# ANCHOR: melflufen plus dexamethasone and daratumumab or bortezomib in relapsed/refractory multiple myeloma: final results of a phase I/IIa study

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## Abstract

Melphalan flufenamide (melflufen), a first-in-class, alkylating peptide-drug conjugate, demonstrated clinical benefit in combination with dexamethasone in triple-class refractory multiple myeloma (MM). The phase I/IIa ANCHOR study evaluated melflufen (30 or 40 mg) and dexamethasone (40 mg with daratumumab; 20 mg followed by 40 mg with bortezomib; dose reduced if aged ≥75 years) in triplet combination with daratumumab (16 mg/kg; daratumumab arm) or bortezomib (1.3 mg/m$^2$; bortezomib arm) in patients with relapsed/refractory MM refractory to an immunomodulatory agent and/or a proteasome inhibitor and who had received one to four prior lines of therapy. Primary objectives were to determine the optimal dose of melflufen in triplet combination (phase I) and overall response rate (phase IIa). In total, 33 patients were treated in the daratumumab arm and 23 patients received therapy in the bortezomib arm. No dose-limiting toxicities were reported at either melflufen dose level with either combination. With both triplet regimens, the most common grade ≥3 treatment-emergent adverse events were thrombocytopenia and neutropenia; thrombocytopenia was the most common treatment-emergent adverse event leading to treatment discontinuation. In the daratumumab arm, patients receiving melflufen 30 mg remained on treatment longer than those receiving the 40-mg dose. In the daratumumab arm, the overall response rate was 73% and median progression-free survival was 12.9 months. Notably, in the bortezomib arm, the overall response rate was 78% and median progression-free survival was 14.7 months. Considering the totality of the data, melflufen 30 mg was established as the recommended dose for use with dexamethasone and daratumumab or bortezomib for future studies in relapsed/refractory MM.

## Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and is a disease of terminally differentiated plasma cells.[1] The introduction of newer therapies over the past few years has improved the outcome of patients with MM; however, the disease will eventually develop resistance mechanisms toward treatment, with subsequent relapse as a result.[2,3] Because MM becomes increasingly refractory as the disease progresses, and remission duration with each subsequent relapse is shorter, new therapy combinations with deeper and more prolonged responses are urgently needed.[2,4]

Melphalan flufenamide (melflufen) is a first-in-class, alkylating peptide-drug conjugate.[5-10] Due to its high lipophilicity, melflufen is rapidly and passively taken up by tumor

cells. Once inside the cell, melflufen is rapidly hydrolyzed by peptidases and esterases, which leads to the intracellular distribution and enrichment of cytotoxic, hydrophilic alkylating agents (melphalan and desethyl-melflufen).[8-10] Melflufen plus dexamethasone was approved for use in Europe in patients with triple-class refractory (i.e., refractory to ≥1 immunomodulatory agent, ≥1 proteasome inhibitor, and ≥1 anti-CD38 monoclonal antibody) relapsed/refractory MM (RRMM) who have received ≥3 prior lines of therapy, who have demonstrated disease progression on or after the last line of therapy, and who have progressed ≥3 years after a previous autologous stem cell transplant (ASCT), if one was received.[11] Approval was based on results from the pivotal, phase II HORIZON study and was supported by results from the phase III, randomized, controlled OCEAN study.[11-13]

Proteasome inhibitors (e.g., bortezomib), immunomodulatory agents (e.g., lenalidomide), and anti-CD38 monoclonal antibodies (e.g., daratumumab) are standard-of-care drug classes for patients with MM,[14] but development of resistance to these agents is of clinical concern.[3] Current treatment guidelines recommend triplet combination regimens when available for patients in first relapse and beyond.[14] Furthermore, regimens should contain at least two new drugs to which the patient is not refractory.[14,15] In preclinical studies, melflufen showed anti-myeloma activity in bortezomib-resistant MM cell lines,[16] suggesting that it may also have the potential to synergize with bortezomib therapy. Thus, the ANCHOR study evaluated the safety and efficacy of the triplet combinations of melflufen plus dexamethasone and daratumumab or bortezomib.

# Methods

## Study design and patients

ANCHOR (OP-104; NCT03481556) was an open-label, phase I/IIa, non-comparative study investigating melflufen in combination with dexamethasone and either daratumumab or bortezomib in patients with RRMM.

Eligible patients aged ≥18 years had a prior diagnosis of MM with disease progression after one to four prior lines of therapy, were refractory to (or intolerant of) an immunomodulatory agent and/or a proteasome inhibitor, and had measurable disease at the time of screening. In the bortezomib arm, prior proteasome inhibitor therapy was allowed, but patients could not be refractory to proteasome inhibitors in the last line of therapy. In the daratumumab arm, prior anti-CD38 monoclonal antibody therapy was not allowed (see the *Online Supplementary Data* for full eligibility criteria).

The phase I portion of the study followed a standard 3+3 dose-escalation design. The starting dose of melflufen was 30 mg. If no dose-limiting toxicities were reported, the next cohort received melflufen 40 mg. Patients received melflufen intravenously on day 1 of each 28-day cycle. In the daratumumab arm, patients also received daratumumab 16 mg/kg intravenously on days 2, 8, 15, and 22 in cycle 1, days 1, 8, 15, and 22 in cycle 2, days 1 and 15 in cycles 3 to 6, and day 1 in cycle 7 and beyond, and dexamethasone 40 mg on days 1, 8, 15, and 22 (reduced to 20 mg for patients aged ≥75 years). In the bortezomib arm, patients also received bortezomib 1.3 mg/m$^2$ subcutaneously on days 1, 4, 8, and 11, and dexamethasone 20 mg on days 1, 4, 8, and 11 and 40 mg on days 15 and 22 (reduced to 12 and 20 mg, respectively, if aged ≥75 years). Patients received assigned therapy until disease progression, unacceptable toxicity, or if the patient or physician determined it was not in the patient's best interest to continue therapy. In the phase IIa portion of the study, 20 additional efficacy-evaluable patients were planned to be treated at the recommended dose. Further details of the study design are provided in the *Online Supplementary Data*.

