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Health-related quality of life in relapsed/refractory multiple myeloma treated with melflufen and dexamethasone: analyses from the phase III OCEAN study

Authors

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Author Contributions

The study sponsor, Oncopeptides AB, conceptualized and designed the OCEAN study in collaboration with FSH, M-AD, M-VM, PGR, and PS. Patient data was collected by study site investigators. Data was analyzed by AS, MT, and SN. 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.

Disclosures

FHS: has received grants or contracts from Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Targovax, and Sanofi; payment or honoraria for lectures or speakers' bureau participation from AbbVie, Amgen, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Janssen, Novartis, Oncopeptides, Pfizer, Sanofi, SkylineDX, and Takeda; served on a data safety monitoring or advisory board for AbbVie, Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and

Takeda; and received stock or stock options from Nordic Nanovector and Oncopeptides. **HL:** has received research grants from Sanofi, and Amgen; has served on data monitoring committee for GSK, Janssen, and Takeda; has received payment or honoraria for speakers' bureau participation from Pfizer, BMS, Janssen, Amgen, and Sanofi. **SD:** has received payment or honoraria for speakers' bureau participation from and served on an advisory board for Amgen, GlaxoSmithKline, Janssen, Pfizer, Sanofi, Sobi, and Takeda. **DC:** has received travel support from Genesis Biopharma and Accord Healthcare. **IS:** has received consulting fees from and served on a data monitoring or advisory board for Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, PharmaMar, Sanofi, and Takeda; payment or honoraria for lectures or speakers' bureau participation from Amgen, Bristol Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; and meeting and/or travel support from Amgen, Bristol Myers Squibb, Celgene, and Janssen. **M-AD:** has received payment or honoraria for advisory board participation from Amgen, BeiGene, Bristol Myers Squibb, BeiGene, Inc, GSK, Janssen, Menarini, Regeneron, Sanofi and Takeda. **TM:** has received payment or honoraria for advisory board participation from AbbVie, Janssen-Cilag, Novartis, Pfizer, and Sanofi. **AS, SN, NAB:** are employees of and receive stock or stock options from Oncopeptides. **MT:** is a consultant of and receives stock or stock options from Oncopeptides. **M-VM:** has received payment or honoraria for lectures or speakers' bureau participation from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Pfizer, Sanofi, and Takeda; and served on a data safety monitoring or advisory board for Amgen, bluebird bio, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, Regeneron, Sanofi, and Takeda. **PGR:** has served on advisory committees for Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Karyopharm, Oncopeptides, Regeneron, and Sanofi, and received research grants from Bristol Myers Squibb/Celgene Karyopharm, Oncopeptides, and Takeda. **PS:** has received grants or contracts from Amgen, Celgene, Janssen, Takeda, and SkylineDx. **PR, NGC, LP, WT:** have no competing interests.

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Data sharing statement

Oncopeptides 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 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 de-identified. 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 medinfofglobal@oncopeptides.com.

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Relapsed or refractory multiple myeloma (RRMM) is associated with severe symptoms, some of which have been strongly linked to impairments in health-related quality of life (HRQoL), notably pain, fatigue, and a decline in physical and emotional functioning.¹ Furthermore, HRQoL deteriorates with each subsequent line of therapy in RRMM.² Hence, treatment goals, particularly in later lines of therapy, should include preserving HRQoL. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that utilizes increased peptidase expression to selectively release potent alkylating agents inside tumor cells. Melflufen is approved in Europe for the treatment of patients with triple-class–refractory RRMM with ≥ 3 prior lines of therapy and time to progression (TTP) >36 months after prior autologous stem cell transplant (ASCT), if received. Approval was based on the phase II HORIZON study and further supported by the phase III OCEAN study.³⁻⁵ OCEAN met its primary endpoint; melflufen plus dexamethasone showed superior progression-free survival vs pomalidomide plus dexamethasone in RRMM.⁴ Across trials, the safety profile of melflufen plus dexamethasone has been characterized primarily by hematologic adverse events (AE) that are clinically manageable, with infrequent grade 3/4 non-hematologic AE.^{3, 4, 6} Melflufen plus dexamethasone was shown to preserve HRQoL over time in patients with advanced RRMM from HORIZON.⁷ Pomalidomide plus dexamethasone is also shown to be safe and effective without negatively impacting HRQoL, including in later lines of therapy.⁸ In this letter, we report HRQoL based on patient-reported outcomes (PRO) in a subset of patients from OCEAN receiving either melflufen plus dexamethasone or pomalidomide plus dexamethasone. Overall, melflufen plus dexamethasone treatment resulted in HRQoL comparable to that of pomalidomide plus dexamethasone, further supporting the use of melflufen plus dexamethasone in heavily pretreated patients with RRMM.

