bjh short report

Melflufen plus dexamethasone in relapsed/refractory multiple myeloma: long-term survival follow-up from the Phase II study O-12-M1

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Summary

An updated survival analysis was conducted for the Phase II study O-12-M1 of melphalan flufenamide (melflufen) plus dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM) with two or more prior lines of therapy (including bortezomib and lenalidomide). Partial response or better was seen in 31%. After a 46-month median overall survival (OS) follow-up, melflufen plus dexamethasone had a median OS of 20·7 months (75th percentile OS, 47·5 months). The median time-to-next treatment for melflufen plus dexamethasone was 7·9 months. In summary, melflufen plus dexamethasone resulted in sustained long-term clinical benefit in patients with RRMM.

Keywords: melflufen, melphalan flufenamide, relapsed/refractory multiple myeloma, multiple myeloma.

Introduction

Multiple myeloma (MM) remains an incurable haematological malignancy.[1] Although outcomes have substantially improved with advances in novel therapy, patients ultimately relapse and have limited therapeutic options for long-term disease control.[2]

Melphalan flufenamide (melflufen) is a first-in-class peptide–drug conjugate (PDC) that targets aminopeptidases and rapidly and selectively releases alkylating agents into tumour cells.[3,4] Melflufen is rapidly and passively taken up by cells due to its high lipophilicity.[3,5] Intracellular aminopeptidases hydrolyse melflufen to release the hydrophilic alkylating metabolites melphalan and desethyl-melflufen,[3] triggering robust and irreversible DNA damage and apoptosis.[5,6]

In the Phase I/II study O-12-M1, with a median follow-up of 28 months (data cut-off date, 9 November 2017), melflufen plus dexamethasone treatment demonstrated durable responses in the 45 patients with relapsed/refractory MM (RRMM) and a median of four prior lines of therapy.[7] The

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overall response rate was 31%, and the median duration of response was 8·4 months [95% confidence interval (CI) 4·6–9·6 months]. The median progression-free survival and overall survival (OS) were 5·7 and 20·7 months respectively. The safety profile of melflufen plus dexamethasone consisted primarily of generally manageable haematological adverse events (AEs). The most common Grade 3/4 treatment-emergent AEs included thrombocytopenia (62%) and neutropenia (58%). Grade 3/4 non-haematological AEs were infrequent; no severe bleeding events were observed.

Approximately 49% of patients in the O-12-M1 study were still alive and censored at their end-of-study visit or alive at the time of data cut-off before completing 24 months of follow-up. A protocol amendment was introduced for an updated OS evaluation of these patients. Presented here are an updated survival analysis and a *post hoc* analysis of OS subgroups and time-to-next treatment (TTNT).

Patients and methods

O-12-M1 was an open-label, multicentre Phase I/II study of patients with RRMM (ClinicalTrials.gov Identifier: NCT01897714) as previously described.[7] Patients received two or more prior lines of therapy (including lenalidomide and bortezomib) and were refractory to their last line of therapy (had progressed on or within 60 days of completion of last therapy). Patients received 40 mg melflufen intravenously on day 1 of each 21- or 28-day cycle plus 40 mg (20 mg for patients aged ≥75 years) dexamethasone orally every week for up to eight cycles, with additional cycles at the discretion of the investigator and sponsor. Treatment was continued until progression, unacceptable toxicity, or the investigator and patient determined it was appropriate to discontinue. Patients were followed for survival every 3 months for up to 24 months. By protocol amendment, survival was re-evaluated in patients alive and censored at their end-of-study visit or alive at the time of the data cut-off date before completing 24 months of follow-up.

The primary objectives of this O-12-M1 study analysis were to provide updated survival outcomes and a *post hoc* assessment of TTNT. OS was defined as the time from first dose of treatment to death from any cause. A *post hoc* OS subgroup analysis was conducted and included analyses by International Staging System (ISS) stage at baseline, number of prior lines of therapy and best response to therapy. The TTNT was defined as time from start of treatment to first subsequent therapy or death. An analysis of the TTNT was performed to allow comparison with data from historical real-world studies.