The study sponsor (Oncopeptides AB) together with two authors (EMO and PGR) designed the protocol. National regulatory authorities and independent ethics committees or institutional review boards approved the study, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice guidelines. All patients provided written informed consent. All authors had full access to the data, participated in data interpretation, and reviewed and approved the manuscript before submission.

## Endpoints and analyses

The primary objectives were to determine the optimal dose of melflufen plus dexamethasone and bortezomib or daratumumab (phase I) and to evaluate the overall response rate (ORR) of melflufen in triplet combination at the dosage determined in phase I (phase IIa). Secondary endpoints included best response, duration of response, progression-free survival (PFS), overall survival (OS), and frequency and grade of adverse events (AE). All patients were included in safety and efficacy analyses (see the *Online Supplementary Data* for all endpoints and statistical analyses).

# Results

## Patients

As of February 9, 2022, the data cutoff date, 33 patients had received therapy with melflufen, daratumumab, and dexamethasone (daratumumab arm), whereas 23 patients had received therapy with melflufen, bortezomib, and dexamethasone (bortezomib arm) in 13 sites in four countries (Czech Republic, France, Spain, USA). The study was prematurely terminated on February 23, 2022, due to financial considerations following a partial clinical hold issued by the US Food and Drug Administration for studies evaluating

melflufen. In the daratumumab arm, patients had begun to receive therapy on April 12, 2018, and the study arm was fully enrolled at the time of study termination. Patients in the bortezomib arm had begun to receive therapy on May 7, 2018; the study was still enrolling patients at the time of study termination.

In the daratumumab arm in the dose-finding portion of the study (phase I), four patients received melflufen 30 mg and six patients received melflufen 40 mg (*Online Supplementary Table S1*). No dose-limiting toxicities were observed at either melflufen dose level; thus, 21 more patients were enrolled at the 40-mg dose level in the dose-expansion portion. An additional two patients received melflufen 30 mg in phase IIa due to a site error at the first dosing, and it was decided that these patients would continue with melflufen 30 mg for the remainder of the study. Among a total of 33 patients enrolled in the daratumumab arm (30 mg, n=6; 40 mg, n=27), the most common reasons for treatment discontinuation were progressive disease (30 mg, n=2 [33%]; 40 mg, n=13 [48%]) and AE (30 mg, n=1 [17%]; 40 mg, n=7 [26%]).

The dose-finding portion (phase I) of the bortezomib arm included six patients who received melflufen 30 mg and seven patients who received melflufen 40 mg (*Online Supplementary Table S1*). No dose-limiting toxicities were observed at either dose of melflufen. Phase IIa enrolled nine patients into the 30-mg cohort and one patient into the 40-mg cohort due to a site error at the first dosing, but the patient continued at the 30-mg dose thereafter. Among the total of 23 patients enrolled in the bortezomib arm (30 mg, n=15; 40 mg, n=8), the most common reason for treatment discontinuation was study termination (30 mg, n=7 [47%]; 40 mg, n=3 [38%]).

The patients' baseline characteristics and demographics are shown in Table 1. In the daratumumab arm, the median age was 63 years (range, 35-78), the median number of prior lines of therapy was 2.0 (range, 1-4), 26 patients (79%) had undergone a prior ASCT in front-line therapy, 21 patients (64%) had disease refractory to an immunomodulatory agent, and four patients (12%) had evidence of extramedullary disease. In the bortezomib arm, the median age was 70 years (range, 55-82), the median number of prior lines of therapy was 3.0 (range, 1-4); nine patients (39%) had undergone a prior ASCT in front-line therapy, 21 patients (91%) had disease refractory to an immunomodulatory agent, and four patients (17%) had evidence of extramedullary disease.

### Melflufen, daratumumab, and dexamethasone (daratumumab arm)

Among 33 patients who received melflufen, dexamethasone, and daratumumab treatment in phase I and phase IIa, the most common any-grade and grade ≥3 treatment-emergent (TE)AE were thrombocytopenia (88% and 85%), neutropenia (79% and 73%), and anemia (64% and 24%) (*Online Supplementary Table S2*). In total, 12 patients (36%; 30 mg, 3 [50%]; 40 mg, 9 [33%]) reported a treatment-emergent infection in association with grade ≥3 neutropenia, defined as an infection with an onset date within ±7 days of the onset and/or resolution date of a grade 3 or 4 decrease in absolute neutrophil count. No TEAE related to bleeding occurred in >10% of patients. Second primary malignancies were reported in two patients (6%). One patient (3%) with prior exposure to cyclophosphamide and a prior ASCT with high-dose melphalan had osteosarcoma while in OS follow-up, occurring 17.1 months after the first dose of study treatment and 9 months after the last dose of melflufen. One case (3%) of acute myeloid leukemia was reported in a patient with no prior exposure to cyclophosphamide who had received prior ASCT with high-dose melphalan while in OS follow-up, occurring 21.2 months after the first dose of study treatment and 3.9 months after the last dose of melflufen. Of a total of four fatal AE reported, two occurred ≤30 days after the last dose of study drug (sepsis, 30-mg group; chronic cardiac failure, 40-mg group), and two occurred >30 days after the last dose of study drug (sepsis and general physical health deterioration, both in the 40-mg group). Among these deaths, only one (the sepsis event) was considered related to melflufen by the site investigator.