The OCEAN study design has been previously published.⁴ The study was conducted per the ethical principles set forth in the Declaration of Helsinki and International Conference on

Harmonisation Good Clinical Practice Guidelines and was approved by national regulatory authorities and independent ethics committees/review boards. All patients provided written consent. PRO assessments were added as an exploratory endpoint on May 24, 2019 (protocol v4.1), approximately 2 years after the study started.⁴ Only patients enrolled on/after protocol v4.1 and who completed ≥ 1 PRO questionnaire were included. PRO questionnaires were administered before dosing at baseline and day 1 of each treatment cycle, at the end-of-treatment visit, disease progression, and start of a new treatment. Three PRO assessments were used: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) version 3, scored from 0-100, with higher scores indicating better functional status/QoL and functional scales, and an increase in severity of symptoms for the symptom scales^{9, 10}; EORTC Quality of Life Questionnaire-Multiple Myeloma module (EORTC MY20), ranging from 0-100 with higher scores indicating higher symptom severity¹⁰; and the European Quality of Life 5 Dimensions 3-Level Version (EQ-5D-3L) questionnaire that evaluates generic health status, also ranging from 0-100 (death=0; perfect health=100) with higher scores indicating a better health state.¹¹ PROs were compared between the treatment groups (melflufen and pomalidomide), and also within the melflufen group – between patients with TTP >36 months after prior ASCT or without prior ASCT (target population) and those with TTP <36 months post ASCT (nontarget population). Mean scores at baseline, at each treatment cycle up to cycle 6, and mean change from baseline through cycle 6 were analyzed. Responder analysis was conducted, defined as proportion of patients with improved, stable, or worsening EORTC QLQ-C30 and MY20 scales at cycle 6. We used a cutoff of a 10-point change for improvement or worsening scores, since this is the minimal important difference resulting in clinical benefit.¹²

Of the 495 patients enrolled and randomized in OCEAN, 158 with PRO assessments were included in the pre-specified PRO analysis (melflufen group, n=77; pomalidomide group, n=81).

Forty-four patients in the melflufen group had not received previous ASCT or had TTP >36 months after previous ASCT, and 33 had TTP <36 months after previous ASCT.

Baseline characteristics were generally well matched between treatment groups in patients reporting PROs. Both treatment groups showed similar PRO scores at baseline with respect to general health and well-being, as measured by the EORTC QLQ-C30 multi-item scales, including global health status/QoL and physical and emotional functioning; symptom burden, as measured by the EORTC QLQ-C30 fatigue and pain scales; EORTC MY20 disease symptom scale and side effects of treatment score; and “health today,” as measured by the EQ-5D-3L VAS score (Table 1). Importantly, mean PRO scores remained generally consistent with baseline through cycle 6 in both treatment groups (Fig. 1). Similarly, mean change from baseline in PRO scores through cycle 6 was also largely unchanged (Supplementary Fig. S1).

Overall, there was no difference in the proportion of patients with improvements or stable or worsening PRO measures over time between treatment groups, as exemplified by a snapshot at cycle 6 (Fig. 2). Most patients had improved or stable PRO measures at cycle 6. The proportion of patients with improved PRO measures at cycle 6 ranged from 20% to 39% in the melflufen group and 11% to 33% in the pomalidomide group, and with stable PRO measures ranged from 26% to 72% for melflufen and 37% to 67% for pomalidomide. In contrast, the proportion of patients with worsening PRO measures was generally low, particularly for physical functioning (melflufen: 13% and pomalidomide: 15%), emotional functioning (8% and 20%), disease symptoms (10% and 20%), and side effects of treatment (13% and 26%).

Because a TTP <36 months after previous ASCT has been shown to be associated with worse outcomes in patients treated with melflufen and dexamethasone,⁵ PRO assessments were compared between the target and nontarget populations within the melflufen group. Mean PRO

scores at baseline with melflufen and dexamethasone were similar between the target and nontarget populations and trended similar to those in the overall population (Supplementary Table S1). Mean baseline global health status/QoL scores were 65.3 in the target population and 61.9 in the nontarget population, physical functioning scores were 73.2 and 71.5, and emotional functioning scores were 83.3 and 78.0. Similarly, mean baseline scores for fatigue (30.7 and 40.7), pain (26.2 and 35.4), MM-specific disease symptoms (23.0 and 27.1), side effects of treatment (15.9 and 16.3), and EQ-5D-3L VAS (64.8 and 62.8) were similar between the target and nontarget populations. Likewise, mean PRO scores remained generally consistent through cycle 6 of treatment with melflufen and dexamethasone between the target and nontarget populations (Supplementary Fig. S2).

