OP-106 HORIZON - Melflufen therapy for RRMM patients refractory to daratumumab and/or pomalidomide; updated results and clinical outcome

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Background: Melflufen is an alkylating peptide belonging to the novel class of Peptidase Enhanced Compounds (PEnCs) which targets multiple myeloma (MM) through a unique mechanism of action. Aminopeptidases are heavily over-expressed and are key for the transformation process in MM, being critically involved in tumor migration, cell proliferation and angiogenesis. Specifically, melflufen selectively targets MM cells through aminopeptidase-driven accumulation, leading to a 50-fold enrichment of alkylating metabolites. This enrichment results in selective cytotoxicity, with increased on-target cell potency and decreased off-target toxicity. It also overcomes resistance pathways of existing myeloma treatments, including alkylators, as well as demonstrating strong anti-angiogenic properties (*Clin Can Research* 2013 19(11):3019-31).

In a Phase 1/2 study O-12-M1 (NCT01897714), melflufen was evaluated in relapsed-refractory multiple myeloma (RRMM) patients (pts) that had received 2+ prior lines of therapy, were exposed to immunomodulatory agents and proteasome inhibitors (IMiDs and PIs) and were refractory to their last line of therapy. Overall response rate (ORR) was 31%, with a median progression-free survival (PFS) of 5.7 months and a median overall survival of 20.7 months (*Blood* 2017 130:3150).

The Phase 2 HORIZON-study further evaluates the benefit of melflufen in highly refractory pts who have progressed on treatment with IMiDs and PIs and are refractory to pomalidomide (pom) and/or daratumumab (dara), with few remaining treatment options.

Methods: RRMM pts with 2 or more prior lines of therapy exposed to IMiDs and PIs and are refractory to pom and/or dara received melflufen 40 mg i.v. on Day 1 of each 28-day cycle and dexamethasone 40 mg weekly (NCT02963493). The primary objective is ORR (PR or better)

with investigator assessed response by IMWG criteria. Pts receive treatment until disease progression (PD) or unacceptable toxicity.

Results: As of 10 May 2018, 62 pts had been dosed. Median age was 62 (41-82), median time since diagnosis was 6.1 years (1-16); 50% of the pts were ISS stage 3 at diagnosis (missing data for 18 pts) and 54% had high-risk cytogenetics at study entry defined as del(17p), t(4;14), t(14;16), t(14;20) or gain(1q). Median number of prior lines of therapy was 5.5 (2-12). 90% of the pts were pom exposed and 63% were dara exposed; 56% of pts were refractory to both pom and dara and 89% were double refractory (IMiDs and PIs). In addition, 89% had received prior alkylator therapy with 58% refractory and 76% had received prior ASCT therapy.

In total, 188 doses (1-11 cycles) of melflufen were administered. 79% pts completed 2 or more cycles of melflufen, and at data cut-off, treatment was ongoing in 34% of pts. Treatment had been discontinued in 47% of pts due to PD, 15% due to AE, 3% due to physician's decision and in 1 case at pt's request. Treatment-emergent AEs were reported in 60 (97%) pts. Treatment-related grade 3/4 AEs were reported in 48 (77%) pts including neutropenia (60%), thrombocytopenia (60%), and anemia (27%). Treatment-related non-hematologic grade 3/4 events were rare, with infections in only 6% of pts. Thirteen (21%) pts experienced melflufen-related SAEs including febrile neutropenia (6%) and pneumonia (3%). No treatment-related deaths were reported.

A total of 56 pts were evaluable for response: ORR was 32% and clinical benefit rate (CBR, MR or better) 39%. Per protocol, efficacy evaluable pts ($\geq$ 2 doses of melflufen) had an ORR of 38% and a CBR of 46%. Pts with ISS stage 3 at diagnosis showed benefit from treatment with an ORR of 24% and a CBR of 33%, and pts with high-risk cytogenetics had an ORR. The next data-cut will be made in Nov 2018, and will include first analysis of PFS and DOR.

Conclusion: Melflufen has promising activity in heavily pre-treated and refractory late stage RRMM pts, in whom the majority of available, approved and experimental therapies have failed. Analysis of the preliminary efficacy results showed an encouraging ORR of 32% and a CBR of 39% in a population with a median of 5.5 prior lines of therapy, including 54% with high-risk cytogenetics. Melflufen was generally well tolerated with discontinuation due to AE in only 15% of pts. Thrombocytopenia and neutropenia were the most frequent AEs and non-hematologic AEs were infrequent. Updated data, including PFS and DOR, will be presented at the meeting.