Results

In the Phase II O-12-M1 study, 45 patients were treated with 40 mg melflufen plus dexamethasone. Detailed baseline characteristics were reported previously.[7] The median [interquartile range (IQR)] age was 66 [47–78] years; 27 patients (60%) had baseline ISS Stage II/III RRMM, and 20 patients (44%) had high-risk cytogenetics [del(17p), t(14;16), t(4;14), t(14;20), or gain(1q) by fluorescence *in situ* hybridisation and del(13q) by karyotyping]. Patients had received a median (IQR) of four (two–14) prior lines of therapy; 30 patients (67%) were double refractory (proteasome inhibitor and immunomodulator).[7] Of the 22 patients (49%) censored at the data cut-off date (9 November 2017), 19 patients were re-evaluated in the present follow-up analysis (three patients were lost to follow-up), none of which remained on treatment.

With a median survival follow-up of 46 months (data cut-off date 29 October 2019), the median OS was unchanged at 20·7 months (95% CI 11·8–41·3 months) in the overall population [30 of 45 patients with events (67%) and 15 censored patients (33%); Fig. 1]. The 75th percentile OS was 47·5 months [95% CI 31·1 months to not evaluable (NE)]. The median progression-free survival was also unchanged at 5·7 months (95% CI 3·7–9·2 months).

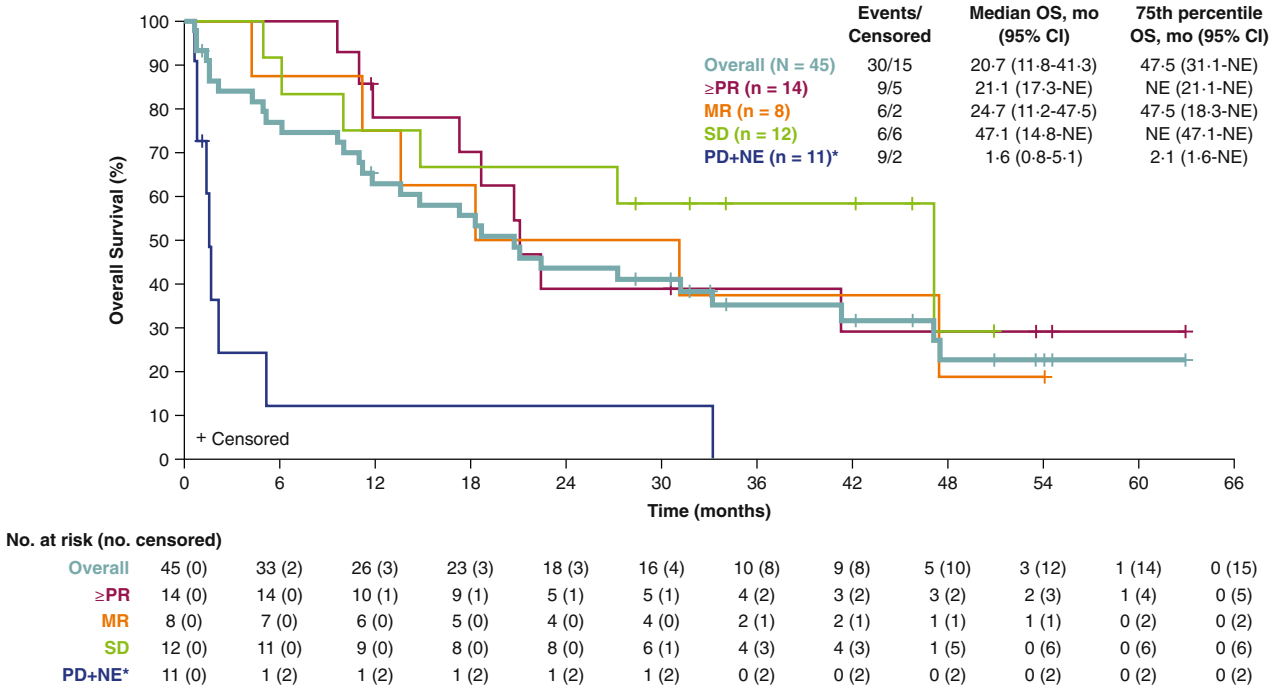
In a *post hoc* OS subgroup analysis (Table 1), the median OS was NE for the patients with ISS Stage I RRMM at baseline (n = 15) and 18·7 months (95% CI 6·1–41·3 months) and 5·0 months (95% CI 1·7–10·0 months) respectively, for patients with ISS Stage II (n = 18) and III (n = 9) RRMM. Patients aged <65 years had a median OS of 34·3 months (95% CI 10·0 months to NE), and those with two to three prior lines of therapy had a median OS of 47·1 months (95% CI 21·1 months to NE). Patients with high-risk cytogenetics had a median OS similar to that of patients without high-risk features, at 22·4 months (95% CI 10·0 months to NE) *versus* 20·7 months (95% CI 11·0–47·1 months). Overall best response was unchanged with further follow-up. Patients achieving a best response of ≥partial response (n = 14) had a median OS of 21·1 months (95% CI 17·3 months to NE; Fig. 1); those achieving stable disease (SD) as best response (n = 12) had a median OS of 47·1 months (95% CI 14·9 months to NE). Best response did not appear to adversely affect outcome of OS (Fig. 1).