These results are consistent with the preserved HRQoL seen with melflufen plus dexamethasone in the HORIZON study.⁷ Although progression <36 months after prior ASCT is a negative prognostic factor for overall survival,⁵ PRO measures of the target and nontarget populations within the melflufen group were similar at baseline and remained consistent through cycle 6 of therapy. In patients with RRMM, HRQoL tends to decrease with each subsequent line of therapy.² Currently available therapeutic options for RRMM mostly maintain HRQoL but do not achieve clinically meaningful improvements.¹³ Comparisons across trials, however, are limited by differences in reporting of clinically meaningful improvements, and differences in patient population and trial design. In the phase III APOLLO study of pomalidomide plus dexamethasone with or without daratumumab, HRQoL measured using the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires, remained generally consistent with baseline in both arms, although between-group differences did not favor the pomalidomide-dexamethasone arm for most QoL scales.¹⁴ In the phase II DREAMM-2 study, HRQoL measured by the EORTC QLQ-MY20 scale was maintained with long-term follow-up with belantamab mafodotin, with only

up to 38% of evaluable patients (n=45) experiencing improvements in pain in different locations at Week 7.¹⁵

Results from our analysis are limited by the fact that PRO assessments were collected only from patients who were randomized after protocol amendment 4.1. Subgroup analyses for the target and nontarget populations within the melflufen group were further limited by small patient numbers. Nevertheless, in both groups, more than half of the patients for whom PRO assessments were available were still on study at cycle 6. Although not a statistically powered comparison, 31% of patients receiving melflufen and 13% receiving pomalidomide showed improvement (≥ 10 points' change) in global health status/QoL scores at cycle 6, whereas 46% of patients receiving melflufen and 57% receiving pomalidomide showed stable global health status/QoL scores at cycle 6. These results from later timepoints likely suggest a continuous selection of patients benefiting from therapy and being able to tolerate it.

Pomalidomide plus dexamethasone was the standard-of-care for patients with RRMM when the OCEAN study was initiated, and the combination does not negatively impact HRQoL. Despite the higher frequency of hematologic AE in the melflufen group than the pomalidomide group in OCEAN,⁴ these AE had limited impact on patients' HRQoL in the melflufen group. A greater proportion of patients were stable or even experienced improvements than those with worsening PRO measures with both treatment regimens, suggesting that in terms of impact on HRQoL, melflufen plus dexamethasone is comparable to pomalidomide plus dexamethasone, despite the different routes of administration (intravenous for melflufen and oral for pomalidomide). These findings aid in meaningful translation of melflufen plus dexamethasone treatment to real-world practice.

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Tables

Table 1. Baseline characteristics of patients with and without patient-reported outcomes (PRO) assessments.

	Patients With PRO Assessments			Patients Without PRO Assessments ^a (N=310)
	Melflufen Group (n=77)	Pomalidomide Group (n=81)	Overall (N=158)	
Age, y, median (range),	69 (41–91)	67 (44–82)	68 (41–91)	67 (39–87)
Age group, <i>n</i> (%)				
< 65	27 (35)	27 (33)	54 (34)	118 (38)
65-74	34 (44)	39 (48)	73 (46)	154 (50)
≥ 75	16 (21)	15 (19)	31 (20)	38 (12)
Male, <i>n</i> (%)	46 (60)	41 (51)	87 (55)	178 (57)
Race, <i>n</i> (%)				
White	70 (91)	69 (85)	139 (88)	284 (92)
All other races	5 (6)	11 (14)	16 (10)	11 (4)
Missing	2 (3)	1 (1)	3 (2)	15 (5)
ECOG PS, <i>n</i> (%)				
0	34 (44)	35 (43)	69 (44)	104 (34)
1	37 (48)	43 (53)	80 (51)	173 (56)
2	6 (8)	3 (4)	9 (6)	33 (11)
EORTC QLQ-C30 multi-item scales, mean score (range) ^b				
Global health status/QoL	63.8 (16.7-100)	64.3 (16.7-100)	64.0 (16.7-100)	
Physical functioning	72.4 (20-100)	74.2 (33.3-100)	73.3 (20-100)	
Emotional Functioning	81.0 (0-100)	79.8 (16.7-100)	80.4 (0-100)	
EORTC QLQ-C30 symptom scales, mean score (range) ^c				
Fatigue	35.1 (0-100)	32.6 (0-100)	33.8 (0-100)	
Pain	30.2 (0-100)	28.7 (0-100)	29.5 (0-100)	
EORTC MY20 score, mean score (range) ^d				
Disease symptoms	24.7 (0-83.3)	22.6 (0-88.9)	23.6 (0-88.9)	
Side effects of treatment	16.1 (0-73.3)	16.1 (0-60)	16.1 (0-73.3)	
EQ-5D-3L VAS score, mean score (range) ^e	64.0 (20-100)	66.9 (9-100)	65.5 (9-100)	