In the daratumumab arm, the median duration of treatment was 24.2 months (range, 0.9-44.7) in the 30-mg cohort and 6.2 months (range, 0.9-41.2) in the 40-mg cohort at a median follow-up of 34.0 months and 18.4 months, respectively (*Online Supplementary Table S3*). TEAE that led to melflufen dose interruptions occurred in 29 patients overall (6 of 6 patients [100%] in the 30-mg group and 23 of 27 patients [85%] in the 40-mg group) (*Online Supplementary Table S4*), most commonly thrombocytopenia (4 patients [67%] in the 30-mg group and 19 patients [70%] in the 40-mg group) and neutropenia (3 patients [50%] in the 30-mg group and 7 patients [26%] in the 40-mg group). The interval between doses while on the assigned melflufen dose was longer in the 30-mg group than in the 40-mg group (median interval: 35 days and 28 days, respectively), but a similar number of patients experienced at least one prolonged treatment cycle (lasting ≥32 days) in the 30-mg group as in the 40-mg group (5 of 6 patients [83%] and 21 of 27 patients [78%], respectively). A total of 12 patients (4 of 6 [67%] in the 30-mg group, 8 of 27 [30%] in the 40-mg group) experienced a prolonged treatment cycle in their first cycle, which delayed initiation of cycle 2 treatment; hematologic toxicities were the reason for treatment delay in nine of these patients (2 [33%] in the 30-mg group; 7 [26%] in the 40-mg group). TEAE leading to melflufen dose reductions occurred in three of six patients (50%) in the 30-mg group and 19 of 27 patients (70%) in the 40-mg group. At the 30-mg and 40-mg doses, the median number of cycles before the first melflufen dose reduction was 5.0 (range, 1-5) and 3.0 (range, 1-12), respectively, whereas the median number of treatment cycles after the first melflufen

dose reduction was 9.0 (range, 1-15) and 2.0 (range, 1-19), respectively. The most common TEAE leading to study treatment discontinuation were thrombocytopenia (1 of 6 patients [17%] in the 30-mg group, 11 of 27 patients [41%] in the 40-mg group). In the 30-mg and 40-mg groups, the patients received a median of 21.5 (range, 1-45) and 6.0 (range, 1-41) treatment cycles, respectively; two patients (33%) and seven patients (26%) discontinued melflufen but continued daratumumab and dexamethasone for a median of 8.5 (range, 8-9) and 9.0 (range, 1-13) treatment cycles. In the 30-mg and 40-mg groups, red blood cell transfusions were required by 67% *versus* 33% of the patients, respectively, and platelets were needed by 50% *versus* 33% of patients, respectively. The median total cumulative dose of melflufen administered was 334 mg (range, 30-1,350) in the 30-mg group and 150 mg (range, 40-870) in the 40-mg group (*Online Supplementary Table S3*). Overall, these data show that patients in the 30-mg group remained on treatment for a longer time than those in the 40-mg group, leading to higher drug exposure in the 30-mg group.

In total, 24 of 33 patients achieved a partial response or better for an ORR of 73% (95% confidence interval [95% CI]: 55-87) in the overall population (i.e., 30-mg and 40-mg groups combined), with one patient (3%) achieving a stringent complete response, two patients (6%) a complete response, eight patients (24%) a very good partial response, and 13 patients (39%) a partial response (Table 2). A ≥25% reduction in M-protein was observed in 28 of 33 (85%) patients (*Online Supplementary Figure S1*). The median duration of response was 12.0 months (95% CI: 7.6-24.2) (*Online Supplementary Figure S2*). At a median follow-up of 30.2 months, the median PFS was 12.9 months

**Table 1.** Baseline patient and disease characteristics.

| **Triplet regimen evaluated** | **Melflufen, dexamethasone, daratumumab** | | | **Melflufen, dexamethasone, bortezomib** | | |
|---|---|---|---|---|---|---|
| **Melflufen dose** | **30 mg N=6** | **40 mg N=27** | **Overall N=33** | **30 mg N=15** | **40 mg N=8** | **Overall N=23** |
| Age in years, median (range) | 57 (49-78) | 66 (35-77) | 63 (35-78) | 70 (55-82) | 71 (61-76) | 70 (55-82) |
| Female, N (%) | 3 (50) | 8 (30) | 11 (33) | 7 (47) | 1 (13) | 8 (35) |
| Time since diagnosis in years, median (range) | 3.1 (1.9-8.0) | 3.9 (0.7-15.6) | 3.8 (0.7-15.6) | 5.8 (1.4-10.7) | 2.0 (1.2-8.0) | 5.1 (1.2-10.7) |
| ECOG PS, N (%) | | | | | | |
| 0 | 3 (50) | 11 (41) | 14 (42) | 7 (47) | 2 (25) | 9 (39) |
| 1 | 2 (33) | 14 (52) | 16 (48) | 7 (47) | 6 (75) | 13 (57) |
| 2 | 1 (17) | 2 (7) | 3 (9) | 1 (7) | 0 | 1 (4) |
| ISS at study entry, N (%) | | | | | | |
| I | 6 (100) | 20 (74) | 26 (79) | 10 (67) | 5 (63) | 15 (65) |
| II | 0 | 4 (15) | 4 (12) | 3 (20) | 2 (25) | 5 (22) |
| III | 0 | 3 (11) | 3 (9) | 2 (13) | 1 (13) | 3 (13) |
| Cytogenetic risk group, N (%)[a] | | | | | | |
| High risk | 3 (50) | 12 (44) | 15 (45) | 6 (40) | 3 (38) | 9 (39) |
| Standard risk | 1 (17) | 3 (11) | 4 (12) | 3 (20) | 1 (13) | 4 (17) |
| Unknown | 2 (33) | 12 (44) | 14 (42) | 6 (40) | 4 (50) | 10 (43) |
| Extramedullary disease, N (%) | 0 | 4 (15) | 4 (12) | 3 (20) | 1 (13) | 4 (17) |
| Previous lines of therapy, median (range) | 2.5 (1-3) | 2.0 (1-4) | 2.0 (1-4) | 4.0 (2-4) | 2.5 (1-4) | 3.0 (1-4) |
| Prior ASCT, N (%) | | | | | | |
| As front-line therapy | 5 (83) | 21 (78) | 26 (79) | 6 (40) | 3 (38) | 9 (39) |
| As salvage therapy | 2 (33) | 4 (15) | 6 (18) | 1 (7) | 1 (13) | 2 (9) |
| Refractory to prior therapy, N (%) | 3 (50) | 21 (78) | 24 (73) | 15 (100) | 7 (88) | 22 (96) |
| Alkylator[b] | 1 (17) | 3 (11) | 4 (12) | 3 (20) | 1 (13) | 4 (17) |
| Anti-CD38 monoclonal antibody | 0 | 0 | 0 | 5 (33) | 2 (25) | 7 (30) |
| Immunomodulatory agent | 3 (50) | 18 (67) | 21 (64) | 15 (100) | 6 (75) | 21 (91) |
| Proteasome inhibitor | 0 | 15 (56) | 15 (45) | 3 (20) | 1 (13) | 4 (17) |
| Double refractory[c] | 0 | 12 (44) | 12 (36) | 3 (20) | 1 (13) | 4 (17) |
| Last line[d] | 3 (50) | 18 (67) | 21 (64) | 13 (87) | 6 (75) | 19 (83) |

