Clinical Activity of Melflufen in Patients With Triple-Class Refractory Multiple Myeloma and Poor-Risk Features in an Updated Analysis of HORIZON (OP-106), a Phase 2 Study in Patients With Relapsed/Refractory Multiple Myeloma

Poster 1883

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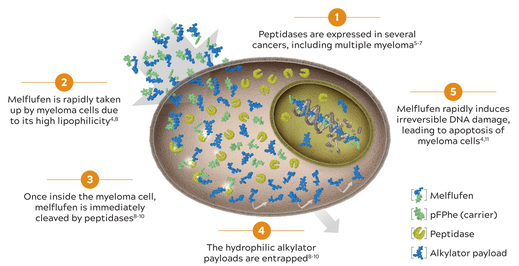
BACKGROUND

- Despite recent advances that have improved survival, multiple myeloma remains incurable[1]
- There is a need for new treatment strategies for patients who are triple-class refractory (IMiD + proteasome inhibitor [PI] + anti-CD38 monoclonal antibody [mAb]),[2] and in particular those with high-risk features including extramedullary disease (EMD), who have a very poor prognosis[3]
- Introducing a treatment-class switch with a novel compound may represent an important therapeutic strategy for these patients
- Melflufen is a novel peptide-drug conjugate that rapidly delivers a highly cytotoxic payload into tumor cells (**Figure 1**)[4-11]
  - Melflufen and dexamethasone (dex) was initially studied in a phase 1/2 study (O-12-M1) in 75 patients with relapsed/refractory multiple myeloma (RRMM). The study showed efficacy in combination with an acceptable safety profile.[12] The overall response rate (ORR) was 31%, median duration of response (DOR) was 8.4 months, median progression-free survival (PFS) was 5.7 months, and median overall survival (OS) was 20.7 months[12,13]

Figure 1. Melflufen Mechanism of Action



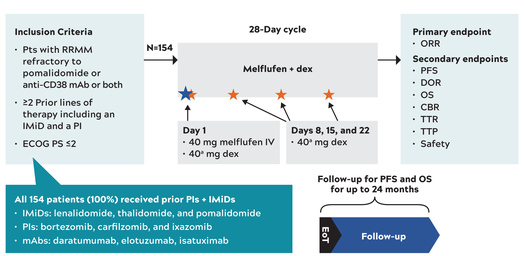
pFPhe, p-Fluorophenylalanine.

METHODS

STUDY DESIGN

- The ongoing phase 2 trial HORIZON is investigating the safety and efficacy of melflufen plus dex in patients with advanced RRMM. All patients must have been refractory (per International Myeloma Working Group [IMWG] criteria) to previous pomalidomide or anti-CD38 mAb treatment or both and have been previously treated with lenalidomide- and PI-based treatment (**Figure 2**)
- The HORIZON trial population includes patients who are triple-class refractory, have relapsing EMD, and/or have high-risk cytogenetic features

Figure 2. HORIZON: Phase 2, Single-Arm, Open-Label, Multicenter Study of Melflufen and Dex in RRMM (NCT02963493)



ᵃPts aged >75 years received dex 20 mg.
CBR, clinical benefit rate; dex, dexamethasone; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IV, intravenous; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pts, patients; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

STUDY POPULATIONS

- Efficacy population (n=125): patients dosed on or before 15 May 2019 with additional follow-up of 20 weeks until 01 October 2019 data cutoff
- Safety population (N=154): all patients dosed on or before 01 October 2019 data cutoff

RESULTS

Table 1. Baseline Patient Characteristics

Baseline Characteristics[a]	N=154
Age, median (range), y	64.5 (35-86)
Gender (male / female), %	56 / 44
Time since diagnosis, median (range), y	6.5 (0.7-24.6)
No. of prior lines of therapy, median (range)	5 (2-12)
ISS stage I / II / III / unknown, %	37 / 27 / 32 / 4
ECOG PS 0 / 1 / 2, %	25 / 60 / 15
High-risk cytogenetics,[b] %	38
≥2 High-risk abnormalities, %	13
Del(17p), %	12
Extramedullary disease, %	32