ECOG PS: Eastern Cooperative Oncology Group performance status, EORTC: European Organisation for Research and Treatment of Cancer, EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version, melflufen: melphalan flufenamide, MY20: Multiple Myeloma Module, PRO: patient-reported outcome, QLQ-C30: Core Quality of Life Questionnaire, QoL: quality of life, VAS: visual analog score.

^aBaseline characteristics in the PRO analysis population and in patients not included in the PRO analysis population were comparable, except for a higher proportion of patients in the PRO analysis population having an ECOG PS score of 0 (44% vs 34%).

^bEORTC QLQ-C30 global health status/QoL, emotional functioning, and physical functioning scores range from 0 to 100; a higher score indicates better function.⁹

^cEORTC QLQ-C30 fatigue and pain symptoms range from 0 to 100; a higher score indicates a higher severity of symptoms.¹⁰

^dEORTC MY20 disease symptoms and side effects of treatment scores range from 0 to 100; a higher score indicates a higher severity of symptoms.¹⁰

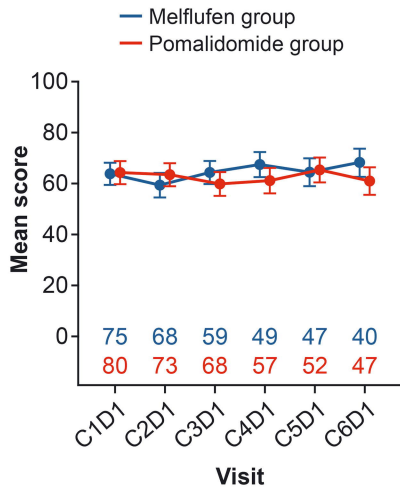
^eEQ-5D-3L VAS scores range from 0 to 100; a higher score indicates a better health state (0 equals death; 100 equals perfect health).¹¹

Figure Legends

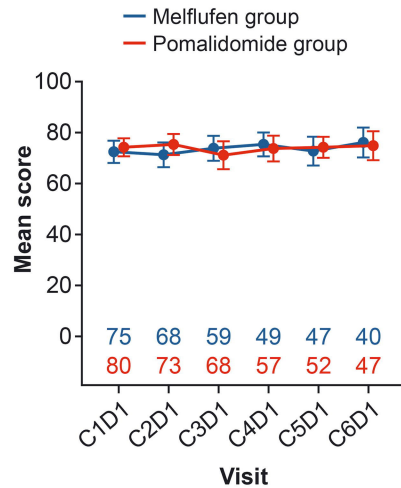
Figure 1. Mean scores at baseline through cycle 6 of treatment with melflufen plus dexamethasone or pomalidomide plus dexamethasone. C, cycle; D, day; dex, dexamethasone; melflufen, melphalan flufenamide; QoL, quality of life; VAS, visual analog scale.

Figure 2. Proportion of patients with improvement (≥ 10 points' change) in patient-reported outcomes (PRO), stable PRO measures, or worsening PRO measures at cycle 6. QoL, quality of life.