[a]Cytogenetics identified by fluorescent *in situ* hybridization and karyotype at study entry. [b]In total, 29 patients (5 [83%] in the 30-mg group; 24 [89%] in the 40-mg group) in the daratumumab arm and 20 patients (15 [100%] in the 30-mg group; 5 [63%] in the 40-mg group) in the bortezomib arm had been exposed to an alkylator. [c]Double refractory was defined as refractory to both an immunomodulatory agent and a proteasome inhibitor. [d]Failure to achieve at least a minimal response or progression on therapy within 60 days of the last dose of treatment. ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System; ASCT: autologous stem cell transplantation.

(95% CI: 7.7-15.4) (Figure 1A). At a median follow-up of 32.8 months, the median OS was 26.1 months (95% CI: 16.4-not estimable) (Figure 1B). Of four patients with extramedullary disease, four (100%) achieved a partial response or better while on therapy with melflufen (40 mg), daratumumab, and dexamethasone.

### Melflufen, bortezomib, and dexamethasone (bortezomib arm)

The most common any-grade and grade ≥3 TEAE among the 23 patients who received therapy in the bortezomib arm were thrombocytopenia (91% and 87%, respectively), neutropenia (78% and 48%, respectively), and anemia (70% and 43%, respectively) (*Online Supplementary Table S5*). In total, nine patients (39% overall; 5 of 15 [33%] in the 30-mg group; 4 of 8 [50%] in the 40-mg group) reported a treatment-emergent infection in association with grade ≥3 neutropenia. TEAE related to bleeding occurred in <10% of

**Table 2.** Overall response rate.

| Response category | Daratumumab arm N=33 | Bortezomib arm N=23 |
|---|---|---|
| Best confirmed response, N (%) | | |
| Stringent complete response | 1 (3) | 1 (4) |
| Complete response | 2 (6) | 1 (4) |
| Very good partial response | 8 (24) | 5 (22) |
| Partial response | 13 (39) | 11 (48) |
| Minimal response | 1 (3) | 1 (4) |
| Stable disease | 2 (6) | 3 (13) |
| Progressive disease | 1 (3) | 0 |
| Missing | 5 (15)[a] | 1 (4)[b] |
| ORR, N (%) [95% CI] | 24 (73) [55-87] | 18 (78) [56-93] |

[a]In the daratumumab arm, five patients had unconfirmed responses: one progressive disease, two stable disease, one partial response, and one not evaluable (no response assessment). [b]In the bortezomib arm, one patient had an unconfirmed best response of stable disease. ORR: overall response rate; 95% CI: 95% confidence interval.

