Updated Progression-Free Survival and Overall Survival With Melflufen and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma: Results From the Phase 2 Study O-12-M1

Poster 1839

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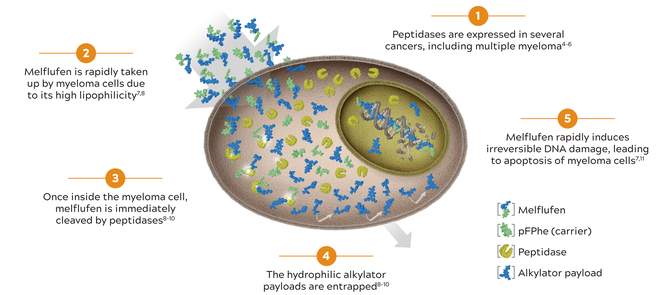
BACKGROUND

- Patients with multiple myeloma (MM) that relapses after conventional treatment have limited therapeutic options for long-term disease control[1]
- Melflufen is a novel peptide-drug conjugate that rapidly delivers a cytotoxic payload into tumor cells (**Figure 1**)
- In this phase 1/2 study O-12-M1, melflufen plus dexamethasone (dex) previously demonstrated durable responses and a manageable safety profile in patients with relapsed/refractory MM (RRMM) and a median of 4 prior lines of therapy (median follow-up, 28 months)[2]:
  - Overall response rate, 31%
  - Median progression-free survival (PFS), 5.7 months
  - Median overall survival (OS), 20.7 months
  - The most common grade 3 and 4 treatment-emergent adverse events were hematologic. Grade 3 and 4 nonhematologic toxicity was infrequent, with an infection rate of 9%, and no severe bleeding events observed
- In a post hoc analysis of the O-12-M1 phase 2 study, melflufen plus dex treatment resulted in disease stabilization (≥ stable disease [SD]) in 76% of patients and a median time to next treatment (TTNT) of 7.9 months, which compares favorably with findings from other relevant trials[3]
- As 40% of patients were still alive and censored at their protocol-defined end-of-study visit (24 months after progressive disease [PD]), a protocol amendment allowed for an additional survival follow-up, which was performed in October 2019 (n=17); here, updated OS and PFS results are reported, with a median OS follow-up of 46 months

Figure 1. Melflufen Mechanism of Action



pFPhe, p-Fluorophenylalanine

OBJECTIVES

- To provide an update of PFS and OS for melflufen and dex in patients with RRMM, including those still participating in long-term follow-up and those who were alive at their protocol-specified end-of-study visit, in an extended long-term follow-up amendment in the O-12-M1 phase 2 study
- To assess TTNT with melflufen and dex in patients with RRMM in an exploratory, post hoc analysis of the O-12-M1 phase 2 study

METHODS

Figure 2. Phase 2 O-12-M1 Study Design (NCT01897714)

N=45
Patients with RRMM and a median of 4 prior lines of therapy including lenalidomide and bortezomib and PD on or within 60 days of completion of last therapy

→ **Melflufen + dexamethasone[a]** →

After PD or start of subsequent therapy, patients were followed for survival every 3 months for up to 24 months

→

Protocol amendment allowed for an updated OS evaluation of patients still participating in long-term follow-up and who were alive at their protocol-specified end-of-study visit

Primary endpoint: ORR
Secondary endpoints: PFS, OS, safety

[a]Phase 1 part of the trial established the maximum tolerated dose of 40 mg/d in combination with dexamethasone 40 mg/d. During the trial, the 21-day dose interval was amended to a 28-day dose interval as the recommended schedule for development to allow for further hematologic recovery.
ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

- Melflufen 40 mg was administered intravenously on day 1 of each 21- or 28-day cycle plus dex 40 mg weekly for up to 8 cycles or longer at the discretion of the investigator and sponsor
- Response was assessed by the investigator at each cycle by International Myeloma Working Group criteria
- After PD or start of subsequent therapy, patients were followed for survival every 3 months for up to 24 months
- TTNT was reviewed retrospectively and was defined in line with guidelines as time from start of melflufen plus dex to first subsequent therapy or death, whichever occurred first
- Survival was re-evaluated in all patients still ongoing in long-term follow-up and in those who were alive at their protocol-specified end-of-study visit 24 months after PD

