Original Study

Benefit Versus Risk Assessment of Melflufen and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Analyses From Longer Follow-up of the OCEAN and HORIZON Studies

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Abstract

These analyses support the approval of melflufen plus dexamethasone by the European Medicines Agency for use in patients with relapsed/refractory multiple myeloma who have received ≥3 prior lines of therapy, whose disease is triple-class refractory, who have demonstrated disease progression on or after their last therapy, and who had no prior autologous stem cell transplant or who progressed ≥3 years from transplantation.

Introduction: Melphalan flufenamide (melflufen), a first-in-class alkylating peptide-drug conjugate, plus dexamethasone demonstrated superior progression-free survival (PFS) but directionally different overall survival (OS) favoring pomalidomide (hazard ratio [HR], 1.10) in OCEAN. **Methods:** These analyses further investigated prognostic subgroups impacting survival in updated data from the randomized, phase 3 OCEAN study (NCT03151811; date: February 3, 2022) and the phase 2 HORIZON study (NCT02963493; date: February 2, 2022). **Results:** In OCEAN, subgroups prognostic for OS were age ($P = .011$; <65 years favored pomalidomide) and no previous autologous stem cell transplant (ASCT) or progression >36 months after ASCT ($P = .001$; favored melflufen). Overall, 245 of 495 (49%) patients randomized had received a previous ASCT, of which 202 (82%) had progressed within 36 months following their ASCT. When excluding patients who had progressed <36 months post-ASCT (melflufen group, n = 145; pomalidomide group, n = 148), median OS was 23.6 months with melflufen and 19.8 months with pomalidomide (HR, 0.83 [95% CI, 0.62-1.12]; $P = .22$). Among patients with triple-class refractory disease in HORIZON, patients who had progressed <36 months post-ASCT (n = 58) had a lower response rate and shorter duration of response and PFS than the remaining patients (n = 52). Safety was consistent with previous reports. **Conclusion:** These analyses demonstrate a consistent benefit for melflufen and dexamethasone in patients with relapsed/refractory multiple myeloma who have not received an ASCT or progressed >36 months after receiving an ASCT (*ClinicalTrials.gov identifier: NCT03151811*).

Clinical Lymphoma, Myeloma and Leukemia, Vol. 000, No.xxx, 1–10

Keywords: Autologous stem cell transplant, Melphalan flufenamide, multiple myeloma, safety, pomalidomide, efficacy

Trial Registration: ClinicalTrials.gov identifier: NCT03151811 and NCT02963493.

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Submitted: Feb 20, 2023; Revised: May 1, 2023; Accepted: May 4, 2023; Epub: xxx

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2152-2650/$ - see front matter
https://doi.org/10.1016/j.clml.2023.05.004

Please cite this article as: Pieter Sonneveld et al, Benefit Versus Risk Assessment of Melflufen and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Analyses From Longer Follow-up of the OCEAN and HORIZON Studies, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.05.004

Introduction

Despite advances in therapeutics for relapsed/refractory multiple myeloma (RRMM),[1,2] most patients eventually relapse or develop resistance to standard-of-care therapies.[3,4] New therapies are needed, especially for older and frailer patients ineligible for intensive treatments such as high-dose melphalan followed by an autologous stem cell transplant (ASCT) and novel chimeric antigen receptor (CAR) T-cell therapies.[5-7]

Melphalan flufenamide (melflufen) is a first-in-class lipophilic alkylating peptide-drug conjugate that is rapidly distributed via passive transport to enter tumor cells due to its lipophilicity and affinity for aminopeptidases.[8-13] Upon entering tumor cells, melflufen releases cytotoxic, hydrophilic alkylating agents (melphalan and desethyl-melflufen) that remain entrapped within cells.[9,10,13]

Melflufen and dexamethasone received accelerated approval by the US Food and Drug Administration (FDA) in 2021 based on results from the pivotal phase 2 HORIZON study (OP-106; NCT02963493).[12,14,15] Subsequently, primary results from the randomized, head-to-head, open-label, phase 3 OCEAN study (OP-103; NCT03151811) demonstrated superior progression-free survival (PFS) for melflufen and dexamethasone (primary endpoint; hazard ratio [HR], 0.79 [95% CI, 0.64-0.98]; log-rank $P = .032$), but not overall survival ([OS]; key secondary endpoint; HR, 1.10 [95% CI: 0.85-1.44]; log-rank $P = .47$) compared with pomalidomide and dexamethasone in lenalidomide-refractory RRMM with 2 to 4 previous lines of therapy. No safety signals were identified, but an exploratory analysis suggested that previous ASCT therapy was a negative prognostic factor for OS with melflufen. The overall safety profile of melflufen and dexamethasone has been consistent across studies and is characterized primarily by hematologic toxicities.[14-16] In OCEAN, rates of grade 3/4 thrombocytopenia (76% vs 13%) and neutropenia (64% vs 49%) were higher with melflufen than with pomalidomide, whereas rates of grade 3/4 infection (13% vs 22%) were lower. Although treatment-emergent adverse events (TEAE) leading to dose delays (60% vs 44%) and dose reductions (47% vs 15%) were more common with melflufen than pomalidomide, permanent discontinuation due to TEAEs occurred at similar rates (26% vs 22%).[16] In July 2021, due to the primary OS HR of 1.10, the FDA issued a safety alert for melflufen.[16,17] In June 2022, melflufen and dexamethasone were approved by the European Commission for use in adult patients with multiple myeloma who have received ≥3 prior lines of therapies and whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 monoclonal antibody and have demonstrated disease progression on or after the last therapy.[18] For patients with a previous ASCT, the time to progression (TTP) should be ≥3 years after transplant. Approval was based on data from HORIZON and the confirmatory study, OCEAN.[18]

