Deadline: August 1, 2019, 11:59 p.m. Pacific time

ANCHOR (OP-104): Updated Efficacy and Safety from a Phase 1/2 Study of Melflufen and Dexamethasone plus Bortezomib or Daratumumab in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD or a Proteasome Inhibitor (PI)

Authors: Enrique M. Ocio[1]; Yvonne A. Efebera[2]; Miquel Granell[3]; Roman Hájek[4]; Vladimir Maisnar[5]; Lionel Karlin[6]; María-Victoria Mateos[7]; Paul G. Richardson[8]; Albert Oriol[9;] Stefan Norin[10]; Malin Sydvander[10]; Jakob Obermüller[10]; and Luděk Pour[11]

Affiliations: [1]University Hospital Marqués de Valdecilla (IDIVAL), University of Cantabria, Santander, Spain; [2]Division of Hematology, The Ohio State University, Columbus, OH, USA; [3]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]Department of Hemato-oncology, University Hospital Ostrava, Ostrava, Czech Republic; [5]Fourth Department of Medicine - Hematology, FN and LF UK Hradec Králové, Hradec Králové, Czech Republic; [6]Department of Hematology, Centre Hospitalier Lyon-Sud, University Claude Bernard Lyon 1, Pierre-Benite, France; [7]Hospital Clinico Universitario de Salamanca, Salamanca, Spain; [8]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [9]Hospital Germans Trias i Pujol, Badalona, Spain; [10]Oncopeptides AB, Stockholm, Sweden; and [11]Fakultní nemocnice Brno, Brno, Czech Republic

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Keywords (Up to 3 keywords are permitted; suggestions from prespecified list): chemotherapy, DNA damage, multiple myeloma
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Updated Analyses (yes/no): Yes. This analysis has an updated data cutoff of 8 May 2019 versus the 6 February 2019 data cutoff reported in the abstract accepted by EHA 2019, with safety and efficacy data for 14 additional patients enrolled to the melflufen and dexamethasone plus daratumumab cohort
Interim Analysis of Clinical Trial: No
Off-Label Disclosure: Yes, this is a phase 1/2 investigational study of melflufen in RRMM
First time submitting an abstract to the ASH annual meeting? No
Funded in part or in whole by U.S. Federal Government? No
Is the presenter a hematologist in training? No
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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

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/m^2 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.