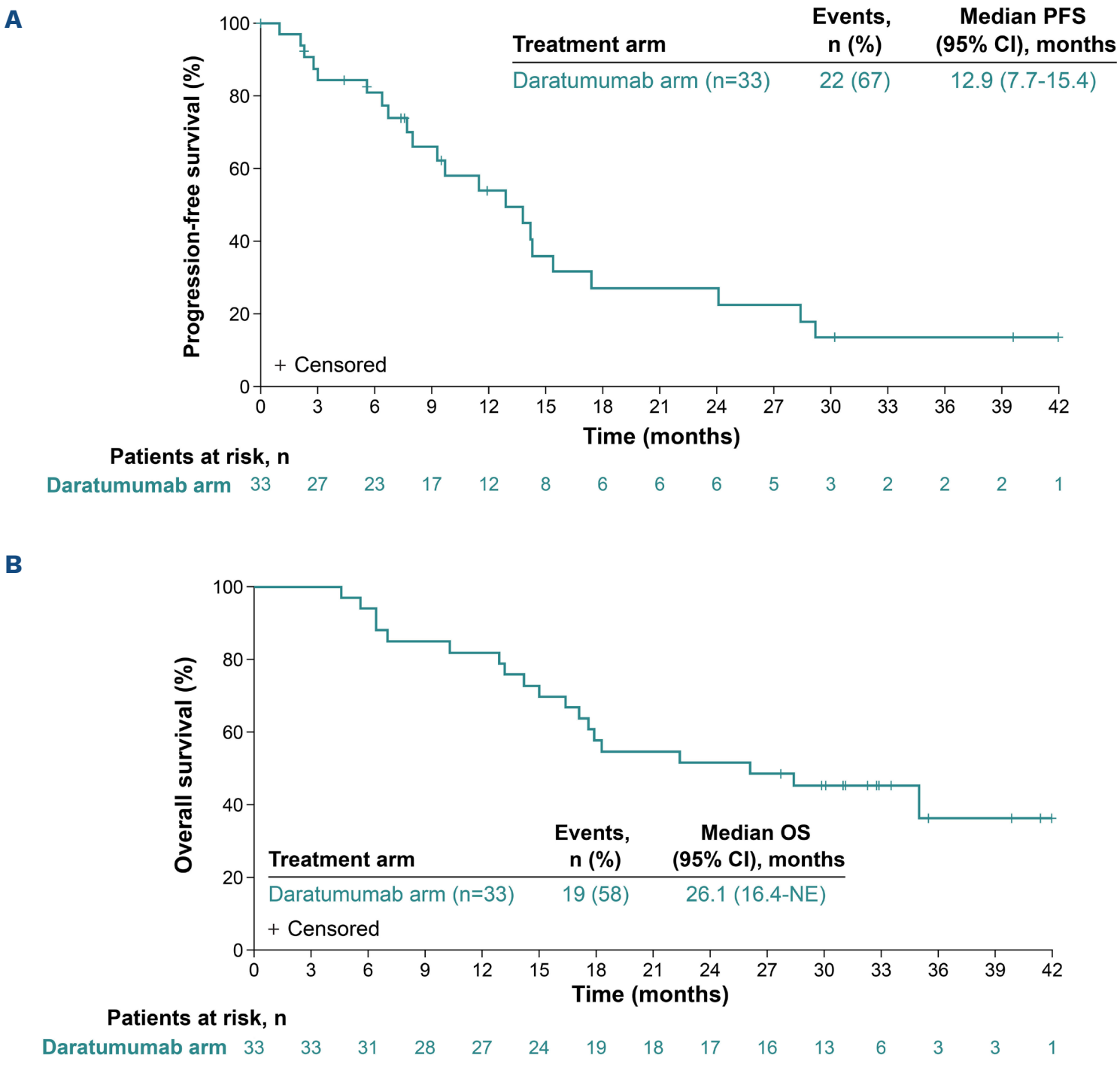



**Figure 1. Survival outcomes with melflufen, daratumumab, and dexamethasone (daratumumab arm).** (A) Progression-free survival. (B) Overall survival. PFS: progression-free survival; 95% CI: 95% confidence interval; OS: overall survival; NE: not estimable.

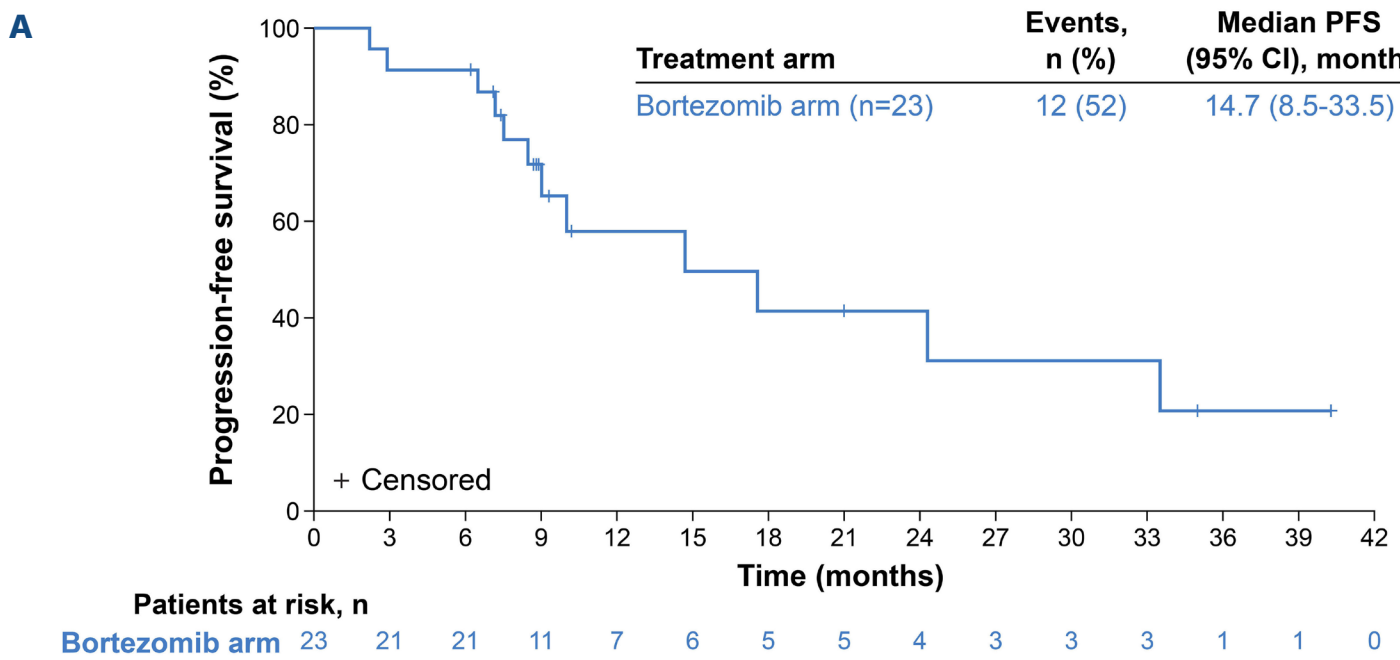
patients. No secondary primary malignancies were reported. In total, three fatal AE were reported ≤30 days after the last dose of study drug (COVID-19 pneumonia, 1 event each in the 30-mg and 40-mg groups; chronic cardiac failure, 1 event in the 30-mg group). No fatal AE were reported >30 days after the last dose of study drug. None of the fatal AE was considered related to melflufen.