The longer follow-up and subgroup analyses herein aim to evaluate the benefits and risks of melflufen and dexamethasone in OCEAN and HORIZON and put these data into context given the nonconventional regulatory processes thus far.[16,19] We also further characterized the association between having received a previous ASCT and melflufen using the most recent clinical practice guidelines as a framework.[16,20] In these guidelines, factors considered for eligibility for frontline and salvage ASCT include age (<70 years) and previously successful ASCT (ie, not having progressed <36 months after the last ASCT), respectively.[20]

Methods

Study Design and Participants

Study designs for OCEAN and HORIZON have been previously reported.[14,16] In brief, OCEAN was a randomized, controlled, open-label, phase 3, head-to-head study. Eligible patients had RRMM, had received 2 to 4 previous lines of therapy, and had a disease that was refractory to both lenalidomide and their last line of therapy. HORIZON was a single-arm, open-label, phase 2 study. Eligible patients had RRMM, had received at least 2 prior lines of therapy, and had a disease that was refractory to pomalidomide, an anti-CD38 monoclonal antibody, or both. Studies were compliant with the ethical principles set forth in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines.[21] Study protocols were reviewed and approved by national regulatory authorities and an independent ethics committee or institutional review board at each study center before implementation and written consent was obtained from all patients.

Procedures

In OCEAN, patients were randomized 1:1 (between June 12, 2017 and September 3, 2020) to 28-day cycles of melflufen (40 mg as centrally administered intravenous infusion for 30 minutes on day 1) and dexamethasone (40 mg orally [20 mg if aged ≥75 years] on days 1, 8, 15, and 22) or pomalidomide (4 mg orally on days 1-28) and dexamethasone (as with melflufen).[16] Patients were stratified by age (≤75 vs >75 years), number of previous lines of therapy (2 vs 3-4), and International Staging System score (I vs II or III). In HORIZON, patients received the same melflufen and dexamethasone regimen as in OCEAN.[14] Patients received study treatment until documented disease progression per International Myeloma Working Group (IMWG) uniform response criteria,[2,22] unacceptable toxicity, or if the patient/treating physician determined it was not in the patient's best interest to continue.

Outcomes and Statistical Analysis

In OCEAN, the primary endpoint was PFS assessed by an independent review committee according to the IMWG uniform response criteria.[2,16] Key secondary endpoints included overall response rate (ORR), OS, and safety and tolerability with melflufen and pomalidomide.[16] In HORIZON, the primary endpoint was ORR, assessed by the investigator per IMWG uniform response criteria.[2,14] Secondary endpoints included duration of response (DOR), PFS, OS, and safety. In both studies, PFS was defined as the time from randomization to the earlier of confirmed disease progression or death from any cause, whichever occurred first. OS was defined as the time from the date of randomization to death due to any cause. The ORR was defined as the proportion of patients with a stringent complete response, complete response, very good partial response, or partial response as a best-confirmed response. PFS assessments were scheduled monthly until disease progression

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or the initiation of subsequent therapy; thereafter, assessments for OS were scheduled every 3 months ± 1 week for up to 24 months.

Prespecified subgroups included randomization stratification factors (age [≤75 vs >75 years], number of previous lines of therapy [2 vs 3-4], and International Staging System score [I vs II or III]), previous autologous stem cell transplant status (yes vs no), age (<65 vs ≥65 years), sex (male vs female), body surface area (below vs above median), race (White vs all other races), geographical region (United States vs Europe vs rest of world), refractory to lenalidomide (last line vs earlier line), refractory to alkylators (yes vs no), refractory to anti-CD38 monoclonal antibody (yes vs no), refractory to a proteasome inhibitor and immunomodulatory drug (yes vs no), extramedullary disease at baseline (yes vs no), and other baseline disease characteristics, and laboratory values (ie, maximum plasma cell involvement, creatinine clearance, lactate dehydrogenase, albumin, and cytogenetic risk group). Additional posthoc subgroups included age (<65 vs 65 to 74 vs ≥75 years), International Staging System score (I vs II vs III), and progression within 36 months of having received an ASCT (yes vs no; the "no" group also included patients who had not received a previous ASCT).

Post hoc analyses from OCEAN aimed to understand factors that drove differences between PFS and OS in the intention-to-treat population (ITT). PFS and OS were compared between treatment groups based on a log-rank test, stratified by the randomization stratification factors, to determine the *P* value for the treatment comparison. HR and 95% CI were determined using a 2-sided 0.05 level stratified Cox proportional hazards regression model stratified by randomization stratification factors. This analysis used OS data with 1 year of additional follow-up from the previous analysis. Efficacy endpoints were analyzed in the ITT (ie, all patients randomized), in the safety population (ie, patients who received ≥1 dose of melflufen, pomalidomide, or dexamethasone), with patients analyzed by the treatment received, and in prespecified and post hoc subgroups. The interaction between treatment and subgroups was tested using Cox regression models.[16] These analyses used OS data with 1 year of follow-up from previous data.[16]

Post hoc analyses from HORIZON included 110 patients with triple-class refractory disease—defined as refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 monoclonal antibody—from 157 patients treated in the study and further subdivided by progression <36 months of having received an ASCT, as in OCEAN. The data cut of this updated analysis was February 2, 2022.

