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Melflufen in relapsed/refractory multiple myeloma refractory to prior alkylators: A subgroup analysis from the OCEAN study

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Abstract

Melphalan flufenamide (melflufen), a first-in-class alkylating peptide-drug conjugate, plus dexamethasone demonstrated superior progression-free survival (PFS), but not overall survival (OS), versus pomalidomide plus dexamethasone in relapsed/refractory multiple myeloma in the OCEAN study. Time to progression (TTP) <36 months after a prior autologous stem cell transplantation (ASCT) was a negative prognostic factor for OS with melflufen. This post hoc exploratory analysis evaluated patients refractory to prior alkylators (e.g., cyclophosphamide and melphalan) in OCEAN. In 153 patients refractory to prior alkylators (melflufen, $n = 78$; pomalidomide, $n = 75$), the melflufen and pomalidomide arms had similar median PFS (5.6 months [95% CI, 4.2–8.3] vs. 4.7 months [95% CI, 3.1–7.3]; hazard ratio [HR], 0.92 [95% CI, 0.63–1.33]) and OS (23.4 months [95% CI, 14.4–31.7] vs. 20.0 months [95% CI, 12.0–28.7]; HR, 0.92 [95% CI, 0.62–1.38]). Among alkylator-refractory patients with a TTP ≥ 36 months after a prior ASCT or no prior ASCT (melflufen, $n = 54$; pomalidomide, $n = 53$), the observed median PFS and OS were longer in the melflufen arm than the pomalidomide arm. The safety profile of melflufen was consistent with previous reports. These results suggest that melflufen is safe and effective in patients with alkylator-refractory disease, suggesting differentiated activity from other alkylators.

KEYWORDS
alkylating agent, melflufen, melphalan flufenamide, multiple myeloma, pomalidomide, stem cell transplantation

Novelty statements

What is the new aspect of this work?

This post hoc exploratory analysis provides data for melphalan flufenamide (melflufen), an alkylating peptide-drug conjugate, in combination with dexamethasone in the subgroup of patients

with relapsed/refractory multiple myeloma (RRMM) and alkylator-refractory disease who received treatment in the randomized, controlled phase 3 OCEAN study.

What is the central finding of this work?

Compared with pomalidomide and dexamethasone, melflufen and dexamethasone showed similar progression-free survival (PFS) and overall survival (OS) in the overall alkylator-refractory group but longer PFS and OS in the subset of alkylator-refractory patients with no prior autologous stem cell transplantation (ASCT) or a time-to-progression ≥36 months after a prior ASCT.

What is (or could be) the specific clinical relevance of this work?

Results from this post hoc analysis suggest that melflufen plus dexamethasone is a safe and effective treatment option for patients with RRMM and alkylator-refractory disease, support the approved indication for melflufen and dexamethasone in Europe, and suggest that melflufen has differentiated activity from other alkylators.

1 | INTRODUCTION

Multiple myeloma (MM) is a malignant disorder characterized by the proliferation of plasma cells derived from B cells in the bone marrow. In recent years, MM treatment has seen the inclusion of new, more effective therapeutic options that have increased survival.[1,2]

One of the newer drugs to become available to patients with relapsed/refractory MM (RRMM) is melphalan flufenamide (melflufen), a first-in-class peptide-drug conjugate that utilizes increased peptidase expression to selectively release potent alkylating agents inside tumor cells. It is rapidly distributed via passive transport to enter tumor cells due to its lipophilicity.[3–8] Upon entering tumor cells, the peptide carrier functions as an enzymatic substrate using the increased metabolic activity in cancer cells to release cytotoxic, hydrophilic alkylating metabolites (melphalan and desethyl-melflufen), leading to intracellular enrichment.[5,7,8] Melflufen plus dexamethasone was recently approved in Europe for the treatment of adult patients with MM who have received at least three prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody and have demonstrated disease progression on or after the last therapy.[9] The approval was based on results from the phase 2 HORIZON study and the phase 3 OCEAN study.[10,11] Post hoc analyses from OCEAN identified previous autologous stem cell transplantation (ASCT) as significantly impacting overall survival (OS) outcomes.[11] Specifically, not having received a prior ASCT or time to progression (TTP) >36 months after prior ASCT favored melflufen and dexamethasone over pomalidomide and dexamethasone, whereas TTP < 36 months after prior ASCT was a negative prognostic factor with melflufen and dexamethasone.[9,12] Because a consistent benefit was seen with melflufen plus dexamethasone in this patient population in HORIZON, the approved European indication recommends patients with RRMM to have not received a prior ASCT or have had a TTP > 36 months after prior ASCT.

