HORIZON (OP-106): Melflufen Plus Dexamethasone in Relapsed/Refractory Multiple Myeloma Refractory to Pomalidomide and/or an Anti-CD38 Monoclonal Antibody – Primary and Subgroup Analysis

Poster
EP945

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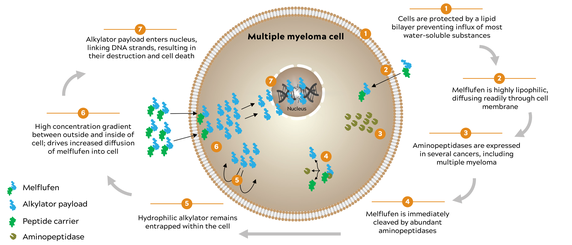
BACKGROUND

- Despite advances in therapy, outcomes remain poor for patients with relapsed/refractory multiple myeloma (RRMM)[1-2]
- Treatment choice after relapse generally depends on patient characteristics, prior therapy received, and prior response to therapy[3-4]
- Although class switching is generally prioritized, this is becoming increasingly hard to achieve because patients are being exposed to novel combinations in earlier lines of therapy, resulting in disease that is resistant to multiple drug classes[3-5]
- Melphalan flufenamide (melflufen) is a fist-in-class anticancer peptide-drug conjugate that rapidly delivers an alkylating payload into tumor cells (**Figure 1**)[6-10]
- The efficacy and safety of melflufen plus dexamethasone (dex) was initially demonstrated in O-12-M1, a phase 1/2, dose-finding study in patients with RRMM who had received a median of 4 prior lines of therapy (including lenalidomide and bortezomib), and had disease refractory to their last line of therapy[11]
  - Among 45 patients who received melflufen plus dex, overall response rate (ORR) was 31%, median duration of response (DOR) was 8.4 months, and median progression-free survival (PFS) was 5.7 months
  - The safety profile of melflufen plus dex was primarily characterized by clinically manageable hematologic adverse events (AEs) and a low frequency of nonhematologic AEs

Figure 1. Melflufen Mechanism of Action



OBJECTIVE

- To evaluate the efficacy and safety of melflufen plus dex in patients with RRMM in the pivotal, single-arm, multicenter, phase 2 HORIZON study

METHODS

- HORIZON is a pivotal, single-arm, multicenter, phase 2 study of melflufen plus dex in patients with RRMM who had received ≥ 2 prior lines of therapy and were refractory to pomalidomide (pom) and/or an anti-CD38 monoclonal antibody (mAb; **Figure 2**)
  - Treatment: melflufen 40 mg (day 1) in combination with dex 40 mg (days 1, 8, 15, and 22; 20 mg in patients aged ≥75 years) during each 28-day treatment cycle until disease progression or unacceptable toxicity
- The intention-to-treat (ITT) population was used for all analyses. Subgroups of special interest included patients with triple-class–refractory disease (refractory to or intolerant of ≥1 IMiD + ≥1 proteasome inhibitor [PI] + ≥1 anti-CD30 mAb) and patients with extramedullary disease (EMD)

Figure 2. Phase 2 HORIZON Study Design (NCT02963493)

Adult patients with
- RRMM refractory to pom or anti-CD38 mAb or both
- ≥2 Prior lines of therapy, including an IMiD and a PI
- ECOG PS ≤2

(N=157)

→ **Melflufen 40 mg + dex 40 mg**[a] *(until disease progression or unacceptable toxicity)*

	28-Day Cycle			
	D1	D8	D15	D22
Melflufen (IV)	✔			
Dex (oral)	✔	✔	✔	✔

→ EoT → **PFS and OS follow-up for ≤24 mo**

Primary endpoint
- ORR

Secondary endpoints
- DOR
- PFS
- OS
- CBR
- TTR
- TTP
- TTNT
- Safety
- HRQoL

[a]Patients 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; HRQoL, health-related quality of life; IMiD, immunomodulatory agent; IV, intravenous; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTP, time to progression; TTR, time to response.

RESULTS

- In total, 157 patients were enrolled and received ≥1 dose of study medication (data cutoff date, Jan 14, 2020); 131 patients (83%) had discontinued therapy and 26 patients (17%) remained on therapy
  - The most common primary reasons for treatment discontinuation were disease progression (56%) and AEs (17%)
- The study is fully recruited with median follow-up time of 14 months
  - The last patient enrolled into the study began treatment ≥3 months prior to the data cutoff date
- Baseline patient demographics and characteristics are shown in **Table 1**

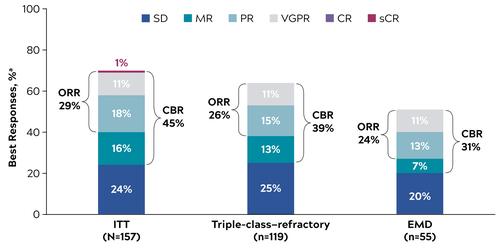
Table 1. Baseline Patient Characteristics