[a]Baseline is defined as the most recent assessment before administration of the first dose of study drug.
[b]High-risk cytogenetics at study entry was based on fluorescence in situ hybridization defined as t(4;14), del(17/17p), t(14;16), t(14;20), gain(1q) per Sonneveld P, et al.[14] 77 patients (50%) had unknown cytogenetics.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

- As of 01 October 2019, 154 patients had been treated with melflufen and dex
- Patients were heavily pretreated and had poor-risk features including 32% with International Staging System stage III disease, 38% with high-risk cytogenetics, and 32% with EMD (**Table 1**)

Table 2. Prior Treatment and Refractory Status

Prior Therapy Status, %	N=154
Double-class (IMiD + PI) exposed / refractory	100 / 88
Anti-CD38 mAb exposed / refractory	79 / 79
Triple-class (IMiD + PI + anti-CD38 mAb) exposed / refractory	79 / 71
Alkylator exposed / refractory	83 / 57
≥1 Prior ASCT	69
≥2 Prior ASCTs	21
Refractory in last line of therapy	97

ASCT, autologous stem cell transplantation; mAb, monoclonal antibody; PI, proteasome inhibitor.

- In total, 71% of patients were triple-class refractory and 97% were refractory to treatment in the last line (**Table 2**)

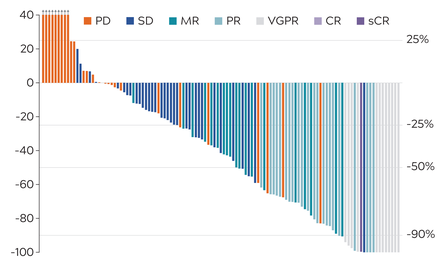
Table 3. Patient Disposition

Disposition, n (%)	N=154
On treatment at data cutoff	46 (30)
Discontinued treatment at data cutoff[a]	108 (70)
Disease progression	73 (47)
Adverse event(s)[a]	21 (14)
Lack of response	5 (3)
Patient request	5 (3)
Physician decision	4 (3)

[a]Thrombocytopenia was the event leading to discontinuation of therapy in 14 of the 21 patients who discontinued due to an AE.

- Overall, 30% of the patients were on ongoing treatment at the data cutoff (**Table 3**) with a median treatment duration of 14.3 weeks (range, 4.1-91.1)

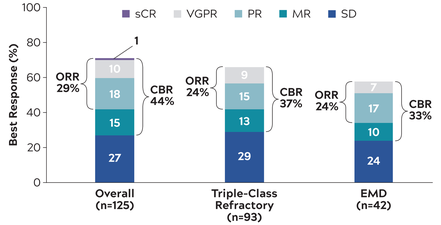
Figure 3. Best M-Protein Response (n=125 with ≥20 weeks of follow-up)[a]



[a]In total, 10 patients had missing M-protein data.
M-protein, monoclonal protein; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

- Overall, 83% of the patients had a reduction of M-protein despite all patients having progressing disease at study entry (**Figure 3**)

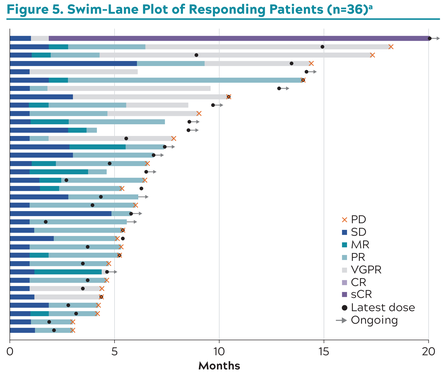
Figure 4. Best Confirmed Response by IMWG Criteria[a] Overall and in Triple-Class Refractory Patients or Patients With EMD



[a]Response was investigator assessed.
CBR, clinical benefit rate; EMD, extramedullary disease; IMWG, International Myeloma Working Group; MR, minimal response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

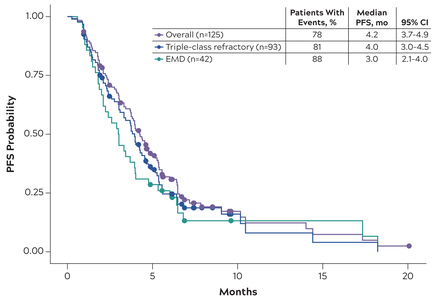
- Overall response rate (ORR) was 29% and clinical benefit rate (CBR; ≥minimal response [MR]) was 44% in the overall patient population (**Figure 4**)
- ORR for patients with high-risk cytogenetics (n=47) was 21% (data not shown)