In the bortezomib arm, at a median follow-up of 9.0 months and 22.9 months, treatment duration was 8.2 months (range, 2.9-40.0) in the 30-mg group and 11.8 months (range, 2.1-34.7) in the 40-mg group (*Online Supplementary Table S3*). In total, 19 of 23 patients (83%) who received therapy in the bortezomib arm experienced at least one TEAE leading to dose interruptions of melflufen (*Online Supplementary Table S4*), most commonly thrombocytopenia (5 of 15 patients [33%] in the 30-mg group and 7 of 8 patients [88%] in the 40-mg group) and neutropenia (3 patients [20%] in the 30-mg group and 3 patients [38%] in the 40-mg group). In total, 19 patients (11 of 15 [73%] in the 30-mg group; 8 of 8 [100%] in the 40-mg group) experienced at least one prolonged treatment cycle (lasting ≥32 days) at some time and ten patients (5 [33%] in the 30-mg group and 5 [63%] in the 40-mg group) experienced a prolonged treatment cycle in their first treatment cycle, with the reason for the delayed initiation of cycle 2 being a hematologic toxicity in four of the ten patients (1 [7%] in the 30-mg group; 3 [38%] in the 40-mg group). TEAE leading to dose reductions occurred in eight of 15 patients (53%) in the 30-mg group and six of eight patients (75%) in the 40-mg group. At the 30-mg and 40-mg doses, the median number of cycles before the first melflufen dose reduction was 4.5 (range, 1-28) and 2.0 (range, 1-6), respectively, whereas the median number of treatment cycles after the first melflufen dose reduction was 5.0 (range, 3-18) and 5.5 (range, 2-16). The most common TEAE leading to study treatment discontinuation was thrombocytopenia (in 1 of 15 [7%] patients in the 30-mg group and in 2 of 8 [25%] patients in the 40-mg group). Patients in the bortezomib arm received a median of 8.0 (range, 3-35) and 9.5 (range, 2-31) treatment cycles in the 30-mg and 40-mg groups, respectively (*Online Supplementary Table S3*). In the 30-mg and 40-mg groups, red blood cell transfusions were required by 47% *versus* 50% and platelets by 40% *versus* 50% of patients, respectively. The median total cumulative dose of melflufen administered was 210 mg (range, 90-940) in the 30-mg group and 225 mg (range, 80-1,240) in the 40-mg group. Overall, these data show that treatment duration and melflufen exposure were similar between the 30-mg and 40-mg groups. Among 23 patients in the bortezomib arm, 18 achieved a partial response or better for an ORR of 78% (95% CI: 56-93), with one patient (4%) each achieving a stringent complete response and complete response, five patients (22%) a very good partial response, and 11 patients (48%) a partial response (Table 2). A ≥25% reduction in M-protein was observed in 20 of 23 (87%) of patients (*Online Supplementary Figure S3*). The median duration of response was 15.8 months (95% CI: 5.8-not estimable) (*Online Supplementary Figure S4*). At a median follow-up of 21.0 months, the median PFS was 14.7 months (95% CI: 8.5-33.5) (Figure 2A). At a median follow-up of 17.6 months, OS data were immature, with 17 patients (74%) alive as of the data cutoff date (Figure 2B). Among four patients with extramedullary disease, two (50%) achieved a partial response or better while on therapy with melflufen, bortezomib, and dexamethasone (30-mg group, n=1; 40-mg group, n=1).

# Discussion

The ANCHOR study builds on the doublet backbone of melflufen plus dexamethasone evaluated in previous clinical studies in heavily pretreated patients with RRMM[12,17] and adds a third agent, daratumumab or bortezomib, to demonstrate the potential of melflufen in a triplet combination therapy. In the daratumumab combination arm, no dose-limiting toxicities were observed at either the 30-mg or 40-mg dose level in the phase I part of the study. The safety profile of melflufen in triplet combination with daratumumab was consistent with previous reports, with any-grade and grade ≥3 TEAE primarily being hematologic and clinically manageable with dose reductions, dose delays, and supportive interventions such as red blood cell and platelet transfusions.[12,13,17] In the daratumumab arm, the most common any-grade non-hematologic TEAE was fatigue, with the most common grade ≥3 non-hematologic TEAE being pneumonia and influenza. These safety results, including rates of grade ≥3 infections, are also comparable with those of other clinical studies investigating triplet combinations with daratumumab in patients with RRMM who had received ≥1 prior lines of therapy, albeit with higher rates of thrombocytopenia observed in the present study.[18-22] Overall, the frequency of hematologic toxicity in early cycles was higher in the 40-mg group than in the 30-mg group, which prevented new cycle initiation, led to earlier and longer (≥2 weeks) cycle delays, greater melflufen dose reductions, and increased discontinuation of therapies due to AE with melflufen 40 mg. In contrast, patients in the 30-mg group stayed on treatment longer at the assigned melflufen dose without dose reductions and continued treatment for a longer time with melflufen after their first dose reduction, which, collectively, led to higher drug exposure in the 30-mg group. Furthermore, two of the four patients (50%) in the 30-mg group who had a prolonged treatment cycle in their first cycle had hematologic toxicity preventing initiation of cycle 2 compared with seven of eight patients (88%) in the 40-mg group. Notably, the number of missed daratumumab doses was small, thus not affecting treatment intensity in a substantial way.