RESULTS

PATIENTS

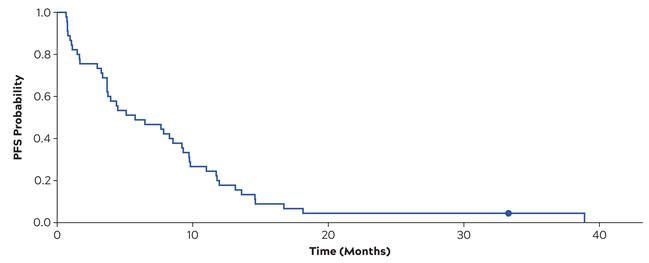
- As of 10 October 2019 (median OS follow-up, 46 months), 45 patients were treated in the O-12-M1 study (**Table 1**)
  - 17 Patients were followed and had additional data after the previous 9 November 2017 data cutoff

Table 1. Baseline Patient Characteristics for the ITT Population

Characteristic	ITT (N=45)
Age, median (range), y	66 (47-78)
Sex (men / women), %	67 / 33
Time since initial diagnosis, median (range), y	5 (1-21)
ISS stage at study entry (I / II / III), %	33 / 40 / 20
No. of prior lines, median (range)	4 (2-14)
High-risk cytogenetics,[a] n (%)	20 (44)
Double refractory,[b] n (%)	30 (67)
Alkylator refractory,[c] n (%)	24 (53)
Last-line refractory, n (%)	39 (87)
Exposed to IMiDs / PIs / alkylators[c] / melphalan, %	100 / 98 / 93 / 80

[a]Defined as del(17p), t(4;14), t(14;16), t(14;20), or gain(1q).
[b]At least 1 PI and IMiD.
[c]Melphalan, cyclophosphamide, or bendamustine.
ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; PI, proteasome inhibitor; ULN, upper limit of normal.

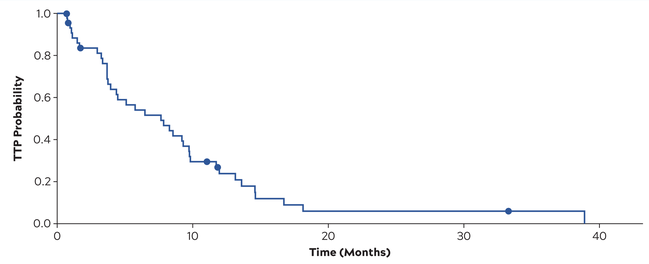
Figure 3. PFS in the ITT Population (N=45)



An event was defined as PD or death, whichever occurred first for the PFS analysis.
ITT, intention-to-treat; PD, progressive disease; PFS, progression-free survival.

- As of 10 October 2019, median PFS was 5.8 months (95% CI, 3.7-9.7), with 44 events in 45 patients (**Figure 3**)

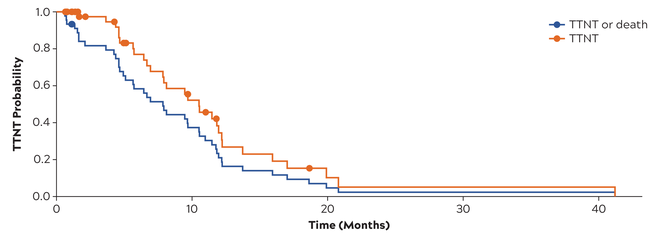
Figure 4. TTP in the ITT Population (N=45)



An event was defined as PD for the TTP analysis. Patients who did not experience PD were censored at last response assessment.
ITT, intention-to-treat; PD, progressive disease; TTP, time to progression.

- Median time to progression was 7.7 months (95% CI, 4.4-9.8), with 38 events in 45 patients (**Figure 4**)

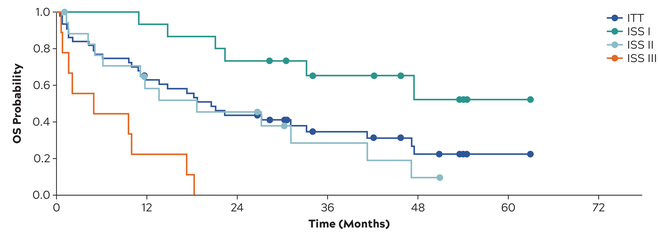
Figure 5. TTNT in the ITT Population (N=45)



An event was defined as subsequent treatment or death for the TTNT analysis (in the auxiliary analysis, death was instead censored).
ITT, intention-to-treat; TTNT, time to next treatment.