In recent times, it is likely that there may be patients not exposed to alkylators during the course of their disease; however, 88% of patients had been exposed to an alkylator in at least 1 prior line of therapy (LOT), and 16% were refractory to alkylators in at least 2 prior LOTs in a pooled analysis of the O-12-M1 and HORIZON trials that evaluated melflufen and dexamethasone in patients with relapsed/refractory multiple myeloma.[13] Thus, it is important to assess the efficacy of melflufen in patients previously treated with or refractory to standard-dose alkylators. Further, salvage ASCT therapy is not currently recommended for patients who have relapsed <36 months after their frontline ASCT.[14] This is in line with the knowledge that recent prior exposure to alkylators impairs the effectiveness of alkylator-based conditioning and the subsequent ASCT.[15] Furthermore, patients with low stem cell reserve in the bone marrow due to stem cell harvest and myeloablative regimens before ASCT therapy may have difficulty tolerating subsequent treatments that induce cytopenias.[16] Because having received a previous ASCT with a short-term remission was a negative prognostic factor for melflufen and dexamethasone, the objective of this post hoc exploratory analysis was to investigate the effects of refractoriness to standard-dose prior alkylators on the effectiveness of melflufen and dexamethasone in a considerable subset of patients from OCEAN.

2 | METHODS

2.1 | Study design and patients

The details of study design for OCEAN have been previously reported (ClinicalTrials.gov identifier: NCT03151811).[11] In brief, OCEAN is a randomized, controlled, open-label, phase 3 head-to-head study conducted at 108 sites in 21 countries across Europe, North America, and Asia. Eligible patients with RRMM had received two to four prior lines of therapy, including lenalidomide and a proteasome inhibitor, and were refractory to lenalidomide and to the last line of therapy. Refractoriness for patients in this study was defined as a failure to achieve a minimal response or disease progression while on primary or salvage therapy or within 60 days of the last dose according to International Myeloma Working Group (IMWG) uniform response criteria.[17]

Patients were randomized 1:1 to receive 28-day cycles of melflufen 40 mg intravenously (Day 1) or pomalidomide 4 mg orally (daily, Days 1–21), and all patients received dexamethasone 40 mg (20 mg if aged ≥75 years) orally on Days 1, 8, 15, and 22. Patients received treatment until documented disease progression according to IMWG uniform response criteria, unacceptable toxicity, or if the patient or treating physician determined it was not in the patient's best interest to continue.[14,17]

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was reviewed and approved by national regulatory authorities and an independent ethics committee or institutional review board at each study center before implementation. Written informed consent was obtained from each patient. All authors had full access to the data, participated in data interpretation, and reviewed and approved the manuscript before submission.

2.2 | Endpoints

The primary endpoint was PFS, defined as the time from randomization to the earlier of confirmed disease progression or death from any cause, whichever occurred first, as assessed by an independent review committee (IRC) according to the IMWG uniform response criteria.[11,17] Key secondary endpoints included OS, defined as the time from the date of randomization to death due to any cause; overall response rate (ORR), defined as the proportion of patients with a stringent complete response, complete response, very good partial response, or partial response as best confirmed response; and safety and tolerability of the melflufen and pomalidomide arms.[11] The IRC used local laboratory assessments to assess response and progression per the IMWG uniform response criteria.[17] PFS assessments were scheduled monthly until disease progression or initiation of subsequent therapy; thereafter, assessments for OS were scheduled every 3 months plus or minus 1 week for up to 24 months.

2.3 | Statistical analysis

This post hoc exploratory subgroup analysis included patients who had disease refractory to an alkylator, either as a single agent or in a combination regimen, before entering the OCEAN study. Efficacy endpoints (PFS, OS, and ORR) were further assessed in patients by type of alkylator received (cyclophosphamide, melphalan, or bendamustine) and by prior ASCT status: patients who had not received a prior ASCT or who had TTP ≥ 36 months after prior ASCT (i.e., reflecting the approved European indication population) and those who had TTP < 36 months after prior ASCT.

PFS and OS are presented as median with two-sided 95% confidence intervals based on the Kaplan–Meier method, and comparison with pomalidomide was performed using unstratified Cox regression models. ORR is presented with exact binomial two-sided 95% confidence intervals. Safety was assessed for the overall subgroup of patients refractory to prior alkylators and by prior ASCT status.

3 | RESULTS

3.1 | Patients

Among the 495 patients randomized in the OCEAN study, 246 patients were randomized to the melflufen arm, and 249 were randomized to the pomalidomide arm, with 78 patients (32%) and 75 patients (30%) refractory to prior alkylators, respectively. Patients with disease refractory to a prior alkylator, the focus of this article, had received cyclophosphamide (melflufen arm, 81%; pomalidomide arm, 69%), standard-dose melphalan (<140 mg/m^2; melflufen arm, 19%; pomalidomide arm, 31%), high-dose melphalan (melflufen arm, 6%; pomalidomide arm, 3%), and/or bendamustine (melflufen arm, 4%; pomalidomide arm, 5%). Most patient characteristics and demographics were balanced at baseline between treatment arms. Differences between the melflufen and pomalidomide arms, respectively, included median time since initial diagnosis (4.6 years vs. 3.4 years), proportion of patients with International Staging System stage I (58% vs. 40%), and number of patients who received previous bortezomib (71% vs. 83%). The median exposure to study treatment was similar between arms (melflufen arm: 25.6 weeks [range, 4.1–164.3]; pomalidomide arm: 22.1 weeks [range, 1.1–189.4]).