The triplet combination of melflufen, daratumumab, and



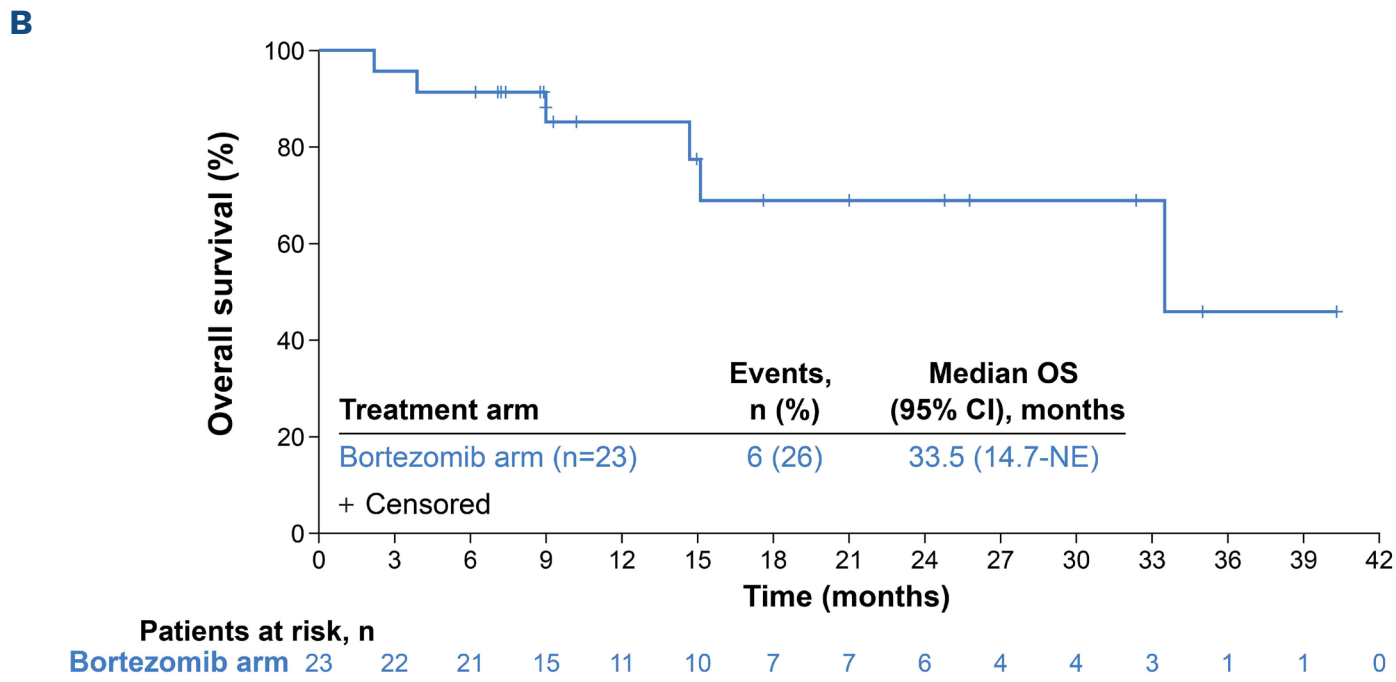




**Figure 2. Survival outcomes with melflufen, bortezomib, and dexamethasone (bortezomib arm).** (A) Progression-free survival. (B) Overall survival. 95% CI: PFS: progression-free survival; 95% confidence interval; OS: overall survival; NE: not estimable.

dexamethasone resulted in encouraging clinical responses that were durable. The ORR of 73% was comparable to those of larger phase III studies, such as the ICARIA-MM study of isatuximab plus pomalidomide and dexamethasone in patients with RRMM who had received a median of three prior lines of therapy and in the APOLLO study of daratumumab plus pomalidomide and dexamethasone in patients with RRMM who had received a median of two prior lines of therapy, which showed ORR of 60% and 69%, respectively.[22,23] The median PFS of 12.9 months was also comparable to that observed in the APOLLO and ICARIA-MM studies (12.4 and 11.5 months, respectively).[22,23] Overall, similar total drug exposure and efficacy results were observed with melflufen 30 mg and 40 mg, with more frequent early dose adjustments and discontinuations due to hematologic AE at the 40-mg dose level, leading to melflufen 30 mg being selected as the recommended dose in combination with dexamethasone and daratumumab in patients with RRMM.

The triplet combination of melflufen, bortezomib, and dexamethasone also showed promising clinical activity and a manageable safety profile. No dose-limiting toxicities were reported with either melflufen dose (30 mg or 40 mg). The safety profile of melflufen, bortezomib, and dexamethasone was consistent with that of other triplet combinations with a proteasome inhibitor backbone in patients with RRMM, albeit with higher rates of hematologic toxicities but lower rates of peripheral neuropathy.[20,24,25] Similar to the daratumumab arm, hematologic toxicities were clinically manageable with dose reductions, dose delays, and supportive care (red blood cell and platelet transfusions). As with the daratumumab combination, the triplet combination of melflufen, bortezomib, and dexamethasone resulted in high clinical response rates (ORR of 78%), and responses were durable. These response rates were comparable to those reported in phase III studies in patients with RRMM who had received fewer lines of therapy, including the BOSTON

study of selinexor, bortezomib, and dexamethasone (ORR, 76%; median 2 prior lines of therapy) and the OPTIMISMM study of pomalidomide, bortezomib, and dexamethasone (ORR, 82%; median 2 prior lines of therapy).[24,26] Similarly, the median PFS of 14.7 months observed in our study was comparable to that seen in the BOSTON and OPTIMISMM studies (13.9 and 11.2 months, respectively); however, the small sample size in our study (early termination of the bortezomib arm) precludes effective comparison.[24,26] Based on the overall data for the bortezomib arm, including the higher incidence of hematologic toxicities leading to dose adjustments or treatment discontinuation with the 40-mg dose of melflufen, the 30-mg dose was chosen as the recommended dose of melflufen for use in triplet combination with bortezomib and dexamethasone. However, small numbers of patients, differences in baseline characteristics (e.g., median prior lines of therapy and proportion exposed to previous alkylator therapy) and differences in follow-up times (median follow-up was 2.5 times longer in the 40-mg group) between the melflufen dose groups may be confounding factors.