The median TTNT was 7·9 months (95% CI 5·1–10·6 months) and the median TTNT when censoring for deaths was 10·5 months (95% CI 7·9–12·2 months). These results were compared with data from relevant real-world studies of agents in the RRMM setting (Table S1).

No additional serious AEs or secondary primary malignancies were reported during the additional follow-up period.

Discussion

In this 46-month follow-up survival analysis of the Phase II study O-12-M1, the median OS was 20·7 months in patients with RRMM who relapsed on conventional therapy, including bortezomib and lenalidomide. A retrospective analysis of 286 patients refractory to bortezomib and an



No. at risk (no. censored)

Overall	45 (0)	33 (2)	26 (3)	23 (3)	18 (3)	16 (4)	10 (8)	9 (8)	5 (10)	3 (12)	1 (14)	0 (15)
≥PR	14 (0)	14 (0)	10 (1)	9 (1)	5 (1)	5 (1)	4 (2)	3 (2)	3 (2)	2 (3)	1 (4)	0 (5)
MR	8 (0)	7 (0)	6 (0)	5 (0)	4 (0)	4 (0)	2 (1)	2 (1)	1 (1)	1 (1)	0 (2)	0 (2)
SD	12 (0)	11 (0)	9 (0)	8 (0)	8 (0)	6 (1)	4 (3)	4 (3)	1 (5)	0 (6)	0 (6)	0 (6)
PD+NE*	11 (0)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)

Fig 1. Overall survival (OS) with melflufen plus dexamethasone in the overall population ($N = 45$) and by best response ≥PR, MR, SD, and PD + NE*. Ticks represent patients censored for OS. MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. *Includes four patients who were not evaluable for response due to having a missing post-baseline assessment: one patient stopped treatment after one cycle of therapy due to adverse events and three patients died before their first response assessment because of aggressive disease as discussed in Richardson *et al.* 2020.[7] [Colour figure can be viewed at wileyonlinelibrary.com]

immunomodulatory drug showed a median OS of 9 months.[8] In an updated survival analysis of the Phase III MM-003 study, the median OS was 13·1 months for pomalidomide plus low-dose dexamethasone in a similar patient population.[9] The results also compare favourably with the median OS of 20·1 months reported for daratumumab from the GEN501 and SIRUS pooled analysis.[10] The 46-month follow-up for melflufen plus dexamethasone further showed a 75th percentile OS of 47·5 months. These results demonstrate a sustained long-term survival benefit for melflufen plus dexamethasone in patients with late-stage heavily pretreated RRMM, with approximately 20–25% of patients alive at 4 years.

