Melflufen therapy for Relapsed Refractory Multiple Myeloma (RRMM) patients Refractory to Daratumumab and/or Pomalidomide; a report on early efficacy

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Background: Melflufen is a next generation alkylator, designed for efficient targeting of tumor cells with a unique mechanism of action. Melflufen provides a peptidase potentiated therapy with an alkylating payload, and triggers rapid, robust and irreversible DNA damage. The effect of melflufen is exerted through alkylation of DNA. The lipophilicity of melflufen leads to rapid and extensive distribution into cells where it is readily metabolized by intracellular peptidases (often over-expressed in malignant cells) into hydrophilic alkylating metabolites leading to 50-fold enrichment of these metabolites in MM cells. In addition, melflufen has potent anti-angiogenic properties.

Patients with relapsed refractory multiple myeloma now have an abundance of available therapeutic options. However, even with these advances, patients still relapse and an unmet medical need remains. Here we report on the early efficacy of melflufen in myeloma patients that are exposed to proteasome inhibitors (PI) and immunomodulatory drugs (IMiD), and are refractory to pomalidomide and/or daratumumab. Phase 1/2 of melflufen in combination with dexamethasone has been completed (O-12-M1), while phase 2 (Horizon) and phase 3 (Ocean) studies are ongoing.

Methods: Melflufen 40 mg is given i.v. on Day 1 of each 28-day cycle, with dexamethasone 40 mg weekly, in RRMM patients refractory to pomalidomide and/or daratumumab with measurable disease and at least 2 prior lines of therapy including an IMiD) and a PI (NCT02963493). Response is investigator assessed at each cycle by IMWG criteria. The primary objective is overall response rate (ORR). Patients receive treatment until there is documented disease progression or unacceptable toxicity.

Results: As of 27 July 2017, 20 patients were dosed and included in the analyses of the data presented, while recruitment was ongoing. The median time from initial diagnosis was 6.0 years (0.6-13). The median number of prior therapies was 6 (3-11). 11 patients had received prior melphalan (55%). 15 patients (75%) were double refractory (IMiDs and PIs), 14 (70%) triple refractory (2 PIs + 1 IMiD or 1 PI + 2 IMiDs) and 8 (40%) were quadruple refractory (lenalidomide, bortezomib, pomalidomide and daratumumab). In total, 42 doses of melflufen had been given (1-6 cycles). Ten patients (50%) had completed at least two cycles of melflufen. Treatment had been discontinued in one patient (5%) due to adverse events (AE) and in 8 patients (40%) due to progression, while treatment was still ongoing in 11 patients (55%). Treatment-emergent AEs, regardless of grade, were reported in 17 patients (85%); including thrombocytopenia (60%), neutropenia (40%), anemia (25%), pyrexia (25%), hypocalcaemia (15%), and in 2 patients (10%) each of asthenia, bone pain, constipation, headache, hypokalaemia, hypomagnesaemia, leukopenia, nausea, oral pain and peripheral sensory neuropathy. Treatment-related grade 3/4 AEs were reported in 12 patients (60%); with those occurring in >10% of the patients included thrombocytopenia (45%), neutropenia (30%) and anemia (15%).

Ten of the 20 patients were evaluable for response (protocol defined as received ≥ 2 doses of melflufen and had a baseline and at least one post-baseline disease assessment). All 10 patients were refractory to pomalidomide, and 7 were refractory to both pomalidomide and daratumumab. Two patients (20%) achieved very good partial response (VGPR) and one (10%) achieved partial response (PR) for an overall response rate (ORR) of 30%. One patient achieved minimal response (MR) for a clinical benefit rate (CBR) of 40%. Six patients (60%) had maintained stable disease (SD) as their best response. Six of the 10 patients were still ongoing.

Conclusion: Melflufen has promising activity in late stage RRMM patients (median 6 prior lines) where conventional therapies have failed, and is well tolerated. Thrombocytopenia and neutropenia were as expected, the primary toxicities and non-hematologic AEs were infrequent. The ORR of 30% and CBR 40% in an early analysis are encouraging results and recruitment is ongoing.

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