Figure 5. Swim-Lane Plot of Responding Patients (n=36)[a]



[a]The swim-lane plot is based on response assessments reported by the investigators. Gaps between the bar and latest dose indicate no response data are currently available for that time.
CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

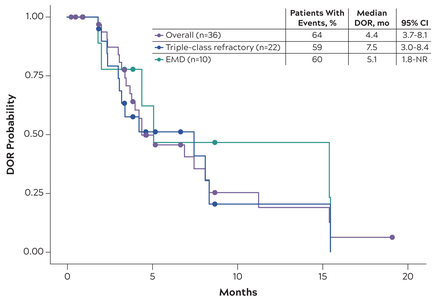
Figure 6. PFS Overall and in Triple-Class Refractory Patients or Patients With EMD



EMD, extramedullary disease; PFS, progression-free survival.

- Median PFS in the overall population was 4.2 months (**Figure 6**)

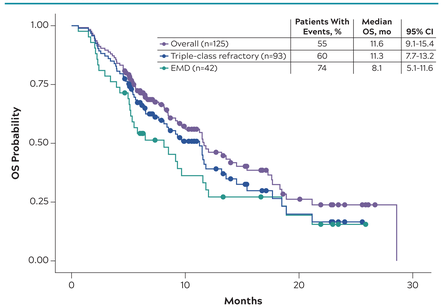
Figure 7. DOR Overall and in Triple-Class Refractory Patients or Patients With EMD



DOR, duration of response; EMD, extramedullary disease; NR, not reached.

- Median DOR in the overall population was 4.4 months (**Figure 7**)

Figure 8. OS Overall and in Triple-Class Refractory Patients or Patients With EMD



EMD, extramedullary disease; OS, overall survival.

- Median OS in the overall population was approximately 1 year (**Figure 8**)

Table 4. Incidence of Grade 3 and 4 TEAEs in the Overall Patient Population (N=154)

TEAE[a]	Grade 3, n (%)	Grade 4, n (%)
Anemia	56 (36)	1 (1)
Neutropenia	47 (31)	54 (35)
Thrombocytopenia	32 (21)	74 (48)
White blood cell count decreased	13 (8)	15 (10)
Pneumonia	11 (7)	2 (1)
Febrile neutropenia	6 (4)	2 (1)
Lymphopenia	6 (4)	2 (1)
Leukopenia	4 (3)	6 (4)

[a]Grade 3 and 4 TEAEs occurring in ≥5% of patients.
TEAE, treatment-emergent adverse event.

- Overall, 97% of patients experienced any-grade treatment-emergent adverse events (TEAEs), and 85% of patients experienced a grade 3 or 4 TEAE
- The most common grade 3 and 4 TEAEs were hematologic (**Table 4**) and nonhematologic TEAEs were infrequent with grade 3 or 4 infections in 18% of the patients
- Grade 5 TEAEs occurred in 5 patients (3%), none of which were related to melflufen
- 29% of patients had a dose reduction, and 11% had more than one dose reduction

Table 5. Serious TEAEs in the Overall Safety Population (N=154)

Serious TEAE	Serious TEAE,[a] n (%)	Serious Melflufen-Related TEAE, n (%)
Infections and infestations	29 (19)[b]	8 (5)[c]
Febrile neutropenia	8 (5)	8 (5)
Thrombocytopenia	7 (5)	7 (5)
Neutropenia	3 (2)	3 (2)
Hypercalcemia	3 (2)	0
Bone pain	2 (1)	0
Pyrexia	2 (1)	2 (1)
General physical health deterioration	2 (1)	0
Acute kidney injury	2 (1)	0
Femur fracture	2 (1)	0