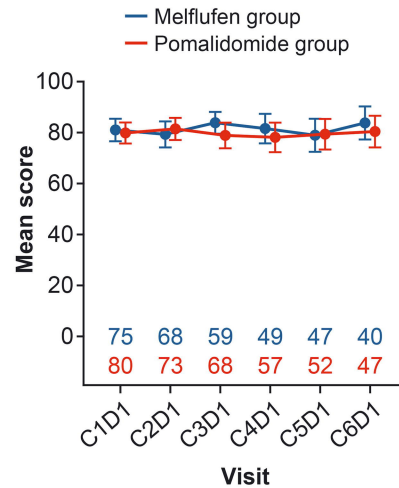
Global Health Status/QoL



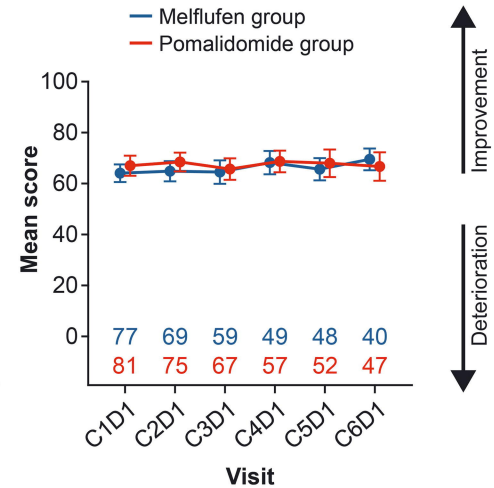
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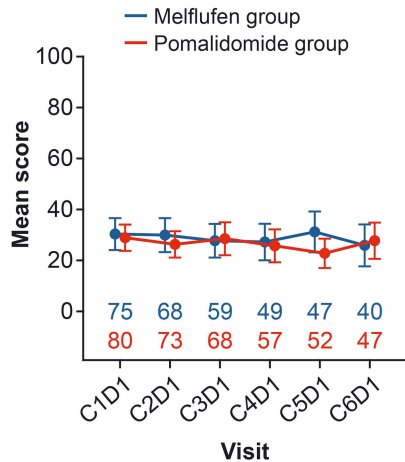
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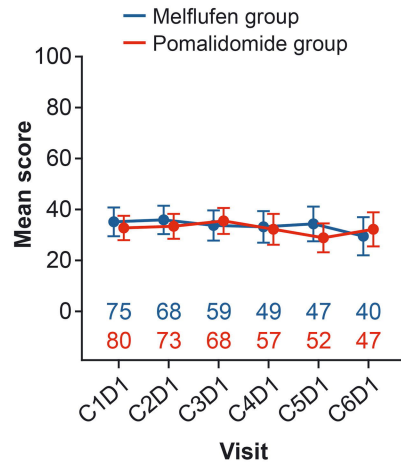
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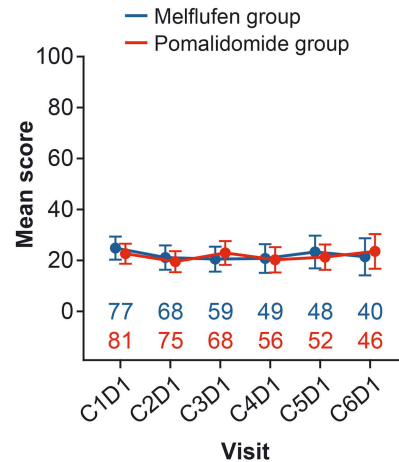
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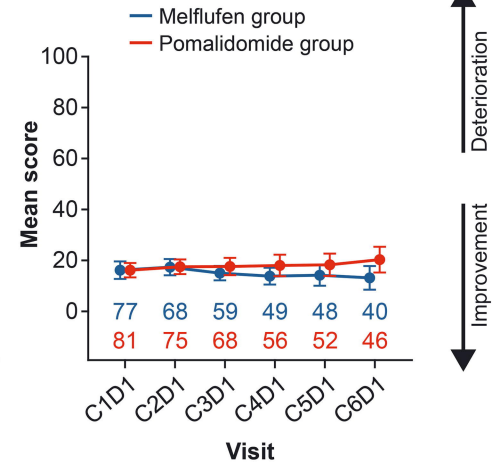
Fatigue

