitor (PI). In combination with bortezomib, patients cannot

be refractory to a PI and in combination with daratumumab patients cannot be previously exposed to any antiCD-38 mAb. Patients must have measurable disease and a maximum of 4 prior lines of therapy. Patients will be treated until documented disease progression or unacceptable toxicity (NCT03481556). The primary objective of phase 1 is to determine the optimal dose of melflufen, up to a maximum of 40 mg, in combination with bortezomib and dex or daratumumab and dex. An additional 20 patients per regimen will be recruited in the phase 2 part of the study where the primary objective is ORR (investigator assessed according to IMWG criteria).

Up to three dose levels of melflufen (30, 40 or 20 mg) are being tested. Melflufen is given i.v. on Day 1 of each 28-day cycle in 2 different combinations. Regimen A, in combination with subcutaneous bortezomib at 1.3 mg/m^2 Days 1, 4, 8 and 11, and 20 mg dex Days 1, 4, 8 and 11, and 40 mg dex Days 15 and 22. Regimen B, in combination with 16 mg/kg daratumumab weekly for 8 doses, every 2 weeks for 8 doses and then every 4 weeks, as well as 40 mg weekly dex. Regimen selection is investigators' choice based on prior therapy.

Results: As of July 18th 2018, 8 patients were enrolled to the study. Two patients in regimen A at 30 mg melflufen, and 6 patients in regimen B, 3 patients at 30 mg melflufen and 3 at 40 mg melflufen.

In regimen A (in combination with bortezomib), the 2 patients treated were 81 and 82 years respectively, had received 4 and 2 prior lines of treatment with 5.6 and 6.9 years since diagnosis respectively. A total of 4 cycles were available for safety evaluation. 30 mg melflufen was well tolerated with no reported DLTs. One patient experienced a grade 3 (G3) neutropenia. After one cycle of treatment, 1 patient achieved an MR and 1 patient achieved SD.

In regimen B (in combination with daratumumab), median age was 56 years, median number of prior lines was 2 (1-3) and median years since diagnosis was 2.3 years. A total of 9 cycles were available for safety evaluation in 3 patients at 30 mg melflufen. 30 mg melflufen was well tolerated with no reported DLTs. Two patients experienced treatment-related G3 neutropenia. After one cycle of treatment, the 3 patients treated with melflufen 30 mg achieved PR, MR and MR. All patients are ongoing. Safety and efficacy for melflufen 40 mg dose level has not been evaluated yet.

The study is ongoing and updated results on the phase 1 trial will be presented at the meeting.

Conclusion: Combining melflufen with bortezomib or daratumumab seems feasible, and well tolerated with no DLT in the melflufen 30 mg cohorts. Early signs of activity are seen after only 1 cycle of therapy. Updated results on the phase 1 trial will be presented at the meeting.