**Background:** MM remains an incurable disease with current therapeutic options, demonstrating the need for novel therapies. Melflufen is a lipophilic peptide-conjugated alkylator that rapidly delivers a highly cytotoxic payload into myeloma cells through peptidase activity.

In the phase 1/2 study O-12-M1, melflufen + dexamethasone had promising activity in RRMM (overall response rate [ORR], 31%; median progression-free survival [PFS], 5.7 mo; median overall survival, 20.7
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mo), with acceptable safety (Richardson PG, et al. Blood. 2017; Abstract 3150). Daratumumab and bortezomib are 2 approved therapeutic agents with different mechanisms of action commonly used in the treatment of patients with RRMM. The phase 1/2 study OP-104 ANCHOR evaluates the safety and efficacy of melflufen and dexamethasone in a triplet regimen with bortezomib or daratumumab in patients with RRMM (NCT03481556).

Methods: Patients must have RRMM and be refractory (or intolerant) to an IMiD and/or PI, with 1-4 prior lines of therapy. Patients assigned to the bortezomib or daratumumab arms cannot be refractory to a PI or have received prior anti-CD38 therapy, respectively. Regimens were selected based on prior therapy and investigator choice. Melflufen (30, 40, or 20 mg intravenously [IV]) was administered on d 1 of each 28-d cycle for both regimens. Regimen A: bortezomib 1.3 mg/m² subcutaneous + dexamethasone 20 mg (12 mg if aged ≥75 y) on d 1, 4, 8, and 11 and dexamethasone 40 mg (20 mg if aged ≥ 75 y) on d 15 and 22. Regimen B: daratumumab 16 mg/kg IV once weekly (8 doses), every 2 wk (8 doses), then every 4 wk + dexamethasone 40 mg (20 mg if aged ≥75 y) weekly. Patients are treated until progressive disease (PD) or unacceptable toxicity. The phase 1 primary objective is to determine the optimal melflufen dose for the combinations. The primary objective in phase 2 is ORR.

Results: Regimen A: As of data cutoff (8 May 2019), 5 patients had been treated with melflufen (30 mg, n=3; 40 mg, n=2) and dexamethasone in combination with bortezomib. Median age was 73 y (range, 63-82). Median time since diagnosis was 5.8 y (range, 1.2-7.4). Median number of prior lines was 2 (range, 2-4); 2 patients were refractory to their last therapy. No dose-limiting toxicities (DLTs) were observed at any dose level. Three patients (60%) had grade 3/4 treatment-related adverse events (TRAEs), most commonly (≥2 patients) thrombocytopenia (n=3) and neutropenia (n=2). The incidence of nonhematologic TRAEs was low. One patient experienced treatment-related serious AEs (TRSAEs; neutropenia and pneumonia). No deaths were reported. ORR was 100%; 2 patients achieved very good partial response (VGPR), and 3 achieved a partial response (PR). Four patients (80%) remained on treatment; 1 patient discontinued from PD after 10 mo. Median treatment duration was 7.4 mo (range, 2-11).

Regimen B: As of data cutoff (8 May 2019), 24 patients had been treated with melflufen (30 mg, n=6; 40 mg, n=18) in combination with daratumumab. Median age was 62 y (range, 35-78), median number of prior lines was 2 (range, 1-4); 12 patients (50%) were refractory to last therapy; and 19 patients (79%) received prior autologous stem cell transplantation. Median time since diagnosis was 3.7 y (range, 0.7-8.2). Median treatment duration was 7.9 mo (range, 0-11) and 1.2 mo (range, 0-9), in the 30-mg and 40-mg cohorts respectively. ORR in the total population (n=24, 15 with available response data) was 60%, and ORR in patients treated with ≥2 cycles (9/11) was 82%. Median PFS was not reached. No DLTs were observed at any dose level. Nineteen patients had grade 3/4 TRAEs, most commonly (≥2 patients) neutropenia (63%), thrombocytopenia (58%), and anemia (13%). The incidence of grade 3/4 nonhematologic TRAEs was low (13%). Four patients experienced TRSAEs (neutropenia and thrombocytopenia [1 patient], febrile neutropenia, pyrexia, and abdominal pain). Six (100%) and 16 (89%) remained on treatment in the 30-mg and 40-mg cohorts, respectively; 2 patients discontinued treatment due to physician decision (1 for lack of response).

Conclusion: Melflufen and dexamethasone is well tolerated as a triplet regimen with bortezomib or daratumumab and has encouraging efficacy in patients with RRMM, with ORR >80% in evaluable patients. Approximately 90% of patients remain on treatment, and responses with both combinations improved with continued therapy. The ANCHOR study is ongoing using the 40-mg melflufen recommended phase 2 dose.