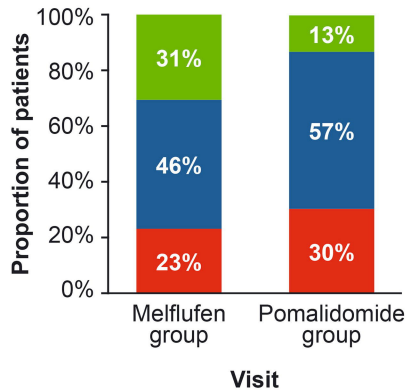
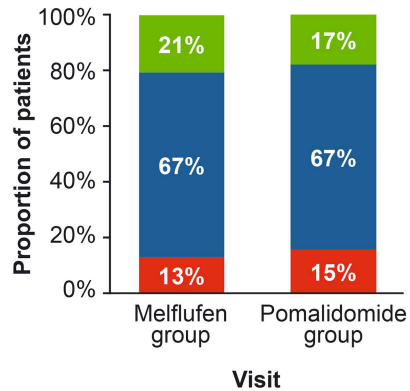
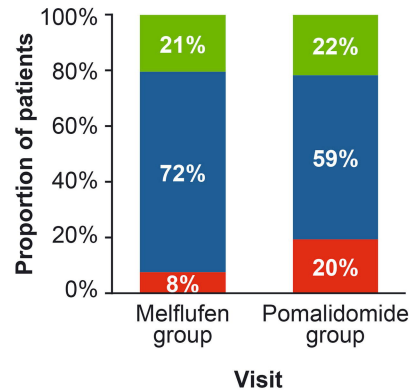
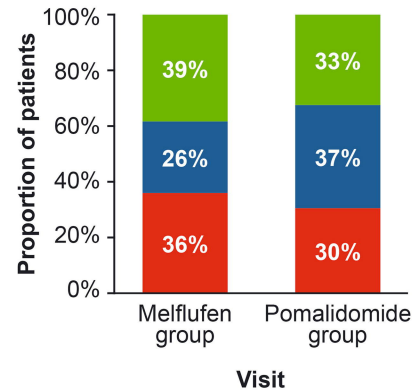
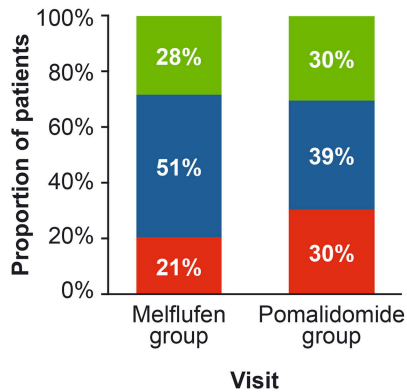
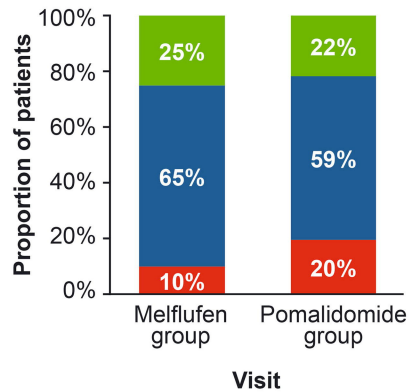
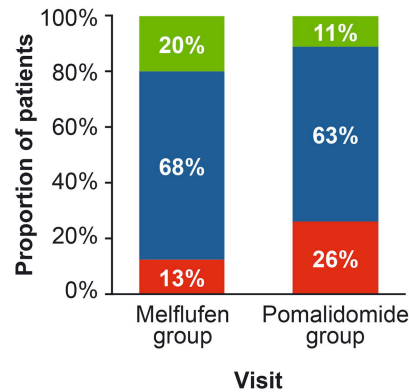


Disease Symptoms



Side Effects of Treatment



Global Health Status/QoL**Physical Functioning****Emotional Functioning****Fatigue****Pain****Disease Symptoms****Side Effects of Treatment**

Improved
Stable
Worsened

ONLINE SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY TABLE

Table S1. Mean scores at baseline in the target and nontarget populations who received melflufen and dexamethasone.

Baseline score, mean (range)	Target Population ^a (n=44)	Nontarget Population ^a (n=33)
EORTC QLQ-C30 multi-item scales ^b		
Global health status/QoL	65.3 (25–100)	61.9 (16.7–100)
Physical functioning	73.2 (33.3–100)	71.5 (20–100)
Emotional functioning	83.3 (33.3–100)	78.0 (0–100)
EORTC QLQ-C30 symptom scales ^c		
Fatigue	30.7 (0–77.8)	40.7 (0–100)
Pain	26.2 (0–100)	35.4 (0–100)
EORTC MY20 score ^d		
Disease symptoms	23.0 (0–66.7)	27.1 (0–83.3)
Side effects of treatment	15.9 (0–73.3)	16.3 (0–66.7)
EQ-5D-3L VAS score ^e	64.8 (30–100)	62.8 (20–100)

ASCT: autologous stem cell transplant, EORTC: European Organisation for Research and Treatment of Cancer, EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version, melflufen: melphalan flufenamide, MY20: Multiple Myeloma Module, QLQ-C30: Core Quality of Life Questionnaire, QoL: quality of life, TTP: time to progression, VAS: visual analog score.

^aThe target population included patients who had not received a prior ASCT or had TTP > 36 months after a prior ASCT; the nontarget population included patients with TTP < 36 months after a prior ASCT.