Results

Of 495 patients randomized in the OCEAN study (melflufen group, n = 246; pomalidomide group, n = 249), 474 patients (96%) received ≥1 dose of study drug (melflufen group, 228 [93%]; pomalidomide group, 246 [99%]; safety population; Suppl. Figure S1). Most patients who did not receive any study treatment were randomized to melflufen (18/246 [7%] vs pomalidomide, 3/249 [1%]) and died (melflufen group, 12/18 died; pomalidomide group, 2/3 died). As of the analysis date (February 3, 2022), 28 patients (melflufen group, n = 10; pomalidomide group, n = 18) were alive and ongoing on study treatment.

In this updated survival analysis, median OS (95% CI) was 20.2 months (15.8-24.3) with melflufen and 24.0 months (19.1-28.7) with pomalidomide (HR, 1.14 [95% CI, 0.91-1.43]; $P = .24$), with a median follow-up time of 31.8 months and 29.8 months, respectively (Figure 1A). Because of imbalance in the number of patients who were randomized but not treated, survival was also evaluated in the safety population: median OS (95% CI) was 21.3 months (16.6-24.8) with melflufen and 24.0 months (19.8-28.7) with pomalidomide (HR, 1.12 [95% CI, 0.89-1.42]; $P = .33$), with the curves overlapping until ≈10 months after randomization (Figure 1B). Sensitivity analyses revealed that the uneven distribution of randomized but not treated patients impacted OS, but not PFS. Although a similar number of patients received subsequent therapy after OCEAN (melflufen group, 169/246 [69%] patients; pomalidomide group, 164/249 [66%] patients), the type of subsequent therapy and timing of subsequent therapy initiation differed between treatment groups (Table 1).

With longer OS follow-up, the significant univariable interaction with patient age ($P = .011$; ≥75 years favored melflufen; <65 years favored pomalidomide) and previous ASCT status ($P = .010$; no previous ASCT favored melflufen; previous ASCT favored pomalidomide) remained (Suppl. Figure S2).[16] In total, 245 of 495 patients (49%) received a previous ASCT (melflufen group, 125/246 [51%] patients; pomalidomide group, 120/249 [48%] patients); of these, 202 (82%) had progressed <36 months following their ASCT (melflufen group, 101/125 [81%] patients; pomalidomide group, 101/120 [84%] patients).

Because many patients had progressed <36 months post-ASCT, we analyzed OS when grouping patients by TTP after a previous ASCT (TTP <36 months post-ASCT vs TTP >36 months post-ASCT; Suppl. Figure S3). TTP >36 months post-ASCT favored melflufen, whereas TTP <36 months post-ASCT favored pomalidomide. A significant treatment difference was seen when comparing patients without a previous ASCT or a TTP >36 months post-ASCT with patients who had a TTP <36 months post-ASCT ($P = .001$; Suppl. Figure S3). When grouping patients with a TTP >36 months post-ASCT and patients without a previous ASCT (melflufen group, n = 145; pomalidomide group, n = 148), the median OS (95% CI) was 23.6 months (18.9-28.0) with melflufen and 19.8 months (12.6-26.5) with pomalidomide (HR, 0.83 [95% CI, 0.62-1.12]; $P = .2249$). Among patients with TTP <36 months post-ASCT (melflufen, n = 101; pomalidomide, n = 101), the median OS (95% CI) was 15.7 months (11.9-20.5) with melflufen and 28.7 months (20.2-34.1) with pomalidomide (HR, 1.80 [95% CI, 1.27-2.55]; $P = .0007$). PFS was also impacted by age ($P = .033$), previous ASCT (yes vs no; $P = .006$), and TTP post-ASCT (>36 months or no ASCT vs <36 months; $P < .001$) subgroups (Suppl. Figure S4).

Given the negative prognostic impact of TTP <36 months post-ASCT before receiving melflufen and dexamethasone, we analyzed outcomes when excluding these patients (n = 202): median PFS (95% CI) was 9.3 months (7.2-11.8) and 4.6 months (3.7-6.3; HR, 0.58 [95% CI, 0.44-0.76]; $P = .0001$), ORR (95% CI) was 42% (34-51) and 26% (20-34), and median OS (95% CI) was 23.6 months (18.9-28.0) and 19.8 months (12.6-26.5; HR, 0.83 [95% CI, 0.62-1.12]; $P = .22$) with melflufen and

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Figure 1 Overall survival in the intention-to-treat population (A) and safety population (B). [a]Stratified hazard ratio. [b]Log-rank P value.