Characteristic	ITT (N=157)	Triple-Class–Refractory (n=119)	EMD (n=55)
Median age (range), years	65 (35-86)	65 (35-86)	64 (43-82)
Male sex, n (%)	89 (57)	70 (59)	31 (56)
High-risk cytogenetics, n (%)[a]	59 (38)	41 (34)	19 (35)
ISS stage (I/II/III) at study entry, %[b]	40/31/25	34/30/30	36/25/33
EMD at study entry, n (%)[c]	55 (35)	50 (42)	55 (100)
Median no. of prior lines of therapy (range)	5 (2-12)	5 (2-12)	5 (2-12)
Triple-class–refractory, n (%)[d]	119 (76)	119 (100)	50 (91)
Refractory to ≥1 anti-CD38 mAb	125 (80)	119 (100)	50 (91)
Refractory to prior alkylator therapy[e]	92 (59)	76 (64)	33 (60)

[a] High-risk cytogenetics at study entry was based on fluorescence in situ hybridization defined as t(4;14), del(17/17p), and t(14;16) per Sonneveld P, et al[1]; 31 patients (20%) had unknown cytogenetics. Cytogenetic assessments were not centralized.
[b] At study entry, 6 patients in the ITT population had unknown or missing ISS stage.
[c] EMD was defined as a multiple myeloma disease originating either in, but extending beyond, the cortical bone or as a separate soft tissue mass.
[d] Defined as refractory to or intolerant of 11 proteasome inhibitor, 11 immunomodulatory drug, and 11 anti-CD38 mAb.
[e] Including 21 patients (13%) refractory to prior melphalan in the ITT population.
EMD, extramedullary disease; ISS, International Staging System; ITT, intention-to-treat; mAb, monoclonal antibody.

- The ORR was 29% (95% CI, 22-37) in the ITT population, 26% (95% CI, 18-35) in the triple-class–refractory population, and 24% (95% CI, 13-37) in the EMD subgroup (**Figure 3**), and were consistent with the findings of the independent review committee (IRC)

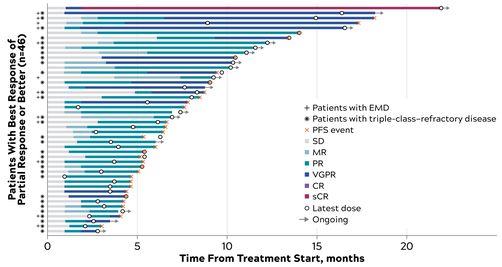
Figure 3. Best Overall Confirmed Response in the ITT and Triple-Class–Refractory Populations, and in Patients with EMD



[a] Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.[12]
CBR, clinical benefit rate; CR, complete response; EMD, extramedullary disease; ITT, intention-to-treat; MR, minor response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

- Median DOR was 5.5 months (95% CI, 3.9-7.6) in the ITT population, 4.4 months (95% CI, 3.4-7.6) in the triple-class–refractory population, and 5.5 months (95% CI, 1.8-not evaluable) in the EMD subgroup
- Median time to best response was 1.9 months in the ITT population, and responses deepened with longer treatment duration (**Figure 4**)
  - In some patients, response was extended beyond last dose of melflufen
- Among patients with a response (≥PR), median PFS was 8.5 months (95% CI, 5.4-13.4) in the ITT population, 8.5 months (95% CI, 5.3-13.4) in the triple-class–refractory population, and 17.3 months (95% CI, 5.3-not evaluable) in the EMD subgroup

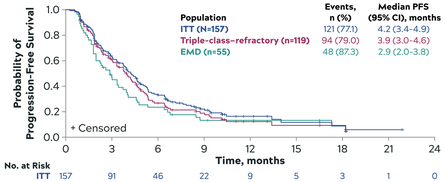
Figure 4. Patients in the ITT Population Who Achieved a Partial Response or Better



[a] Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.[12]
CR, complete response; EMD, extramedullary disease; ITT, intention-to-treat; MR, minimal response; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

- Median PFS was 4.2 months (95% CI, 3.4-4.9) in the ITT population, 3.9 months (95% CI, 3.0-4.6) in the triple-class–refractory population, and 2.9 months (95% CI, 2.0-3.8) in patients with EMD (**Figure 5**)

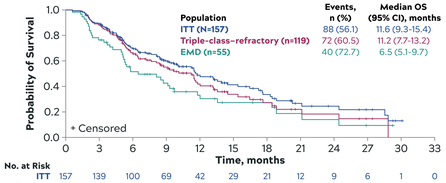
Figure 5. PFS in the ITT and Triple-Class–Refractory Populations, and in Patients with EMD



EMD, extramedullary disease; ITT, intention-to-treat; PFS, progression-free survival.

- Median OS was 11.6 months (95% CI, 9.3-15.4) in the ITT population, 11.2 months (95% CI, 7.7-13.2) in the triple-class–refractory population, and 6.5 months (95% CI, 5.1-9.7) in patients with EMD (**Figure 6**)

Figure 6. OS in the ITT and Triple-Class–Refractory Populations, and in Patients with EMD



EMD, extramedullary disease; ITT, intention-to-treat; OS, overall survival.