Within the alkylator-refractory group, 54 patients (69%) in the melflufen arm and 53 patients (71%) in the pomalidomide arm had not received a prior ASCT or had TTP ≥ 36 months after prior ASCT (i.e., reflecting the approved European indication population), whereas 24 patients (31%) in the melflufen arm and 22 patients (29%) in the pomalidomide arm had TTP < 36 months after prior ASCT (Table 1).

3.2 | Efficacy

In the overall alkylator-refractory group, the melflufen and pomalidomide arms saw a similar median PFS (5.6 months [95% CI, 4.2–8.3] vs. 4.7 months [95% CI, 3.1–7.3]; HR, 0.92 [95% CI, 0.63–1.33]) and median OS (23.4 months [14.4–31.7] vs. 20.0 months [12.0–28.7]; HR, 0.92 [95% CI, 0.62–1.38]; Figures 1 and 2). Corresponding results were observed when evaluating PFS and OS in subgroups by type of prior alkylating agent received (Figure 1). In the melflufen and pomalidomide arms, the ORR was 24.4% and 28.0% in patients refractory to alkylators overall, 22.2% and 25.0% in patients refractory to cyclophosphamide, and 33.3% and 26.1% in patients refractory to melphalan, respectively.

Because the approval of melflufen in combination with dexamethasone by the European Commission is limited to patients who had either not received a prior ASCT or who had TTP ≥ 36 months after prior ASCT, this group of patients was assessed to be of special interest.[9] Among this subgroup of patients (melflufen arm, $n = 54$; pomalidomide arm, $n = 53$), the observed median PFS (8.0 months [95% CI, 4.2–10.8] vs. 4.2 months [95% CI, 2.7–6.8]; HR, 0.67 [95% CI, 0.43–1.04]) and median OS (24.3 months [95% CI, 14.6–33.6] vs. 16.4 months [95% CI, 7.9–24.9]; HR, 0.70 [95% CI, 0.43–1.13])

TABLE 1 Baseline characteristics for patients with disease refractory to alkylators received before enrolling in OCEAN.

Characteristics	Melflufen arm ($n = 78$)	Pomalidomide arm ($n = 75$)
Age, median (range), years	69 (46–85)	66 (43–82)
<65 years, *n* (%)	26 (33)	30 (40)
65–74 years, *n* (%)	42 (54)	34 (45)
≥75 years, *n* (%)	10 (13)	11 (15)
Sex, *n* (%)		
Male	43 (55)	44 (59)
Time since diagnosis, median (range), years	4.6 (0.8–26.3)	3.4 (0.6–19.1)
No. of prior treatment regimens, median (range)	3 (2–4)	3 (2–4)
ECOG PS, *n* %		
0	22 (28)	25 (33)
1	48 (62)	39 (52)
2	8 (10)	11 (15)
ISS at baseline, *n* (%)		
I	45 (58)	30 (40)
II	28 (36)	32 (43)
III	5 (6)	13 (17)
High-risk cytogenetics, *n* (%)	24 (31)	21 (28)
Evidence of extramedullary disease, *n* (%)	10 (13)	10 (13)
Exposed to previous melphalan, *n* (%)	26 (33)	28 (37)
Prior ASCT, *n* (%)		
Yes	34 (44)	29 (39)
No	44 (56)	46 (61)
TTP after prior ASCT, *n* (%)		
<36 months	24 (31)	22 (29)
≥36 months	10 (13)	7 (9)
No prior ASCT or TTP ≥ 36 months after prior ASCT, *n* (%)	54 (69)	53 (71)
No. of lines refractory to alkylators, *n* (%)		
0	0 (0)	0 (0)
1	68 (87)	56 (75)
2	8 (10)	17 (23)
3	2 (3)	2 (3)
Documented exposed status, *n* (%)		
Alkylators	217 (100)	213 (100)
Cyclophosphamide[a]	146 (67)	145 (68)
Melphalan[a]	61 (28)	64 (30)
High-dose melphalan[a]	112 (52)	109 (51)
Bendamustine[a]	6 (3)	8 (4)
Documented refractory status, *n* (%)		
Alkylators	78 (100)	75 (100)
Cyclophosphamide[b]	63 (81)	52 (69)
Melphalan[b]	15 (19)	23 (31)
High-dose melphalan[b,c]	5 (6)	2 (3)
Bendamustine[b]	3 (26)	4 (5)
Lenalidomide	78 (100)	75 (100)
Pomalidomide	0 (0)	0 (0)
Bortezomib	55 (71)	62 (83)
Carfilzomib	8 (10)	12 (16)
Daratumumab	15 (19)	8 (11)
Time since alkylator refractory, median (range), years	1.8 (0.1–25.1)	1.6 (0.1–8.1)

Note: Data cutoff date: February 3, 2021.
Abbreviations: ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; TTP, time to progression.
[a]Percentages based on number of patients who were exposed to prior alkylators.
[b]Percentages based on number of patients who were refractory to prior alkylators.
[c]Patients who were refractory to high-dose melphalan included those who had received high-dose melphalan as salvage treatment.

were longer in the melflufen arm than in the pomalidomide arm (Figures 2 and 3). Consistent with these results, the ORR was higher in the melflufen arm than the pomalidomide arm in the overall alkylator-refractory group (29.6% vs. 24.5%) and in patients refractory to cyclophosphamide (28.6% vs. 16.1%) and melphalan (35.7% vs. 26.1%).