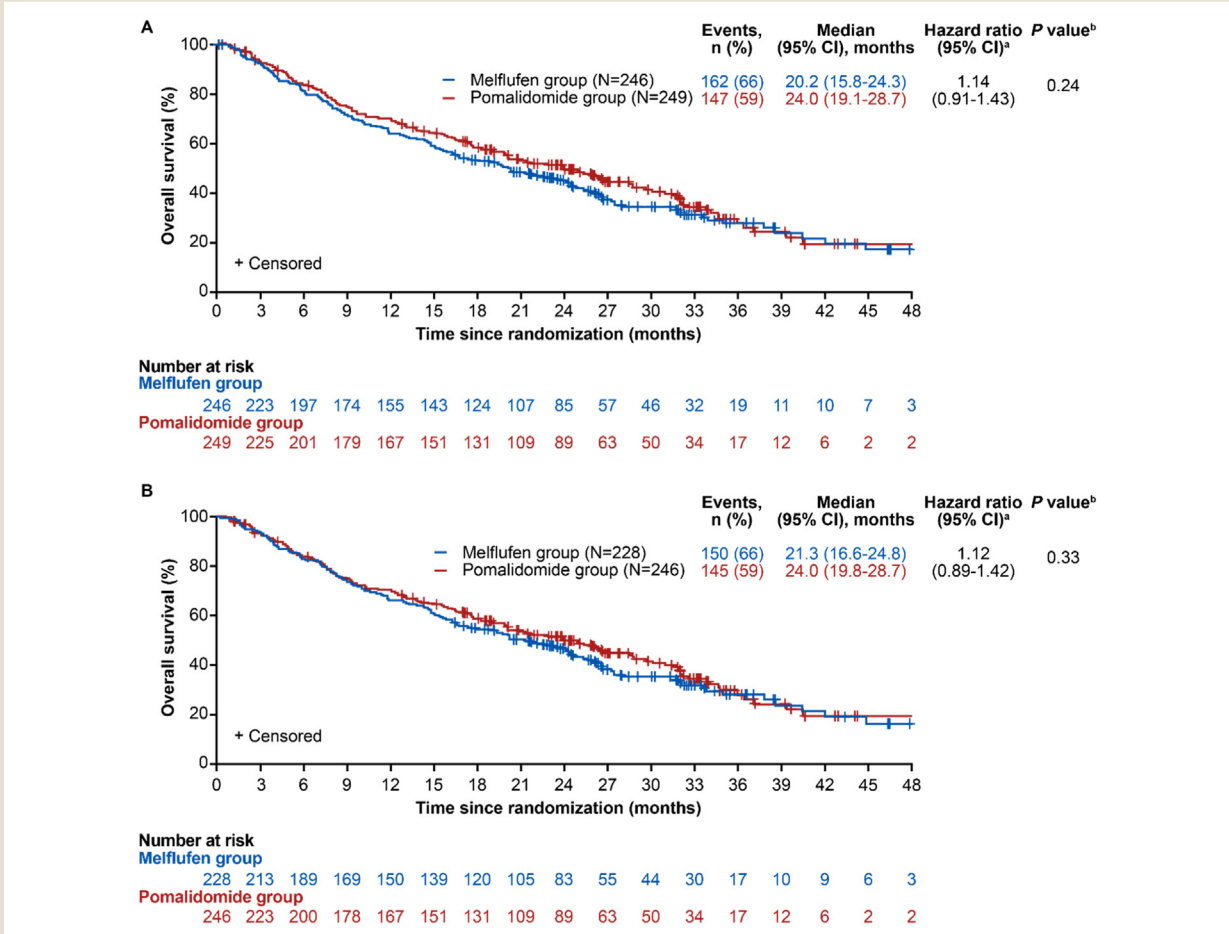

Table 1 Subsequent Therapy Received in the Melflufen and Pomalidomide Groups

	Melflufen Group (n = 246)	Pomalidomide Group (n = 249)
Any subsequent therapy, n (%)	169 (69)	164 (66)
Alkylator	22 (13)	37 (23)
Anti-CD38 monoclonal antibody therapy	51 (30)	81 (49)
Daratumumab	49 (29)	78 (48)
Immunomodulatory drugs	78 (46)	27 (16)
Pomalidomide	61 (36)	7 (4)
Proteasome inhibitors	67 (40)	80 (49)
Median time between progression and subsequent therapy initiation, months	1.4	1.8

pomalidomide, respectively (Figure 2 and Suppl. Table S1). When excluding patients with a TTP <36 months post-ASCT, a trend toward longer OS with melflufen relative to pomalidomide was observed across all subgroups (Figure 3), except age <65 years and creatinine clearance ≥90 mL/min, prompting us to look more closely at the relationship between age and survival outcomes. In the melflufen group, median PFS and OS were longer with increasing age (Table 2). Younger patients were more likely to have received a previous ASCT than older patients (previous ASCT by age: 122/181 [67%] patients aged <65 years; 117/238 [49%] patients aged 65-74 years; 6/76 [8%] patients aged ≥75 years). In patients <65 years old who received melflufen, median OS (95% CI) was 35.0 months (10.2-not estimable) if TTP >36 months post-ASCT or no ASCT (n = 41) and 15.3 months (8.0-19.2)

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Figure 2 Overall survival when excluding patients who progressed <36 months after a previous ASCT. [a]Unstratified hazard ratio. [b]Log-rank *P* value. ASCT, autologous stem cell transplant.