In a *post hoc* OS subgroup analysis, patients aged <65 years and those with ISS Stage I and with two to three prior lines of therapy appeared to benefit most from treatment. High-risk cytogenetics did not appear to adversely affect outcome of OS. Furthermore, the positive trend in OS was consistent among all response categories including SD. Patients achieving SD as a best response had an OS consistent with that of responding patients (≥minimal response) and, thus, seemed to benefit from melflufen treatment. Similarly, an OS benefit in patients who achieved SD or minimal response has been reported with daratumumab.[10] These results with melflufen warrant further evaluation and may provide evidence that achieving SD has clinical relevance in the RRMM setting.

With each relapse, a patient's prognosis worsens, and time to the next relapse decreases.[11] The median TTNT for melflufen plus dexamethasone was similar to that of other agents in the relapsed setting, including single agents (pomalidomide, carfilzomib, daratumumab) and triplet combinations [bortezomib, lenalidomide and dexamethasone (VRd) and carfilzomib, lenalidomide and dexamethasone (KRd)].[12–14] Data suggest that melflufen plus dexamethasone provides encouraging and similar long-term disease control as other approved and frequently used combination regimens.

The interpretation of the present survival analysis is limited by the small size of the study and subgroups. The TTNT does not always accurately reflect treatment effectiveness; the reasons for starting a new therapy are not always related to progression and may vary between study sites. In patients with advanced disease, there is often an uncoupling of the correlation between the myeloma symptoms and paraprotein production. Thus, some patients may have clinical progression without meeting the International Myeloma Working Group criteria for progressive disease and will require immediate initiation of a new therapy. In addition, real-world data are not always captured consistently, which can lead to misleading comparisons. However, the manageable safety profile, consistent efficacy and practical schedule of administration for melflufen plus dexamethasone support the likelihood of successful translation to real-world practice.[15]

Table 1. Overall survival subgroup analyses.

Subgroup	Overall survival	
	Events/ censored, *n*	Median (95% CI), months
Overall (*N* = 45)	30/15	20·7 (11·8–41·3)
Age, years		
<65 (*n* = 20)	12/8	34·3 (10·0–NE)
65–75 (*n* = 23)	16/7	17·3 (11·0–33·2)
>75 (*n* = 2)	2/0	20·4 (9·6–31·1)
ISS Stage at baseline*		
I (*n* = 15)	6/9	NE (33·2–NE)
II (*n* = 18)	13/5	18·7 (6·1–41·3)
III (*n* = 9)	9/0	5·0 (1·7–10·0)
Risk status		
High-risk (*n* = 20)†	12/8	22·4 (10·0-NE)
Not high-risk (*n* = 25)‡	18/7	20·7 (11·0–47·1)
No. of prior therapies		
2–3 (*n* = 17)	10/7	47·1 (21·1–NE)
4–5 (*n* = 17)	16/1	11·0 (4·3–18·7)
>5 (*n* = 11)	4/7	NE (11·8–NE)
Prior transplantation		
Autologous (*n* = 26)¶	17/9	18·3 (11·2–33·2)
Allogeneic (*n* = 4)¶	3/1	33·9 (18·3–47·1)
No prior transplantation (*n* = 17)	12/5	21·1 (5·0–47·5)

ISS, International Staging System; NE, not evaluable.

*Three patients had unknown ISS Stage at baseline.

†Patients with t(4;14), t(14;16), del(17p), gain(1q), or t(14;20) by fluorescence *in situ* hybridisation and del(13q) by karyotyping.

‡Includes 17 patients with standard risk [any other cytogenetic abnormality, including t(11;14), del(13), or t(6;14), and patients with fluorescence *in situ* hybridisation showing normal results (normal or no abnormalities detected)] and eight patients for whom baseline disease risk status could not be categorised as high or standard because of missing, indeterminate, or other baseline fluorescence *in situ* hybridisation, karyotype, or ploidy specification.