^bEORTC QLQ-C30 global health status/QoL, emotional functioning, and physical functioning scores range from 0 to 100; a higher score indicates better function.¹

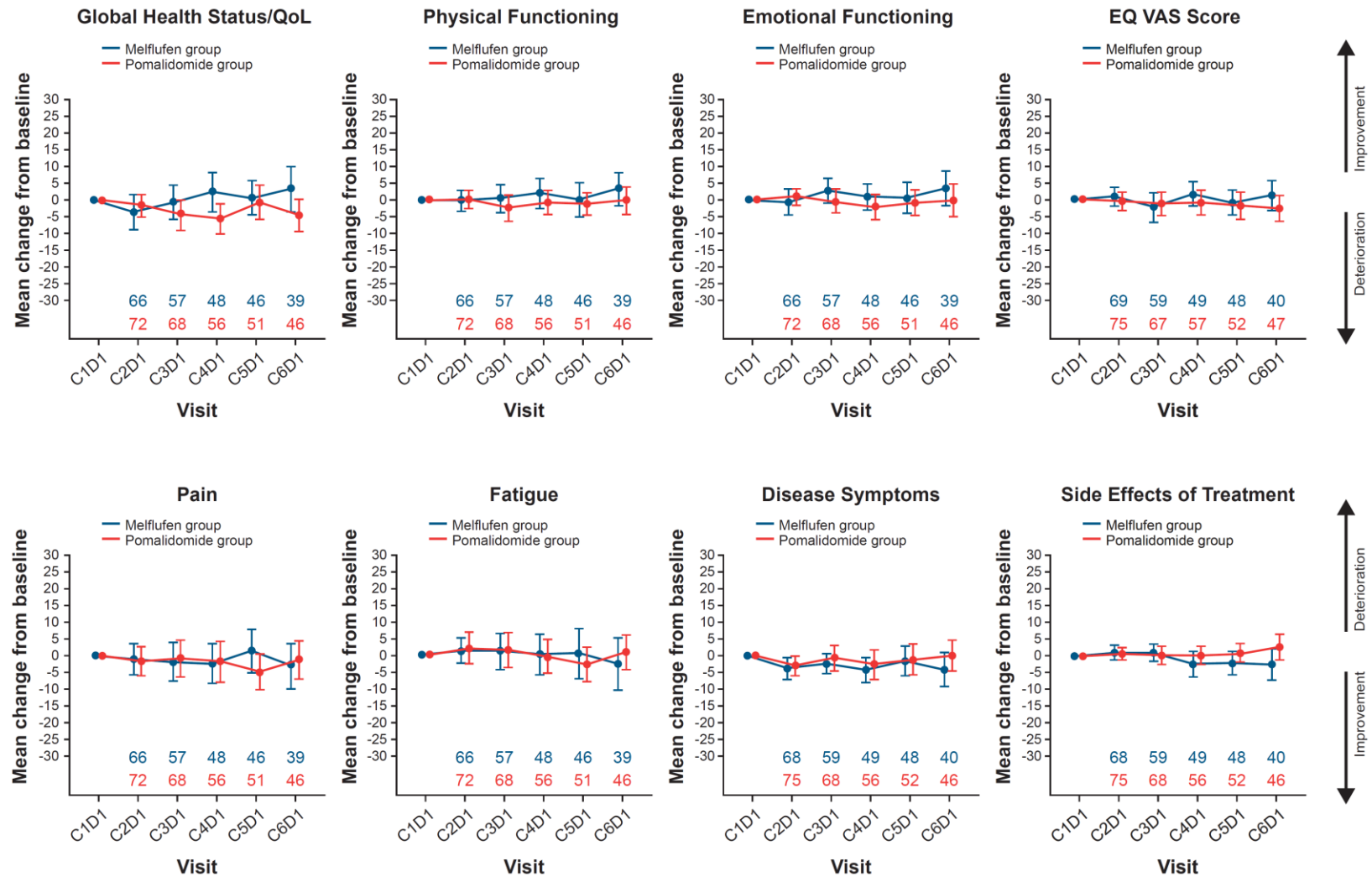
^cEORTC QLQ-C30 fatigue and pain symptoms range from 0 to 100; a higher score indicates a higher severity of symptoms.²

^dEORTC MY20 disease symptoms and side effects of treatment scores range from 0 to 100; a higher score indicates a higher severity of symptoms.²

^eEQ-5D-3L VAS scores range from 0 to 100; a higher score indicates a better health state (0 equals death; 100 equals perfect health).³