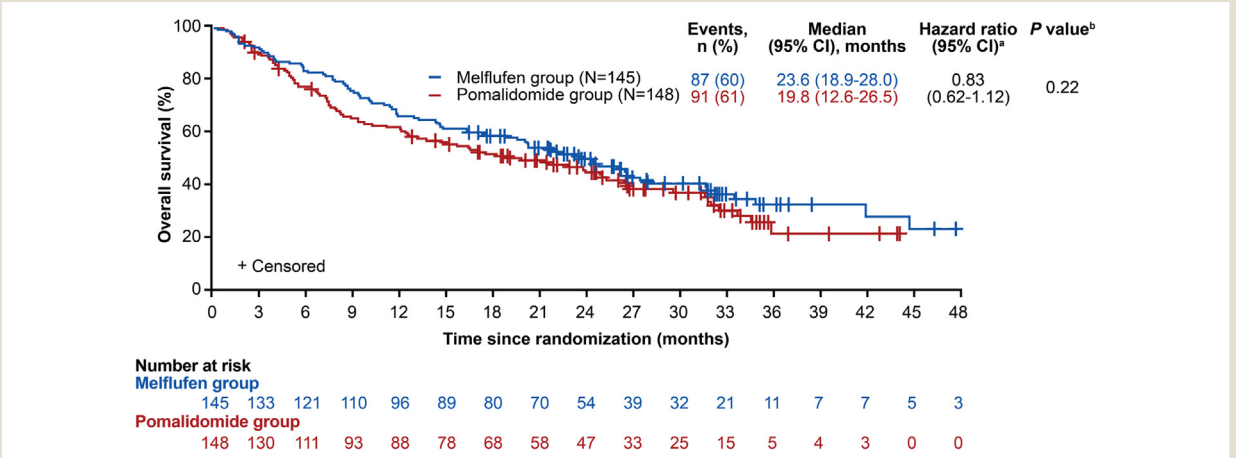
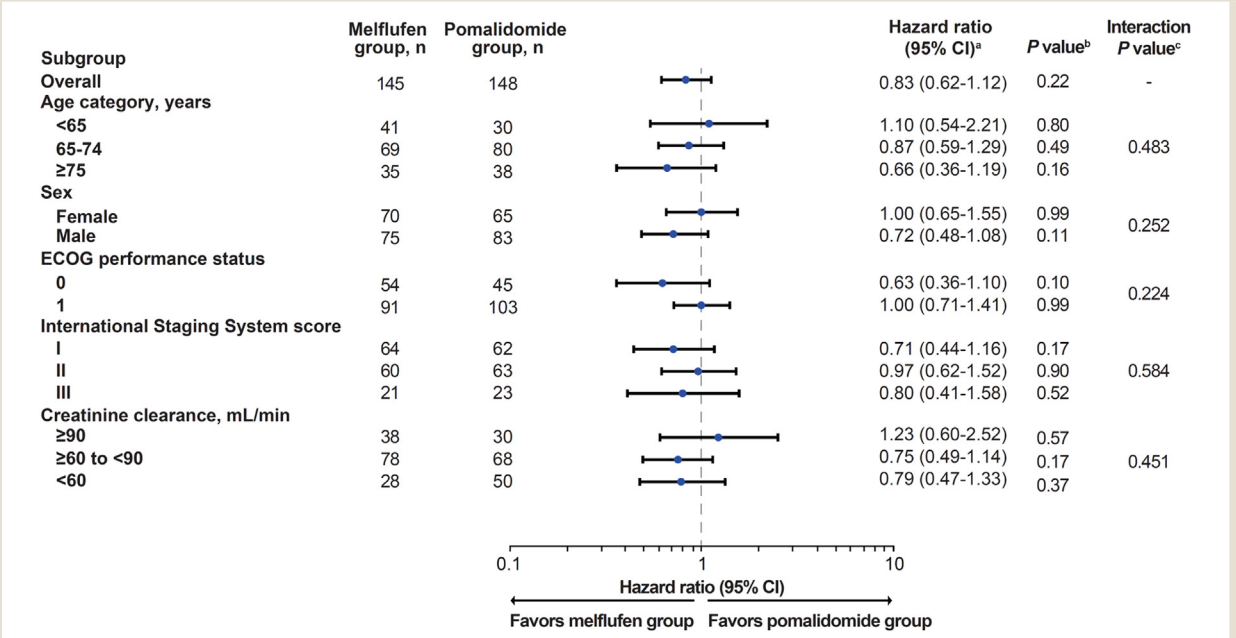


Figure 3 Overall survival by subgroups when excluding patients who progressed <36 months after a previous ASCT. [a]Unstratified hazard ratios were calculated based on a Cox proportional hazards regression model. [b]*P* values were determined using an unstratified log-rank test. [c]Interaction *P* value assessed using a univariable Cox regression model. ECOG, Eastern Cooperative Oncology Group.



if TTP <36 months post-ASCT (n = 55). In contrast, age and PFS were dissociated from OS in the pomalidomide group. Even though the median OS was shorter with increasing age, median PFS remained the same in all age groups with pomalidomide (Table 2). When analyzing outcomes in patients without a previous ASCT but refractory to standard-dose alkylator therapy received outside of the ASCT setting (ie, any alkylator excluding high-dose melphalan in the context of an ASCT), the ORR was higher (30% vs 24%) and PFS (8.3 months vs 3.8 months) and OS (26.5 months vs 13.1 months) were longer with melflufen than pomalidomide (Suppl. Table S2).

Given the prognostic importance of TTP <36 months post-ASCT in OCEAN, we evaluated this prognostic factor in a post hoc analysis from the HORIZON study. Among 110 patients with

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Table 2 Progression-Free Survival and Overall Survival Results by Age Groups and Treatment Group

	Aged <65 Years		Aged 65-74 Years		Aged ≥75 Years	
	Melflufen Group (n = 96)	Pomalidomide Group (n = 85)	Melflufen Group (n = 113)	Pomalidomide Group (n = 125)	Melflufen Group (n = 37)	Pomalidomide Group (n = 39)
Progression-free survival						
Median (95% CI), months	4.4 (3.7-6.5)	4.9 (3.8-5.7)	7.2 (5.6-10.0)	4.9 (3.8-6.9)	9.3 (5.5-23.3)	4.9 (3.0-6.6)
Overall survival						
Median (95% CI), months	16.2 (11.9-24.5)	31.7 (21.3-NE)	20.5 (16.3-24.8)	20.9 (17.0-26.5)	26.5 (14.6-NE)	17.5 (7.2-32.1)
Hazard ratio (95% CI)	1.68 (1.13-2.49)		1.03 (0.76-1.41)		0.62 (0.35-1.13)	