Among the subgroup of patients who had TTP < 36 months after prior ASCT (melflufen arm, $n = 24$; pomalidomide arm, $n = 22$), the observed median PFS (4.4 months [95% CI, 3.2–5.6] vs. 7.5 months [95% CI, 3.8–26.0]; HR 2.09 [95% CI, 1.00–4.37]) and median OS (15.1 months [95% CI, 6.2–27.5] vs. 28.7 months [95% CI, 14.1–not evaluable]; HR, 1.75 [95% CI, 0.84–3.64]) was generally lower in the melflufen arm than in the pomalidomide arm (Figure S1; Figure 3). The observed ORR was also lower with melflufen than pomalidomide in the overall alkylator-refractory group (12.5% vs. 36.4%) and in patients refractory to cyclophosphamide (9.5% vs. 38.1%).

3.3 | Safety

Overall, the safety profile of melflufen plus dexamethasone in the alkylator-refractory group was consistent between treatment arms (Table 2). In the melflufen and pomalidomide arms, respectively, the frequency of treatment-emergent adverse events (TEAEs; 99% vs. 97%), Grade 3 or 4 TEAEs (85% vs. 82%), serious TEAEs (49% vs. 53%), and fatal TEAEs (19% vs. 16%) were similar (Table 2). However, melflufen compared with pomalidomide saw more dose modifications (76% vs. 67%) and dose reductions (47% vs. 14%), comparable dose delays (57% vs. 51%) but less treatment discontinuation (27%