In summary, the safety profile of melflufen in triplet combinations with daratumumab or bortezomib was consistent with the known safety profile of melflufen, namely primarily hematologic AE that were clinically manageable with dose reductions, dose delays, and supportive care, and no treatment-related mortalities were reported, as assessed by the study steering committee. Response rates reported in this study with melflufen, dexamethasone, and daratumumab indicate a clinically meaningful effect of melflufen at a dose of either 30 mg or 40 mg. Response rates observed in patients with extramedullary disease were also highly encouraging. Taken together, melflufen 30 mg plus daratumumab and dexamethasone constitutes the optimal combination regimen and was pursued in the randomized, controlled, open-label, phase III LIGHTHOUSE study (OP-108; NCT04649060) in patients with relapsed MM or RRMM who had received at least three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who were double refractory to a proteasome inhibitor and an immunomodulatory agent. Unfortunately, the LIGHTHOUSE study was also terminated prematurely due to resource considerations resulting from the clinical trial hold issued by the US Food and Drug Administration. Despite this, topline efficacy results from LIGHTHOUSE were very encouraging (superior PFS and ORR with melflufen, daratumumab, and dexamethasone *vs*. daratumumab), and the safety profile of melflufen in triplet combination with daratumumab was consistent with this report.[27] Lastly, results from ANCHOR suggest that the combination of melflufen, bortezomib, and dexamethasone also has meaningful clinical activity and a manageable safety profile in patients with RRMM, supporting the translation of these results, as well as those seen in the LIGHTHOUSE study, to real-world practice.[28]

## Disclosures

*EMO reports consulting or an advisory role for Amgen, AbbVie, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Karyopharm, Menarini-Stemline, Mundipharma, Oncopeptides, Sanofi, Secura Bio, and Takeda; meeting and/or travel expenses from Bristol Myers Squibb, GlaxoSmithKline, Janssen, Lilly, and Sanofi; and honoraria from Amgen, Asofarma, Bristol Myers Squibb, GlaxoSmithKline, Janssen, MSD, Pfizer, Sanofi, and Takeda. YAE reports speakers' bureau fees from Adaptive, Alnylam, Janssen, Oncopeptides, and Takeda; advisory board work for and honoraria from Alnylam, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and Takeda; sitting on independent adjudication committees for Orca and Takeda; and research support from Bristol Myers Squibb/Celgene. RH reports receiving consultancy fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Pharma MAR, Novartis, and Takeda; research funding from Amgen, Celgene, Janssen, and Novartis; being a member of the Board of Directors or advisory committees for Amgen and Takeda; and honoraria from AbbVie, Bristol Myers Squibb, Celgene, and Takeda. VM reports honoraria from Amgen, Bristol Myers Squibb/Celgene, Janssen, Sanofi, and The Binding Site; consulting or advisory role for Amgen, Bristol Myers Squibb/Celgene, Janssen, and Sanofi; and speakers' bureau fees from Amgen, Bristol Myers Squibb/Celgene, Janssen, Sanofi, and The Binding Site. J-RE reports congress travel, accommodation, and other expenses from Amgen, Celgene, Janssen, and Novartis. LK reports honoraria from AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, and Takeda; meeting and/or travel expenses from Amgen, Janssen, and Takeda; and being a member of advisory boards for Amgen, Celgene, GlaxoSmithKline, Janssen, and Takeda. M-VM reports payment or honoraria for lectures, presentations, speakers' bureau, manuscript writing, or educational events from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Pfizer, Sanofi, and Takeda and participation in a Data Safety Monitoring Board or advisory board for Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, Regeneron, Sanofi, and Takeda. AO reports consulting or an advisory role for Bristol Myers Squibb, GlaxoSmithKline, and Sanofi; and participation in speakers' bureau for Amgen, Bristol Myers Squibb, and Sanofi. VR reports personal fees from AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Infinity, MSD, NanoString, and Roche; grants from Argen-X and GlaxoSmithKline; and non-financial support from Astex. PGR reports grants from or contracts with Bristol Myers Squibb/Celgene, Oncopeptides, Karyopharm, and Takeda; and consulting fees from AstraZeneca, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Karyopharm, Protocol Intelligence, Regeneron, Sanofi, Secura Bio, and Takeda. SN reports employment and equity ownership with Oncopeptides. JO reports employment with Oncopeptides. NAB reports employment and holding stock or stock options with Oncopeptides. JS and LP have no conflicts of interest to disclose.*

**Contributions**

*The study sponsor (Oncopeptides AB), EMO, and PGR designed the protocol. EMO, YAE, RH, JS, VM, J-RE, LK, M-VM, AO, VR, PGR, and LP treated the patients and collected the data. SN, JO, and NAB analyzed the data, and a Data Safety Monitoring Committee monitored the overall conduct of the study. All authors had access to the data; contributed to the writing, editing, data analysis, and interpretation of the paper; reviewed the manuscript and approved its submission; and are accountable for all aspects of the work.*

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**Data-sharing statement**

*Oncopeptides commits to sharing clinical study data with qualified researchers to enable enhancement of public health. As such, Oncopeptides will share anonymized patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Oncopeptides' pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the USA and European Union. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approval. Such requests are assessed at Oncopeptides' discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. The applicants should be willing to submit both positive and negative findings to a scientific journal. If Oncopeptides agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release to ensure that the patients' data are deidentified. In case of any risk of re-identification on anonymized data despite measures to protect patients' confidentiality, the data will not be shared. The patients' informed consent will always be respected. If the anonymization process will provide futile data, Oncopeptides will have the right to refuse the request. Oncopeptides will provide access to patient-level clinical trial analysis datasets in a secured environment upon execution of the data-sharing agreement. Oncopeptides will also provide the protocol, statistical analysis plan, and the clinical study report synopsis if needed. For additional information or requests for access to Oncopeptides' clinical trial data for research purposes, please contact medinfo@oncopeptides.com.*

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