Abbreviation: NE, not estimable.

triple-class refractory disease who had received ≥3 prior lines of therapy, 77 (70%) had received a previous ASCT and 58 (53%) had TTP <36 months post-ASCT (Suppl. Table S3). In patients with a TTP >36 months post-ASCT or no ASCT versus patients with a TTP <36 months post-ASCT, ORR was higher (29% vs 22%; Suppl. Table S4) and median DOR (7.6 months vs 3.9 months) and median PFS (4.2 months vs 3.4 months) were longer.

Since pomalidomide and lenalidomide both belong to the immunomodulatory drugs, we analyzed if the duration of previous treatment with lenalidomide could have impacted the results. The median duration of lenalidomide was 14.4 months in patients with ASCT and TTP < 36 months, 38.3 months in patients with ASCT and TTP > 36 months, and 14.6 months in patients with no previous ASCT. However, the median PFS for patients treated with pomalidomide did not differ substantially between these groups of patients (Suppl. Figure S5).

The safety profile of melflufen and dexamethasone was generally consistent between patients with a TTP >36 months post-ASCT or no ASCT and patients with a TTP <36 months post-ASCT (Table 3 and Suppl. Table S5). In OCEAN among the melflufen group, the frequency of grade 3/4 TEAEs (88% and 92%), serious TEAEs (44% and 38%), and fatal adverse events (AEs; 11% and 13%) was similar in patients with a TTP >36 months post-ASCT or no ASCT and patients with TTP <36 months. However, patients with a TTP >36 months post-ASCT or no ASCT had lower rates of TEAEs leading to treatment discontinuation (23% and 31%), the longer median duration of study treatment (35.1 weeks vs 15.1 weeks), and longer median time to experiencing grade 3/4 thrombocytopenia (11.2 weeks vs 4.1 weeks) and grade 3/4 neutropenia (4.8 weeks vs 2.1 weeks) than patients with a TTP <36 months post-ASCT. In HORIZON, patients with a TTP >36 months post-ASCT or no ASCT had lower rates of grade 3/4 TEAEs (88% and 98%), but higher rates of serious TEAEs (64% and 53%) and similar rates of TEAEs leading to treatment discontinuation (29% and 33%) than patients with a TTP <36 months post-ASCT.

Discussion

In the primary analysis from OCEAN, melflufen and dexamethasone demonstrated a significantly longer PFS, but no significant difference in OS versus pomalidomide and dexamethasone.[16] No safety signal that could explain the potential detrimental effect on OS was identified, but having received a previous ASCT was shown to be a negative prognostic factor with melflufen and dexamethasone.[16] This post hoc analysis further demonstrated that having progressed <3 years after receiving a previous ASCT is a negative factor for receiving melflufen and dexamethasone, which is not unexpected given that this is in line with recommendations for patients to receive a salvage ASCT.

Across all studies with melflufen and dexamethasone, the safety profile has been consistent, including between patients with TTP <36 months and TTP >36 months post-ASCT or no ASCT, and shown no excess fatal toxicities.[14-16,19] AEs with melflufen have been generally manageable with dose modifications and supportive care.[14-16] In OCEAN, despite higher rates of dose delays and dose reductions with melflufen than pomalidomide, most patients receiving a melflufen dose reduction were able to continue therapy longer than patients with a pomalidomide dose reduction (17 weeks vs 9 weeks).[16]

OS analyses of the safety population showed that the distribution of randomized but not treated patients influenced OS results, especially during the first 10 months. It is only after these 10 months that the curves start to diverge, suggesting that events after the treatment period contributed to the potentially worse OS with melflufen. Notably, there were imbalances in subsequent therapy between treatment groups; fewer patients in the melflufen group received subsequent daratumumab therapy (29% vs 48%), but more received subsequent pomalidomide therapy (36% vs 4%) than in the pomalidomide group. Often in certain healthcare systems, based upon the approval of pomalidomide combined with bortezomib and dexamethasone in early relapse,[23] to be eligible for daratumumab therapy, patients must have previously used pomalidomide-based therapy, which may have in turn impacted the imbalance between groups seen in the present study. Specifically, country-specific restrictions for sequencing anti-CD38 monoclonal antibody therapy in RRMM will have played a role in patient access to anti-CD38 monoclonal antibody therapy as in some participating centers, patients must have received pomalidomide-based therapy before being eligible to receive anti-CD38 monoclonal antibody therapy. Importantly, previous studies have shown that OS is longer in patients who receive subsequent daratumumab salvage therapy in earlier lines of therapy.[24]

Per the joint European Hematology Association and European Society for Medical Oncology clinical practice guidelines, salvage ASCT is not recommended for patients with <36 months of

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Table 3 Safety Overview in Patients From the OCEAN Study by Duration of Remission to Previous ASCT Subgroup