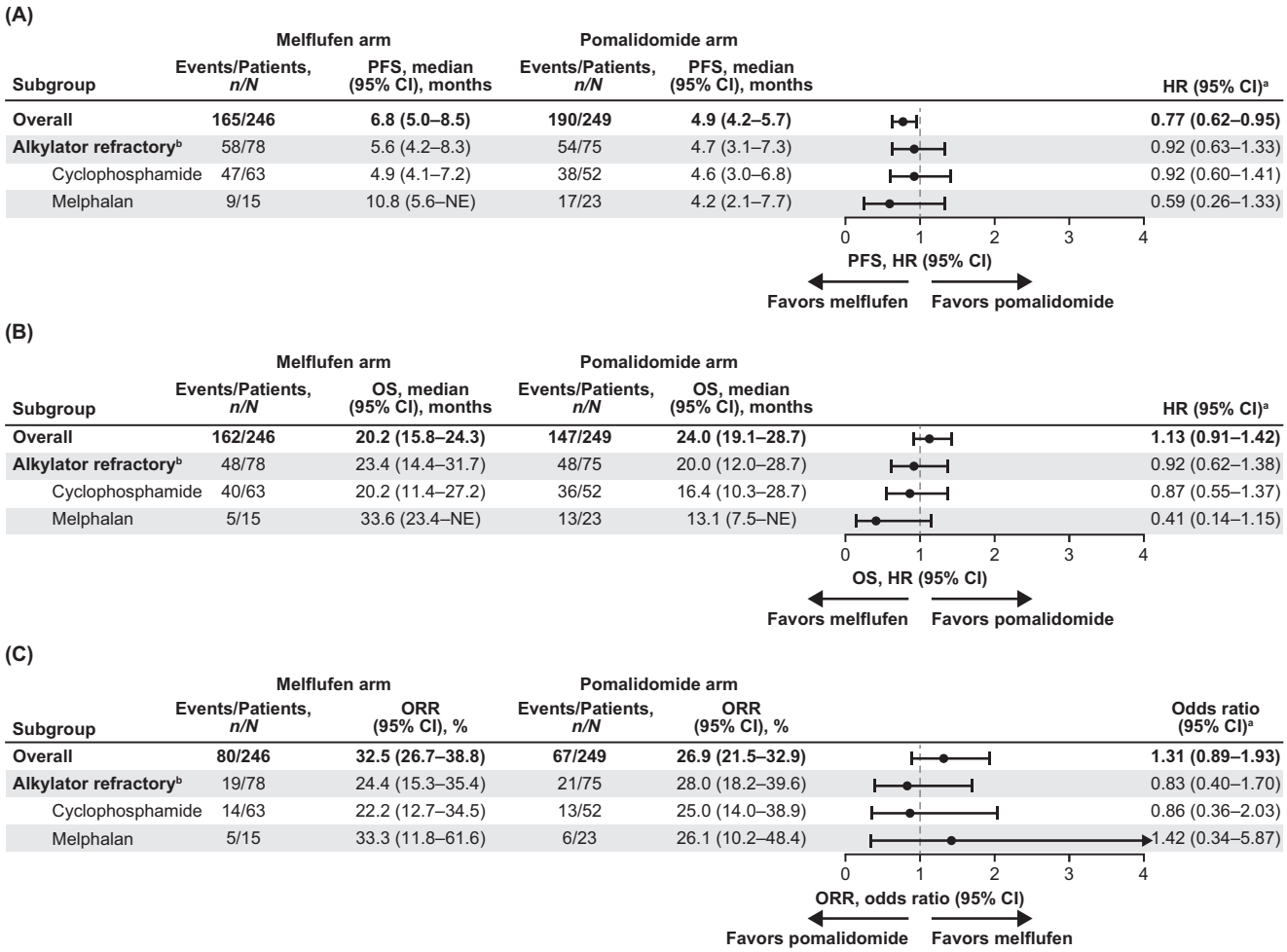


FIGURE 1 Analysis of PFS (A), OS (B), and ORR (C) in patients refractory to prior alkylators by treatment arm. Data cutoff date: February 3, 2021, for PFS and ORR; February 3, 2022, for OS follow-up analysis. [a]Stratified HR for the overall population. Unstratified HR for subgroups analyzed by prior alkylator exposure status. [b]The alkylators bendamustine and high-dose melphalan were also included in this analysis but due to the small size, meaningful conclusions could not be drawn. HR, hazard ratio; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

vs. 34%). When comparing patients refractory and not refractory to prior alkylators, rates of TEAEs were generally comparable except for slightly lower rates of serious and fatal TEAEs observed in patients not refractory to alkylators (Table 2; Table S1).

Among Grade 3 or 4 TEAEs of special interest, melflufen saw more thrombocytopenia (73% vs. 14%), neutropenia (65% vs. 55%), and leukopenia or white blood cell decrease (14% vs. 3%), but less infection (15% vs. 26%), than pomalidomide. Notably, melflufen compared with pomalidomide saw a longer median time to dose reduction (106 days [range, 28–443] vs. 47 days [range, 28–225]), Grade 3 or 4 thrombocytopenia (52 days [range, 15–451] vs. 19 days [range, 8–91]), and Grade 3 or 4 neutropenia (36 days [range, 8–561] vs. 22 days [range, 8–470]; Table 2).

4 | DISCUSSION

This planned subgroup analysis of the OCEAN study showed clinical benefit and manageable safety of melflufen and dexamethasone in patients with RRMM refractory to previous alkylators received outside of the ASCT setting. Consistent with previous reports that identified having TTP < 36 months after prior ASCT as a negative prognostic factor, the treatment effect with melflufen and dexamethasone relative to pomalidomide and dexamethasone was consistently greater in the subset of patients who had not received a prior ASCT or who had TTP ≥ 36 months after prior ASCT compared with the overall alkylator-refractory subgroup.[9,12]

Based on previous reports from the OCEAN study, having TTP < 36 months after prior ASCT was a significant negative factor for OS with melflufen and dexamethasone.[9,11] Results from this post hoc exploratory analysis show that the benefit with melflufen and dexamethasone compared with pomalidomide and dexamethasone in patients who had not received a prior ASCT or who had TTP ≥ 36 months after prior ASCT was more pronounced in the alkylator-refractory group than the overall OCEAN population. These results provide additional support for the hypothesis that the negative prognostic effect of TTP < 36 months after prior ASCT may have been driven by the recent exposure to high-dose melphalan. This is not