[a]Serious TEAEs occurring in ≥2 patients.
[b]Serious TEAEs of infections and infestations included 7% pneumonia, 2% respiratory tract infection, and 1% of each of the following: soft-tissue infection, sepsis; influenza, *Clostridium difficile* infection, urosepsis, viral upper respiratory tract infection, viral infection, upper respiratory tract infection, rhinovirus infection, sinusitis, lower respiratory tract infection, pneumonia viral, bronchitis, cellulitis, bronchiolitis, appendicitis, *Escherichia* sepsis, abdominal infection, and diverticulitis.
[c]Serious melflufen-related TEAEs of infections and infestations included 4% pneumonia and 1% of each of the following: urosepsis, viral upper respiratory tract infection, upper respiratory tract infection, soft-tissue infection, sepsis, bronchitis, *Clostridium difficile* infection, and *Escherichia* sepsis.
TEAE, treatment-emergent adverse event.

- Even though the incidence of thrombocytopenia was high (**Table 4**), the clinical consequences were limited. There were 3 patients (2%) with melflufen-related bleeding events reported as serious TEAEs: one grade 3 lower gastrointestinal hemorrhage, one grade 3 hemorrhoidal hemorrhage, and one grade 4 epistaxis
- The majority of infections reported as serious TEAEs were non-neutropenic

CONCLUSIONS

- Melflufen and dex continue to show efficacy with a manageable safety profile in patients with heavily pretreated RRMM, including those with poor-risk features
  - ORR was 29% and CBR was 44% in the overall population
- The activity in patients with triple-class refractory disease was encouraging with an ORR of 24%, median PFS of 4.0 months, median DOR of 7.5 months, and median OS of 11.3 months
- Similarly, encouraging activity was observed in patients with EMD with an ORR of 24%, median PFS of 3.0 months, median DOR of 5.1 months, and median OS of 8.1 months
- Grade 3 and 4 TEAEs were primarily hematologic. Even though the incidences of neutropenia and thrombocytopenia were high, the clinical consequences were limited with 3 bleedings reported as serious TEAEs
- The incidence of nonhematologic TEAEs was low with grade 3/4 infections occurring in 18% of patients

Additional Ongoing Studies

- OCEAN (OP-103) is a randomized, head-to-head, superiority, open-label, global, phase 3 study of melflufen and dex vs pom and dex in patients with RRMM refractory to lenalidomide (NCT03151811)
- ANCHOR (OP-104) is an ongoing phase 1/2 study evaluating the safety and efficacy of melflufen and dex in combination with daratumumab or bortezomib in patients with RRMM (NCT03481556)[15]

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DISCLOSURES

MVM: honoraria from Amgen, Celgene, Janssen, and Takeda and consultancy/advisory role with AbbVie, Amgen, Celgene, GSK, Janssen, Oncopeptides, and Takeda. **AO:** consultancy/advisory role with Amgen, Celgene, Janssen, and Takeda. **AL:** honoraria from Amgen, Bristol-Myers Squibb, Celgene, and Janssen-Cilag. **PRO:** honoraria from Celgene, Janssen, and Bristol-Meyers Squibb and consultancy/advisory role with Celgene, Janssen, Kite Pharma, and Takeda. **JB:** honoraria from Amgen, Celgene, Janssen, Oncopeptides, and Takeda. **MC:** no conflicts of interest to report. **HH:** consultancy/advisory role with Novartis and research funding from Celgene and Janssen. **XL:** honoraria from AbbVie, Amgen, Carsgen, Celgene, Gilead, Janssen, Karyopharm, Mundipharma, Novartis, Oncopeptides, and Takeda. **AAc:** consultancy/advisory role with Amgen, Celgene, Janssen, Takeda, Sanofi, and Oncopeptides. **CMc:** honoraria from Amgen, Celgene, Gilead, Incyte, Janssen, Takeda, and Verastem. **AP:** honoraria from Amgen and Celgene and consultancy/advisory role with AbbVie, Cellectar, and Takeda. **JH, ST, HZ:** employment and equity ownership with Oncopeptides. **CB:** consultancy/advisory role with Oncopeptides and Takeda and equity ownership with Oncopeptides. **PGR:** consultancy/advisory role with Amgen, Celgene, Janssen, Karyopharm, Sanofi, and Takeda and research funding from Bristol-Myers Squibb, Celgene, Oncopeptides, and Takeda.

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