	No Previous ASCT or TTP >36 Month Post-ASCT[a]		TTP <36 Month Post-ASCT[b]	
	Melflufen Group (n = 145)	Pomalidomide Group (n = 148)	Melflufen Group (n = 101)	Pomalidomide Group (n = 101)
Treatment-emergent adverse event, n (%)[c]				
Any	136 (99)	145 (99)	90 (99)	96 (97)
Grade 3 or 4	121 (88)	105 (71)	84 (92)	78 (79)
Serious	60 (44)	66 (45)	35 (38)	47 (47)
Fatal	15 (11)	25 (17)	12 (13)	7 (7)
Leading to dose reduction	66 (48)	24 (16)	41 (45)	13 (13)
Leading to dose delay	80 (58)	70 (48)	57 (63)	39 (39)
Leading to treatment discontinuation	32 (23)	39 (27)	28 (31)	17 (17)
Grade 3 or 4 treatment-emergent adverse event of special interest, n (%)[d]				
Thrombocytopenia	96 (70)	17 (12)	78 (86)	14 (14)
Hemorrhage	4 (3)	1 (1)	1 (1)	0 (0)
Thrombocytopenia with concurrent hemorrhage[e]	2 (1)	0 (0)	0 (0)	0 (0)
Neutropenia	91 (66)	75 (51)	56 (62)	46 (46)
Infections	20 (15)	31 (21)	10 (11)	22 (22)
Neutropenia with concurrent infection[f]	3 (2)	9 (6)	4 (4)	7 (7)
Median duration of treatment (IQR), weeks	35.1 (16.3-60.3)	21.3 (10.8-43.3)	15.1 (10.1-32.9)	23.1 (10.9-37.6)
Median time to dose reduction (IQR), weeks	21.6 (10.4-33.7)	6.8 (4.1-19.1)	10.1 (7.1-15.7)	9.3 (5.1-28.4)
Median time to grade 3 or 4 thrombocytopenia (IQR), weeks	11.2 (4.0-21.9)	2.6 (1.3-7.3)	4.1 (2.1-11.0)	2.1 (2.1-3.1)
Median time to grade 3 or 4 neutropenia (IQR), weeks	4.8 (2.1-6.9)	3.1 (3.0-3.1)	2.1 (2.0-6.1)	3.1 (3.1-4.2)

Abbreviations: ASCT, autologous stem cell transplant; IQR, interquartile range; TTP, time to progression.
[a] Patients who did not receive an ASCT before enrolling in OCEAN or who had a remission duration of at least 36 months after receiving a previous ASCT.
[b] Patients who progressed less than 36 months after receiving a previous ASCT.
[c] 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.
[d] 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.
[e] Hemorrhages with an onset date within 7 days of the onset and/or resolution dates of grade 3 or 4 thrombocytopenia event.
[f] Infections with an onset date within 7 days of the onset and/or resolution dates of a grade 3 or 4 neutropenia event.

remission following frontline ASCT.[20] In this post hoc analysis, a TTP <36 months post-ASCT was identified as a negative prognostic factor for OS with melflufen. This is not surprising, given that early progression post-ASCT suggests that the high-dose melphalan conditioning may not have been effective. Alternatively, high-dose melphalan may have a negative impact on the bone marrow microenvironment. Thus, further alkylator-based therapy may not be a good treatment choice for patients who progressed early on previous high-dose alkylator therapy. In OCEAN, 82% of all patients who received a previous ASCT had TTP <36 months, which confounded the interpretation of the primary results from the study. Importantly, patients who had not received a previous ASCT but were refractory to standard-dose alkylator therapy saw a longer treatment duration and more favorable outcomes with melflufen than pomalidomide.

This post hoc analysis demonstrated that age is not a prognostic factor for melflufen, but rather a confounding effect due to and the correlation between age and eligibility for ASCT. Eligibility for ASCT is higher among younger patients,[20] which was the case in OCEAN (67% of younger patients had received a previous ASCT). Importantly, outcomes with melflufen were better for patients with a successful ASCT or no ASCT than for patients who had a TTP <3 years post-ASCT in both OCEAN and HORIZON.

In contrast, older age (≥75 years) was identified as a strong negative prognostic factor for OS with pomalidomide. At this stage of RRMM (2-4 prior lines of treatment), age is not expected to be a prognostic factor for OS.[25,26] In addition to this unexpected finding, PFS analyses did not mirror those of OS when it came to age, with median PFS in the pomalidomide group remaining constant regardless of patient age, while OS varied heavily. This is the main factor in OCEAN driving the OS HR to 1.14, as the population of younger patients (who did well on pomalidomide) was much larger than that of older patients in OCEAN. Although the dissociation between age and OS observed with pomalidomide was initially unexpected, a literature search also identified this

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trend in studies including pomalidomide and dexamethasone as the control arm. For example, in the pomalidomide and dexamethasone arm in the ICARIA-MM study, the median OS was shorter with increasing age but the median PFS was not.[27] In a recent phase 2 randomized study, PFS favored ixazomib and dexamethasone regardless of patient age (<65 vs ≥65 years), whereas OS favored pomalidomide and dexamethasone.[28] Of note, pomalidomide is one of the most-often used drugs for the treatment of RRMM due to efficacy and ease of use, with approximately half of the pomalidomide use being in a doublet regimen with dexamethasone in older patients.[29]

Conclusion

In summary, the interpretation of the results from the OCEAN study were impacted by the heterogeneity of the population, with age and previous success of ASCT therapy identified as prognostic factors with study therapies. The safety profile of melflufen and dexamethasone is primarily characterized by hematologic AEs that are clinically manageable.[14–16] Observed infection rates, which included COVID-19, were generally low. Taken together, these data support the use of melflufen and dexamethasone in patients who have not received a previous ASCT or who underwent a successful ASCT (ie, TTP >36 months post-ASCT). In addition, the favorable efficacy profile and convenience of monthly outpatient infusions, especially for patients without access to other therapeutics such as CAR T-cell therapy or bispecific antibodies, bode well for this combination translating successfully into real-world practice.[30]