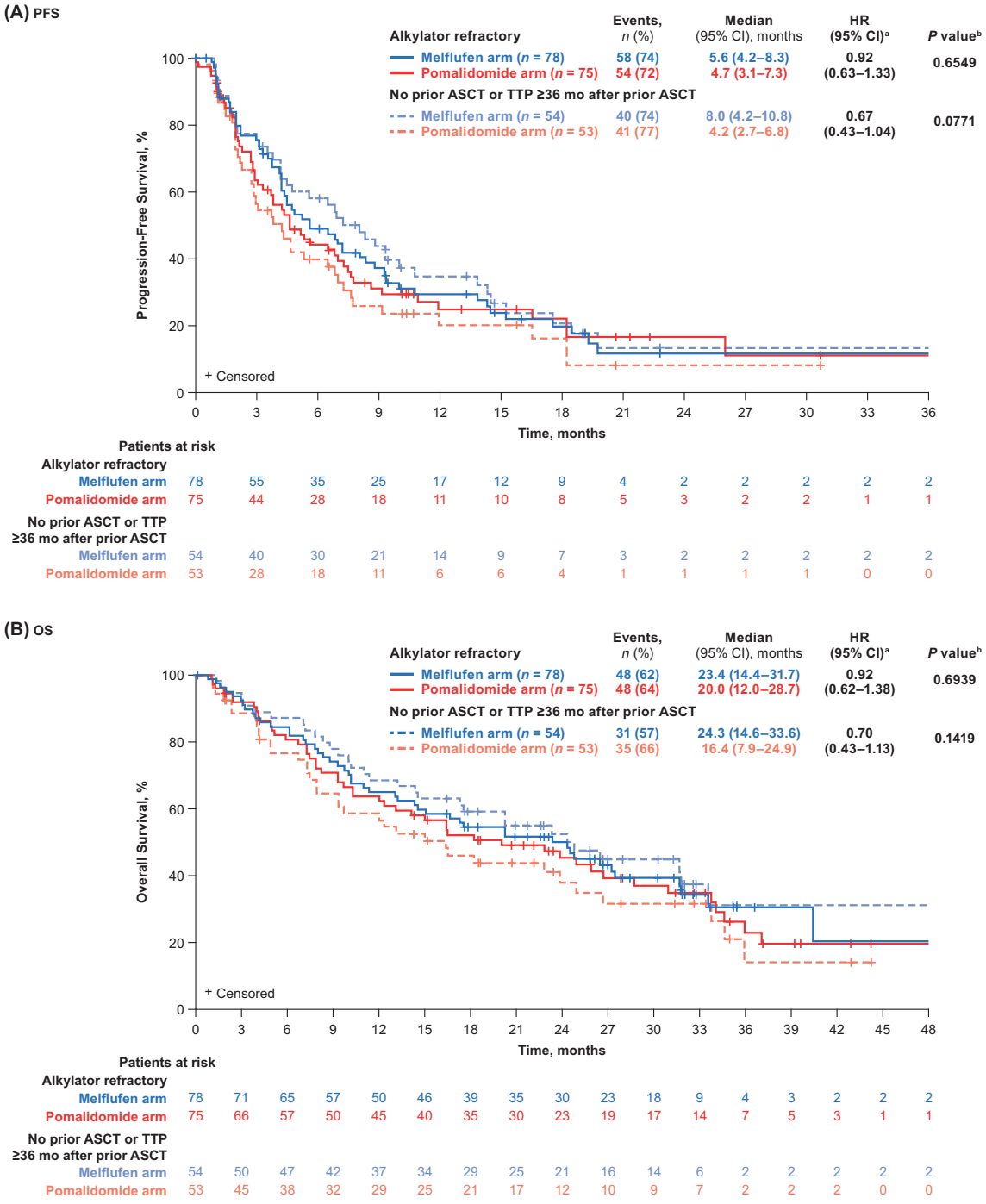


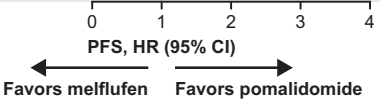
FIGURE 2 Kaplan–Meier analysis of PFS (A) and OS (B) in patients refractory to prior alkylators overall and by prior ASCT status. Data cutoff date: February 3, 2021, for PFS; February 3, 2022, for OS follow-up analysis. [a]Stratified hazard ratio. [b]Log-rank *p* value. ASCT, autologous stem cell transplantation; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

surprising, given that early progression post-ASCT suggests that the high-dose melphalan conditioning may not have been effective and that some of the malignant clones are at least partially insensitive even to high intracellular concentrations of melphalan. In addition, the hematopoietic stem cell reserve and bone marrow microenvironment may be negatively affected by the stem cell harvest procedure and high-dose melphalan used for myeloablation before ASCT therapy.[11,16,18,19] This is further supported by the fact that outcomes were consistent regardless of the type of previous alkylator patients had received, including melphalan outside of the ASCT setting.

Further, in the HORIZON study in patients with heavily pre-treated RRMM refractory to a prior alkylator, the ORR was 21% overall and 28% in patients refractory to a prior alkylator in one previous line of therapy.[10] These data provide further evidence that having

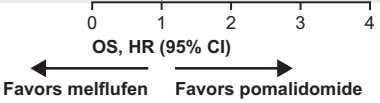
(A)

Subgroup	Melflufen arm Events/Patients, *n/N*	Melflufen arm PFS, median (95% CI), months	Pomalidomide arm Events/Patients, *n/N*	Pomalidomide arm PFS, median (95% CI), months	HR (95% CI)[a]
Alkylator refractory[b]	**58/78**	**5.6 (4.2–8.3)**	**54/75**	**4.7 (3.1–7.3)**	**0.92 (0.63–1.33)**
No prior ASCT or TTP ≥36 mo after prior ASCT	40/54	8.0 (4.2–10.8)	41/53	4.2 (2.7–6.8)	0.67 (0.43–1.04)
Cyclophosphamide	31/42	6.8 (3.5–10.0)	25/31	3.8 (2.2–5.3)	0.57 (0.33–0.98)
Melphalan	9/14	10.8 (5.6–NE)	17/23	4.2 (2.1–7.7)	0.59 (0.26–1.34)
TTP <36 mo after prior ASCT[c]	18/24	4.4 (3.2–5.6)	13/22	7.5 (3.8–26.0)	2.09 (1.00–4.37)
Cyclophosphamide	16/21	4.3 (2.2–5.6)	13/21	7.5 (3.3–26.0)	1.92 (0.90–4.08)