- Median TTNT was 7.9 months (95% CI, 5.7-11.0), with 43 events in 45 patients (**Figure 5**)
- Median TTNT when censoring for deaths was 10.5 months (95% CI, 7.9-12.2)

Figure 6. OS by ISS Stage (N=45)

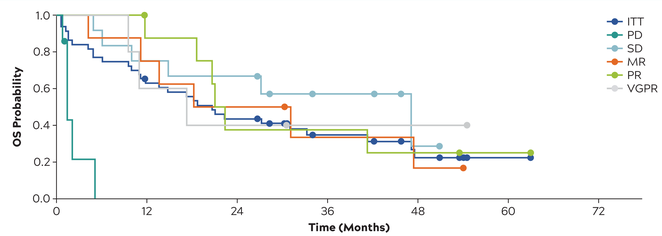


	ITT (N=45)	ISS I (n=15)	ISS II (n=18)	ISS III (n=9)
Events, n (%)	30 (67)	6 (40)	13 (72)	9 (100)
Median, mo	20.7	NR	18.7	5.0
95% CI	13.6-47.2	33.3-NR	11.2-NR	1.7-NR

An event was defined as death for the OS analysis. Fifteen patients were alive and censored at last observation; of these, 3 patients were lost to follow-up, and 3 patients were for administrative reasons not allowed to be followed longer than 24 months after PD.
ISS, International Staging System; ITT, intention-to-treat; NR, not reached; OS, overall survival; PD, progressive disease.

- Median OS was 20.7 months (95% CI, 13.6-47.1) for the intention-to-treat population, with 30 events in 45 patients (**Figure 6**)
- Median OS was not reached for the 15 patients with ISS I at baseline

Figure 7. OS by Best Response (N=45)



	ITT (N=45)	PD (n=7)	SD (n=12)	MR (n=8)	PR (n=9)	VGPR (n=5)
Events, n (%)	30 (67)	5 (71)	6 (50)	6 (75)	6 (67)	3 (60)
Median, mo	20.7	1.6	47.2	24.7	21.8	17.3
95% CI	13.6-47.2	1.4-NR	14.8-NR	13.6-NR	20.7-NR	11.0-NR

An event was defined as death for the OS analysis.
ITT, intention-to-treat; MR, minimal response; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

- Median OS was relatively short for patients with PD as best response but prolonged for all other subgroups (**Figure 7**)
- A post hoc OS subgroup analysis showed that 12 patients with SD as their best response had a median OS of 47.2 months (95% CI, 14.8-not reached)

CONCLUSIONS

- Melflufen plus dex demonstrated sustained long-term benefit in patients with late-stage, heavily pretreated RRMM that relapsed on conventional therapy including bortezomib and lenalidomide
  - Median PFS, 5.8 months
  - Median OS, 20.7 months
  - Median OS, 47.2 months for patients achieving SD as best response, suggesting sustained clinical benefit despite a limited depth of response
- Melflufen plus dex treatment showed a median TTNT of 7.9 months in the updated post hoc analysis
  - Data continue to suggest a similar median TTNT for melflufen plus dex vs other agents in the RRMM setting, including bortezomib-lenalidomide-dex/carfilzomib-lenalidomide-dex (12.9/8.7 months; 1-3 prior lines) and daratumumab (5.9 months; 4 prior lines)[12,13]
- No new safety signals were reported
- Melflufen plus dex vs pomalidomide plus dex is being evaluated in the randomized, head-to-head, superiority, open-label, global, phase 3 OCEAN study of patients with MM refractory to last line of therapy and lenalidomide within 18 months of randomization who received 2-4 prior therapies (NCT03151811)

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DISCLOSURES

SB: honoraria from Celgene, Janssen-Cilag, Amgen, and Bristol-Myers Squibb and consulting/advisory role with Celgene, Janssen-Cilag, Amgen, Takeda, and Karyopharm. **PMV:** consulting/advisory role for Adaptive Biotechnologies, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Oncopeptides, Takeda, and TeneoBio. **TP:** consulting/advisory role for Janssen, Celgene, Takeda, AbbVie, and Genmab and research funding from Janssen. **U-HM:** honoraria from Janssen, Oncopeptides, Celgene, Takeda, and Amgen and consulting/advisory role for Amgen. **BR:** employment with Select Specialty Hospital; consulting/advisory role with Seattle Genetics; speakers' bureau for Celgene; and research funding from Janssen, Amgen, GlaxoSmithKline, Oncopeptides, and Celgene. **PS:** honoraria and consulting/advisory role for Amgen, Celgene, Janssen, Seattle Genetics and research funding from Janssen and Celgene. **CB, EN, JH, JO:** employment and equity ownership with Oncopeptides. **PGR:** consulting/advisory role for Oncopeptides.

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