Clinical Practice Points

- Based on results from the HORIZON (phase 2) and OCEAN (randomized, phase 3) studies, melflufen and dexamethasone was approved by the European Medicines Agency for use in patients with relapsed/refractory multiple myeloma (RRMM) who have received ≥3 previous lines of therapy, whose disease is triple-class refractory, and who have demonstrated disease progression on or after the last therapy; patients with a prior autologous stem cell transplant (ASCT) must have a time to progression (TTP) ≥3 years from transplantation.
- Because in primary analyses from the OCEAN study melflufen and dexamethasone showed significantly longer progression-free survival (PFS; hazard ratio [HR], 0.79 [95% CI, 0.64-0.98]; $P = .032$) but not overall survival (OS; HR, 1.10 [95% CI, 0.85-1.44]; $P = .47$) versus pomalidomide and dexamethasone, this post hoc analysis aimed to further characterize the benefits and risks of melflufen and dexamethasone in the OCEAN and HORIZON studies.
- Post hoc subgroup analyses from OCEAN herein demonstrated that a TTP <36 months after a previous ASCT was a negative prognostic factor for survival with melflufen and dexamethasone, whereas older age was a negative prognostic factor for survival with pomalidomide and dexamethasone; subgroup analyses from HORIZON were consistent with those in OCEAN.
- Melflufen and dexamethasone have shown a consistent safety profile across studies, characterized primarily by hematologic adverse events that are clinically manageable and monitorable, with nonhematologic adverse events being infrequent and generally of grade 1/2.
- Importantly for clinical practice, melflufen and dexamethasone provide meaningful efficacy in adults with triple-class refractory RRMM who have received ≥3 previous lines of therapy and have not received a prior ASCT or have a TTP >36 months after their transplantation.

Authors Contributions

The study sponsor, Oncopeptides AB, conceptualized and designed the HORIZON and OCEAN studies in collaboration with PS, PGR, M-AD, FHS, RH, MT, and M-VM. Patient data were collected by PS, PGR, HL, M-AD, FHS, RH, HA, and M-VM. Data were analyzed by MT, SN, and NAB. FHS, MT, and NAB had access to and verified the underlying study data. All authors had access to the data, participated in the interpretation of the data, took part in drafting and revising the manuscript, and approved the final version before submission.

Data Sharing Statement

Oncopeptides commits to sharing clinical study data with qualified researchers to enable the 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 United States and the European Union. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after 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 de-identified. In case of any risk of reidentification of 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.

Disclosure

Funding was provided by Oncopeptides AB. P.S. has received payment or honoraria and research funding from Amgen, Celgene, Janssen, Karyopharm, and Takeda and payment or honoraria from Bristol Myers Squibb. P.G.R. has received consulting fees from

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AstraZeneca, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Karyopharm, Protocol Intelligence, Regeneron, Sanofi, Secura Bio, and Takeda and grants or contracts from Bristol Myers Squibb/Celgene, Karyopharm, Oncopeptides, and Takeda. H.L. has received grants or contracts from Amgen, Sanofi, and Takeda; consulting fees from Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, and Takeda; payment or honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Pfizer, Sanofi, and Takeda; and has participated on a data safety monitoring board or advisory board for Amgen, Bristol Myers Squibb, Celgene, Sanofi, and Takeda. M.-A.D. has received payment or honoraria for participation on an advisory board for Amgen, BeiGene, Bristol Myers Squibb, Janssen, and Takeda. F.H.S. has received grants or contracts from Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Targovax, and Sanofi; payment or honoraria from AbbVie, Amgen, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Janssen, Novartis, Oncopeptides, Pfizer, Sanofi, SkyliteDX, and Takeda; and participated on a data safety monitoring board or advisory board for AbbVie, Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and Takeda. R.H. has received grants or contracts from Novartis and Takeda; consulting fees and payment or honoraria from AbbVie, Amgen, Bristol Myers Squibb, Janssen, PharmaMAR, and Takeda; consulting fees from Novartis; support for attending meetings and/or travel from Takeda; and has participated on a data safety monitoring board or advisory board for Amgen and Takeda. H.A. has received payment or honoraria from Amgen, Alexion, and Oncopeptides and has participated on a data safety monitoring board or advisory board for Amgen, Bristol Myers Squibb, Genentech, Janssen, MorphoSys and Novartis. M.T. is a consultant of and receives stock or stock options from Oncopeptides. S.N. is an employee of, has participated on a data safety monitoring board or advisory board for, and receives stock or stock options from Oncopeptides. N.A.B. is an employee of and receives stock or stock options from Oncopeptides. M.-V.M. has received payment or honoraria for lectures, presentations, speakers' bureau, manuscript writing, or education events from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Pfizer, Sanofi, and Takeda; and has participated on a data safety monitoring board or advisory board for Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, Sanofi, and Takeda.

Acknowledgments

The authors would like to thank the patients and their families for participating in this trial and the trial investigators and coordinators for their contributions to the trial. We thank Jared D. Hoffman, MS, PhD, and Katherine Mills-Lujan, PhD, CMPP, of Team 9 Science for providing medical editorial assistance under the guidance of the authors, which was funded by Oncopeptides AB in accordance with Good Publication Practice (GPP) 2022 guidelines.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2023.05.004.

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