(B)

Subgroup	Melflufen arm Events/Patients, *n/N*	Melflufen arm OS, median (95% CI), months	Pomalidomide arm Events/Patients, *n/N*	Pomalidomide arm OS, median (95% CI), months	HR (95% CI)[a]
Alkylator refractory[b]	48/78	23.4 (14.4–31.7)	48/75	20.0 (12.0–28.7)	0.92 (0.62–1.38)
No prior ASCT or TTP ≥36 mo after prior ASCT	31/54	24.3 (14.6–33.6)	35/53	16.4 (7.9–24.9)	0.70 (0.43–1.13)
Cyclophosphamide	25/42	20.3 (11.4–NE)	23/31	13.1 (6.7–23.9)	0.61 (0.35–1.08)
Melphalan	5/14	33.6 (23.4–NE)	13/23	13.1 (7.5–NE)	0.43 (0.15–1.21)
TTP <36 mo after prior ASCT[c]	17/24	15.1 (6.2–27.5)	13/22	28.7 (14.1–NE)	1.75 (0.84–3.64)
Cyclophosphamide	15/21	15.9 (6.1–27.5)	13/21	28.7 (10.3–37.1)	1.55 (0.73–3.28)



(C)

Subgroup	Melflufen arm Events/Patients, *n/N*	Melflufen arm ORR (95% CI), %	Pomalidomide arm Events/Patients, *n/N*	Pomalidomide arm ORR (95% CI), %	Oddds ratio (95% CI)[a]
Alkylator refractory[b]	19/78	24.4 (15.3–35.4)	21/75	28.0 (18.2–39.6)	0.83 (0.40–1.70)
No prior ASCT or TTP ≥36 mo after prior ASCT	16/54	29.6 (18.0–43.6)	13/53	24.5 (13.8–38.3)	1.30 (0.55–3.05)
Cyclophosphamide	12/42	28.6 (15.7–44.6)	5/31	16.1 (5.5–33.7)	2.08 (0.65–6.69)
Melphalan	5/14	35.7 (12.8–64.9)	6/23	26.1 (10.2–48.4)	1.57 (0.37–6.62)
TTP <36 mo after prior ASCT[c]	3/24	12.5 (2.7–32.4)	8/22	36.4 (17.2–59.3)	0.25 (0.06–1.11)
Cyclophosphamide	2/21	9.5 (1.2–30.4)	8/21	38.1 (18.1–61.6)	0.17 (0.03–0.94)

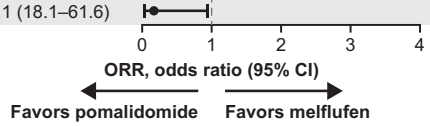


FIGURE 3 Analysis of PFS (A), OS (B), and ORR (C) in patients refractory to prior alkylators by prior ASCT status and type of alkylator received. Data cutoff date: February 3, 2021, for PFS and ORR; February 3, 2022, for OS follow-up analysis. [a]Stratified HR for the overall population. Unstratified HR for subgroups analyzed by prior alkylator exposure status. [b]The alkylator bendamustine was also included in this analysis but due to small subgroup size (melflufen arm, $n = 3$; pomalidomide arm, $n = 4$), meaningful conclusions could not be drawn. [c]No patients were refractory to melphalan in this subgroup. ASCT, autologous stem cell transplantation; HR, hazard ratio; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

received a previous alkylator per se does not adversely impact treatment with melflufen and dexamethasone, but rather supports the notions that the high-dose melphalan conditioning followed by an ASCT is the culprit. Because previous reports show that patients who had TTP < 36 months after prior ASCT may not derive benefit from melflufen and dexamethasone over pomalidomide and dexamethasone,[12] using an alkylator or alkylator-based therapy in patients who progressed <36 months on previous high-dose alkylator therapy may not be an advisable option.

Among studies in the literature of melflufen plus dexamethasone, all have demonstrated a consistent safety profile with the regimen being manageable with dose modifications and supportive care.[10,11,20] In the present analysis among patients who were refractory to previous alkylators, the safety profile was similar between the melflufen and pomalidomide arms, including serious and fatal adverse events (AEs). However, more patients with melflufen compared with pomalidomide had AEs that led to dose reductions and higher rates of certain Grade 3 or 4 TEAEs of special interest, including

TABLE 2 Safety overview in patients refractory to prior alkylators in the OCEAN study.