- Any-grade and grade 3/4 AEs occurred in 100% and 94% of patients, respectively
- The most frequent AEs overall (occurring in ≥ 10% of patients in the ITT population) and by maximum grade are shown in **Table 2**
  - The most common grade 3/4 AEs were neutropenia (79%), thrombocytopenia (76%), and anemia (43%)
  - The most common nonhematologic grade 3/4 AE was pneumonia (10%)

Table 2. AEs Occurring in ≥10% of Patients in the ITT Population

	AEs (N=157), n (%)				
	Any-Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE[a]	**157 (100)**	**0**	**7 (4)**	**40 (25)**	**100 (64)**
Hematologic[b]					
Neutropenia	129 (82)	1 (<1)	4 (3)	50 (32)	74 (47)
Thrombocytopenia	128 (82)	5 (3)	3 (2)	40 (25)	80 (51)
Anemia	111 (71)	3 (2)	41 (26)	66 (42)	1 (<1)
Nonhematologic					
Nausea	50 (32)	31 (20)	18 (11)	1 (<1)	0
Fatigue	46 (29)	17 (11)	25 (16)	4 (3)	0
Asthenia	42 (27)	13 (8)	23 (15)	5 (3)	1 (<1)
Diarrhea	42 (27)	24 (15)	18 (11)	0	0
Pyrexia	38 (24)	24 (15)	11 (7)	3 (2)	0
Cough	26 (17)	16 (10)	10 (6)	0	0
Upper respiratory tract infection	25 (16)	3 (2)	19 (12)	3 (2)	0
Constipation	23 (15)	18 (11)	4 (3)	1 (<1)	0
Decreased appetite	22 (14)	10 (6)	11 (7)	1 (<1)	0
Hypokalemia	22 (14)	14 (9)	6 (4)	2 (1)	0
Peripheral edema	22 (14)	15 (10)	5 (3)	2 (1)	0
Headache	21 (13)	13 (8)	8 (5)	0	0
Vomiting	21 (13)	12 (8)	9 (6)	0	0
Bone pain	20 (13)	9 (6)	8 (5)	3 (2)	0
Pain in extremity	20 (13)	7 (4)	10 (6)	3 (2)	0
Pneumonia	20 (13)[c]	0	3 (2)	14 (9)	2 (1)
Back pain	19 (12)	9 (6)	9 (6)	1 (<1)	0
Insomnia	18 (11)	14 (9)	3 (2)	1 (<1)	0
Dizziness	17 (11)	14 (9)	3 (2)	0	0
Dyspnea	17 (11)	9 (6)	6 (4)	2 (1)	0
Arthralgia	16 (10)	11 (7)	5 (3)	0	0
Exertional dyspnea	16 (10)	13 (8)	3 (2)	0	0
Hypocalcemia	16 (10)	9 (6)	6 (4)	1 (<1)	0

[a] Treatment-emergent adverse events by maximum severity. Adverse events are coded to preferred term using MedDRA, version 19.1.
[b] Hematologic AEs of special interest (neutropenia, thrombocytopenia, and anemia) were categorized by standardized MedDRA query.
[c] Includes one grade 5 event.
AE, adverse event; ITT, intention-to-treat.

- The clinical implications of thrombocytopenia and neutropenia were limited
  - Grade 3/4 thrombocytopenia with concurrent grade 3/4 bleeding events occurred in 4 patients (3%; 1 was grade 4)
  - Grade 3/4 neutropenia with concurrent grade 3/4 infections occurred in 18 patients (11%; 1 was grade 4)
- AEs led to melflufen dose reductions in 42 patients (27%) and dose delays in 95 patients (61%)
  - The most common AE leading to melflufen dose reductions was thrombocytopenia (14%)
- Serious AEs occurred in 49% of patients overall; most commonly pneumonia (9%) and febrile neutropenia (5%)
- Fatal AEs occurred in 10 patients (6%); none were considered related to melflufen

CONCLUSIONS

- Melflufen plus dex demonstrated clinically meaningful efficacy and a manageable safety profile in patients with heavily pretreated RRMM, including those with triple-class–refractory disease and EMD
- These results are consistent with previously reported data,[11] but in an RRMM population that is more reflective of current treatment practices in earlier lines of therapy[14]
- Responses were durable and deepened with prolonged melflufen plus dex treatment, suggesting that patients should remain on treatment for as long as possible
- The safety profile of melflufen plus dex was consistent with previous reports, and no new safety concerns were identified[11]
  - The safety profile of melflufen plus dex consisted primarily of hematologic adverse events that were clinically manageable with dose modifications and supportive care
  - Gastrointestinal events were mostly grade 1/2 and did not result in treatment discontinuation
- Melflufen, with its novel mechanism of action, in combination with dex has the potential to provide a needed therapeutic option to patients with poor-risk and heavily pretreated RRMM. Results from HORIZON will support a submission to the US Food and Drug Administration for the accelerated approval of melflufen in this hard to treat patient population
- The efficacy and safety of melflufen plus dex are being further evaluated in OCEAN (OP-103), a randomized, head-to-head, superiority, open-label, global, phase 3 study of melflufen plus dex vs pom plus dex in patients with RRMM refractory to lenalidomide (NCT03151811)

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