¶Among 28 patients who underwent a prior transplantation, two received both an allogeneic stem cell transplantation and an autologous stem cell transplantation.

Because there is a continued need for further treatment options for RRMM, additional trials are ongoing to evaluate the efficacy and safety of melflufen. HORIZON (OP-106; NCT02963493) is an ongoing pivotal, single-arm, multicentre, Phase II study designed to evaluate the efficacy and safety of melflufen plus dexamethasone in heavily pretreated and poor-risk patients with RRMM refractory to pomalidomide or anti-CD38 monoclonal antibody or both. Melflufen plus dexamethasone *versus* pomalidomide plus dexamethasone is currently being evaluated in the randomised, head-to-head, superiority, open-label, global, Phase III OCEAN (OP-103; NCT03151811) study of patients with MM refractory to last line of therapy and lenalidomide within 18 months of randomisation, who received two to four prior therapies.

In conclusion, the results of the present O-12-M1 long-term survival analysis in the context of a mature Phase I/II study suggest that melflufen plus dexamethasone treatment can lead to long-term benefit in patients with advanced RRMM in whom other available therapies have failed.

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Author contributions

Paul G. Richardson and Johan Harmenberg designed the study with contributions from Peter M. Voorhees, Torben Plesner, Catriona Byrne and Pieter Sonneveld. Paul G. Richardson, Sara Bringhen, Peter M. Voorhees, Torben Plesner, Ulf-Henrik Mellqvist, Brandi Reeves and Pieter Sonneveld enrolled patients. Paul G. Richardson, Sara Bringhen, Peter M. Voorhees, Torben Plesner, Catriona Byrne, Eva Nordström, Johan Harmenberg and Pieter Sonneveld analysed and/or interpreted the study data. Paul G. Richardson, Johan Harmenberg and Pieter Sonneveld reviewed the literature. All authors critically reviewed the manuscript, approved the final version for submission, and are accountable for all aspects of the work.

Conflict of interest

Sara Bringhen has received honoraria from Bristol-Myers Squibb, Celgene, Amgen, and Janssen and has been an advisor/consultant for Celgene, Amgen, Janssen, Takeda, and Karyopharm. Peter M. Voorhees has been an advisor/consultant for Adaptive Biotechnologies, Bristol-Myers Squibb, Oncopeptides, Celgene, Novartis, Janssen, Takeda, and TeneoBio and has received research funding from Celgene, Janssen, Takeda, Amgen, and GlaxoSmithKline. Torben Plesner has been a consultant for Janssen, Celgene, AbbVie, Takeda, and Oncopeptides and has received research support from Janssen, Celgene, AbbVie, and Takeda. Ulf-Henrik Mellqvist has received research funding from Oncopeptides, has been an advisor for Amgen, and has received honoraria from Celgene, Janssen, Amgen, Takeda, Sanofi, Sandoz, and Oncopeptides. Brandi Reeves has received personal fees from Celgene, Takeda Oncology, Incyte, and Seattle Genetics. Pieter Sonneveld has received research support from Amgen, Celgene, Janssen, Takeda, and SkylineDx and is a consultant for Amgen, Celgene, Janssen, Oncopeptides, Takeda, and SkylineDx. Catriona Byrne is a consultant for and owns stock options in Oncopeptides and has been a consultant for

Takeda, the Multiple Myeloma Research Consortium, and Dana-Farber Cancer Institute. Eva Nordström and Jakob Obermüller are employees of and own stock and stock options in Oncopeptides. Johan Harmenberg is a consultant of and owns stock and stock options in Oncopeptides. Paul G. Richardson has been an advisor for Oncopeptides, Celgene, Takeda, Amgen, Janssen, and Karyopharm and has received grants from Bristol-Myers Squibb, Oncopeptides, Celgene, and Takeda.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. TTNT with melflufen plus dexamethasone in O-12-M1 and other agents in RRMM.

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