	Patients refractory to prior alkylators	
	Melflufen arm ($n = 74$)	Pomalidomide arm ($n = 73$)
Treatment-emergent adverse event,[a] *n* (%)		
Any	73 (99)	71 (97)
Grade 3/4	63 (85)	60 (82)
Serious	36 (49)	39 (53)
Fatal	14 (19)	12 (16)
Leading to dose modification	56 (76)	49 (67)
Leading to dose reduction	35 (47)	10 (14)
Leading to dose delay	42 (57)	37 (51)
Leading to treatment discontinuation	20 (27)	25 (34)
Grade 3/4 treatment-emergent adverse event of special interest,[b] *n* (%)		
Thrombocytopenia	54 (73)	10 (14)
Bleeding	1 (1)	0 (0)
Neutropenia	48 (65)	40 (55)
Infections	11 (15)	19 (26)
Thrombocytopenia concurrent with Grade 3/4 bleeding[c]	1 (1)	0 (0)
Neutropenia concurrent with Grade 3/4 infection[d]	1 (1)	3 (4)
Leukopenia or white blood cell decrease	10 (14)	2 (3)
Time to dose reduction, median (IQR), days	106 (28–443)	47 (28–225)
Time to Grade 3/4 thrombocytopenia, median (IQR), days	52 (15–451)	19 (8–91)
Time to Grade 3/4 neutropenia, median (IQR), days	36 (8–561)	22 (8–470)

Abbreviations: IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities.

[a]Treatment-emergent adverse events were defined as adverse events with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever occurred sooner. Adverse events are coded to preferred term using MedDRA, version 23.0 unless noted as an adverse event of special interest.

[b]Events of special interest represent grouped terms, or Standardised MedDRA Queries. For thrombocytopenia, the preferred terms from hematopoietic thrombocytopenia (Standardised MedDRA Queries) were combined. For neutropenia, the preferred terms from neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis, neutropenic infection, cyclic neutropenia, band neutrophil count decreased, band neutrophil percentage decreased, neutrophil percentage decreased, agranulocytosis, granulocyte count decreased, and granulocytopenia were combined.

[c]Bleeding with an onset date within 7 days of the onset and/or resolution dates of a Grade 3/4 thrombocytopenia event.

[d]Infections with an onset date within 7 days of the onset and/or resolution dates of a Grade 3/4 neutropenia event.

thrombocytopenia and neutropenia. Despite these higher rates of thrombocytopenia and neutropenia, the median time to dose reduction (106 vs. 47 days), median time to Grade 3 or 4 thrombocytopenia (52 vs. 19 days), and Grade 3 or 4 neutropenia (36 vs. 22 days) occurred later with melflufen than pomalidomide. Infection rates were lower with melflufen and dexamethasone than with pomalidomide and dexamethasone.

The results of this study further differentiate the mechanism of action of melflufen with that of other alkylators in the RRMM setting. Results in the present study suggest that previous alkylator therapy outside of the ASCT setting might not impact the efficacy of melflufen. Previous data suggest this may not be the case for other alkylators. Indeed, Goldsmith et al found that patients receiving bendamustine who had previously received a cyclophosphamide-containing regimen had a lower ORR (14%) than patients who did not have prior cyclophosphamide exposure (39%).[21]

Limitations to this analysis include the fact that this is an exploratory post hoc analysis of subgroups and the small patient numbers in certain analyzed subgroups. Limitations of the OCEAN study have been previously discussed.[11] A small subset of patients from OCEAN were refractory to bendamustine (melflufen arm, $n = 3$; pomalidomide arm, $n = 4$) and high-dose melphalan (melflufen arm, $n = 5$; pomalidomide arm, $n = 2$); however, due to the small sample size, meaningful conclusions for these subgroups could not be drawn.

In summary, melflufen plus dexamethasone showed a consistent clinical benefit when compared with pomalidomide plus dexamethasone in patients with RRMM who had disease refractory to prior alkylators, with the benefit mainly confined to those who had not received a prior ASCT or who had TTP ≥ 36 months after prior ASCT. No added toxicities were identified in this patient population. These results suggest that melflufen is a safe and effective treatment choice for patients who have disease refractory to prior alkylators, particularly those who had TTP ≥ 36 months after prior ASCT or no prior ASCT. Further, they indicate the possibility of switching to a therapy with a new mechanism of action such as melflufen after immunotherapy failure in patients with RRMM, which may additionally enhance the translation of these findings to current real-world practice.[22]

AUTHOR CONTRIBUTIONS

The study sponsor (Oncopeptides AB) conceptualized and designed the study in collaboration with Fredrik H. Schjesvold, Maria-Victoria Mateos, Marcus Thuresson, Paul G. Richardson, and Pieter Sonneveld. Fredrik H. Schjesvold, Heinz Ludwig, Maria-Victoria Mateos, Alessandra Larocca, Haifaa Abdulhaq, Paul G. Richardson, and Pieter Sonneveld treated the patients and collected the data. Marcus Thuresson, Stefan Norin, and Nicolaas A. Bakker 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 submission of this report; and are accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Oncopeptides AB commits to share 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 (identifier: NCT03151811) and approved by health authorities in the United States and the 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 patient data are deidentified. In case of any risk of reidentification on anonymized data despite measures to protect patient confidentiality, the data will not be shared. Patient 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 us at medinfoglobal@oncopeptides.com.

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SUPPORTING INFORMATION

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