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Clinical Activity of Melflufen in Patients With Triple-Class Refractory Multiple Myeloma and Poor-Risk Features in an Updated Analysis of HORIZON (OP-106), a Phase 2 Study in Patients with Relapsed/Refractory Multiple Myeloma Refractory to Pomalidomide and/or Daratumumab

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Background: Recent advances have improved survival in multiple myeloma (MM; Kumar et al. *Leukemia.* 2014); however, the disease remains incurable. Patients with triple-class refractory MM have a median overall survival (OS) of only 9.2 months (Ghandi et al. *Leukemia*. 2019). These patients and those with poor-risk features, such as high-risk cytogenetics, have few treatment options and represent a patient group with a very poor prognosis and high unmet medical need.

Melflufen is a lipophilic peptide-conjugated alkylator that rapidly delivers a highly cytotoxic payload into myeloma cells through peptidase activity. Meflufen is taken up by myeloma cells and immediately cleaved by peptidases into hydrophilic alkylator payloads that induce irreversible DNA damage and apoptosis. This updated analysis of the ongoing HORIZON study in patients with MM refractory to pomalidomide (pom) and/or daratumumab (dara) includes a subgroup analysis of patients with triple-class refractory (no response or progression on or within 60 days of last dose to at least 1 IMiD, 1 proteasome inhibitor [PI], and 1 anti-CD38 monoclonal antibody) and high-risk cytogenetics at baseline (NCT02963493).

Methods: Patients with relapsed refractory MM (RRMM) must have received ≥2 prior lines, been exposed to an IMiD and PI, and be refractory to pom and/or dara. Patients receive 40-mg melflufen intravenously on day 1 of each 28-day cycle and 40-mg weekly dexamethasone (dex; 20 mg for patients aged ≥75 years) until progressive disease (PD) or unacceptable toxicity. The primary endpoint is overall response rate (ORR; ≥ partial response [PR]; investigator assessed per International Myeloma Working Group criteria). Secondary endpoints include safety, clinical benefit rate (CBR; ≥ minimal response), progression-free survival (PFS), OS, and duration of response (DOR).

Results: As of 6 May 2019, 121 patients were treated. The median age was 64 years (range, 35-86), median time since diagnosis was 6.2 years (range, 0.7-25), 29% of patients had International Staging System stage 3 disease, and 62% with available cytogenetic data (n=81) had high-risk cytogenetics at study entry. The median number of prior lines was 5 (2-12). All patients were pom or dara refractory and received prior PIs and IMiDs; 74% were triple-class refractory. With a median follow-up of 10.8 months, 29% of patients were on ongoing treatment. Of 86 patients (71%) who discontinued treatment, 69% discontinued due to PD, 20% due to adverse events (AEs), and 12% for other reasons.

In total, 113 patients had available response data. ORR was 28%; 1 patient achieved stringent complete response (sCR), 9% very good PR (VGPR), and 19% PR. CBR was 40%. Median PFS for all patients treated (N=121) was 4.0 months (95% CI, 3.7-4.6), median OS was 11.2 months (95% CI, 8.1-13.9), and median DOR was 4.4 months (95% CI, 3.6-8.3). Efficacy was examined in poor-risk patient subsets with available response data. ORR was 20% in patients with triple-class refractory disease (n=83). ORR in patients with high-risk cytogenetics was 28%. Median DOR was 3.6 months in responders with triple-class refractory disease. DOR in patients with high-risk cytogenetics was 5.1 months.

Treatment-related grade 3 and grade 4 AEs were reported in 24% and 49% of patients, respectively. Most common (≥5%) grade 4 AEs were thrombocytopenia (36%) and neutropenia (31%). The incidence of treatment-related grade 3/4 nonhematologic AEs was low; most commonly pneumonia (3%), fatigue (2%), and upper respiratory tract infection (2%). Treatment-related serious AEs occurred in 20% of patients. No treatment-related deaths were reported.

Conclusion: Melflufen continues to show promising activity (ORR, 28%) in patients with late-stage RRMM refractory to dara and/or pom and was generally well tolerated, with infrequent nonhematologic AEs and, of the 121 patients treated, 14% discontinued due to AEs. Additionally, melflufen has comparable efficacy in subsets of patients with poor-risk features, including triple-class refractory and high-risk cytogenetics, relative to the overall HORIZON patient population. Melflufen plus dex is being further investigated vs pom plus dex in the OCEAN phase 3 study (OP-103; NCT03151811) in patients with RRMM refractory to lenalidomide.