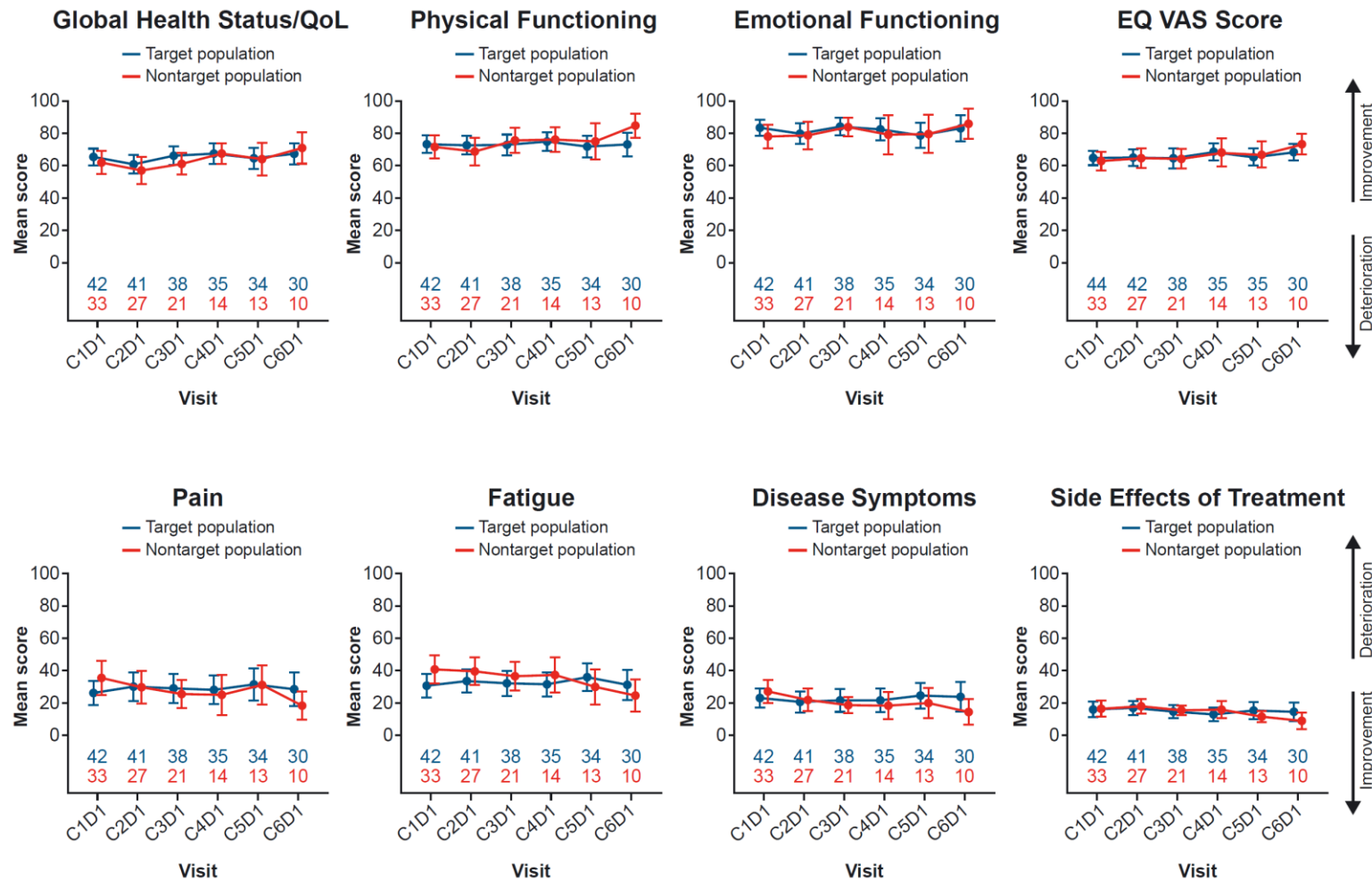
SUPPLEMENTARY FIGURES

Figure S1. Mean change from baseline through cycle 6 by treatment group.



C, cycle; D, day; EQ, European Quality of Life; melflufen, melphalan flufenamide; QoL, quality of life; VAS, visual analog scale.

Figure S2. Mean scores at baseline through cycle 6 in the target and nontarget populations who received melflufen plus dexamethasone.^a



C, cycle; D, day; melflufen, melphalan flufenamide; QoL, quality of life; VAS, visual analog scale. ^aThe target population included patients who had not received a prior ASCT or had TTP > 36 months after a prior ASCT; the nontarget population included patients with TTP < 36 months after a prior ASCT.

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