ANCHOR (OP-104): Updated Efficacy and Safety From a Phase 1/2 Study of Melflufen and Dexamethasone Plus Bortezomib or Daratumumab in Patients With Relapsed/Refractory Multiple Myeloma Refractory to an IMiD and/or a Proteasome Inhibitor

Poster 3124

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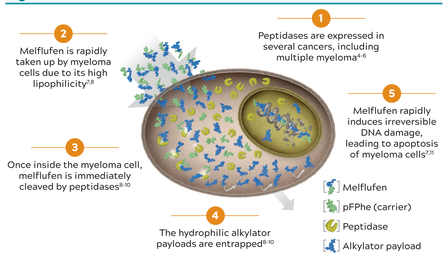
BACKGROUND

- Despite recent advances in therapy, multiple myeloma (MM) remains incurable, showing the need for novel therapies[1]
- Melflufen is a novel peptide-drug conjugate that rapidly delivers a cytotoxic payload into tumor cells (**Figure 1**)
- In the phase 1/2 study O-12-M1, melflufen plus dexamethasone has previously shown promising activity (overall response rate [ORR], 31%; median progression-free survival [PFS], 5.7 months; median overall survival, 20.7 months), with acceptable safety in patients with relapsed/refractory MM (RRMM)[2]
- In initial results from the phase 1/2 ANCHOR study, melflufen plus dexamethasone in combination with either bortezomib or daratumumab in patients with RRMM demonstrated encouraging efficacy and was well tolerated[3]

Figure 1. Melflufen Mechanism of Action



pFPhe, p-Fluorophenylalanine.

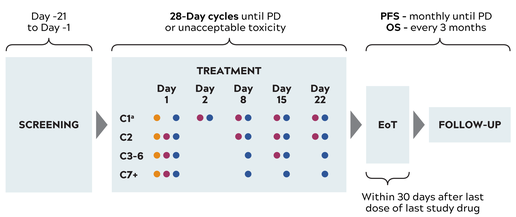
OBJECTIVES

- The primary objective of phase 1 is to determine the optimal dose of melflufen, up to a maximum of 40 mg, in combination with dexamethasone and either bortezomib or daratumumab
- Once the optimal dose has been established, an additional 20 patients per regimen will be recruited into the phase 2 part of the study, for which the primary objective is ORR (investigator assessed according to International Myeloma Working Group criteria)

METHODS

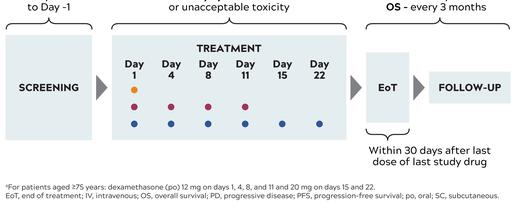
- This is a phase 1/2 study (NCT03481556) of melflufen plus dexamethasone in combination with either daratumumab (**Figure 2**) or bortezomib (**Figure 3**)
- All patients must have had 1-4 prior lines of therapy and be refractory (or intolerant) to an IMiD or a proteasome inhibitor (PI), or both
- In the combination with daratumumab, patients must be anti-CD38 monoclonal antibody-naïve
- In the combination with bortezomib, patients cannot be refractory to a PI
- Patients will be treated until progressive disease (PD) or unacceptable toxicity

Figure 2. Melflufen Plus Dexamethasone in Combination With Daratumumab



[a]In cycle 1, daratumumab is administered on day 2 due to prolonged infusion time of the first dose.
[b]Oral dexamethasone may be substituted for IV dexamethasone before daratumumab infusion only.
EoT, end of treatment; IV, intravenous; OS, overall survival; PD, progressive disease; PFS, progression-free survival; po, oral.

Figure 3. Melflufen Plus Dexamethasone in Combination With Bortezomib



[a]For patients aged ≥75 years: dexamethasone (po) 12 mg on days 1, 4, 8, and 11 and 20 mg on days 15 and 22.
EoT, end of treatment; IV, intravenous; OS, overall survival; PD, progressive disease; PFS, progression-free survival; po, oral; SC, subcutaneous.

- Up to 3 dose levels of melflufen are being tested, starting at 30 mg and either increasing to 40 mg or decreasing to 20 mg based on observed dose-limiting toxicity (DLT)
- Melflufen is administered intravenously on day 1 of each 28-day cycle, in each regimen
- Each regimen is evaluated separately

RESULTS

Melflufen plus dexamethasone in combination with daratumumab

PATIENTS

- At the time of data cutoff (8 October 2019), 33 patients had been treated with melflufen (6 patients with melflufen 30 mg, 27 patients with melflufen 40 mg) plus dexamethasone in combination with daratumumab
- Baseline characteristics were as expected in patients with RRMM (**Table 1**)

Table 1. Patient Characteristics

Characteristics	30 mg[a] (n=6)	40 mg (n=27)
Age, median (range), y	57.0 (49-78)	66.0 (35-77)
Sex (men / women), n (%)	3 (50) / 3 (50)	19 (70) / 8 (30)
Time since diagnosis, median (range), y	3.1 (1.9-8.0)	3.8 (0.7-15.6)
No. of previous lines, median (range)	2.5 (1-3)	2.0 (1-4)
Prior ASCT / alkylator exposed, n (%)	5 (83) / 5 (83)	21 (78) / 24 (89)
Alkylator refractory, n (%)	1 (17)	3 (11)
IMiD refractory, n (%)	3 (50)	15 (56)
PI refractory, n (%)	0	13 (48)
Last-line refractory[b], n (%)	2 (33)	11 (41)
IMID + PI refractory, n (%)	0	10 (37)
ISS at study entry, I / II / III[c], n (%)	6 (100) / 0 / 0	18 (67) / 4 (15) / 4 (15)
High-risk cytogenetics by FISH[d], n/N (%)	3/5 (60)	12/20 (60)

[a]Three patients were erroneously dosed with 30 mg of melflufen instead of the assigned 40 mg.
[b]Failure to achieve at least a minimal response or progression on therapy within 60 days of treatment.
[c]1 patient at the 40-mg dose level had unknown ISS.
[d]High risk defined as t(4;14), t(14;16), t(14;20), del(17/17p), or gain(1q). Missing data for 1 patient at the 30-mg dose level and 7 patients at the 40-mg dose level.
ASCT, autologous stem cell transplantation; FISH, fluorescence in situ hybridization; ISS, International Staging System; PI, proteasome inhibitor.

EFFICACY

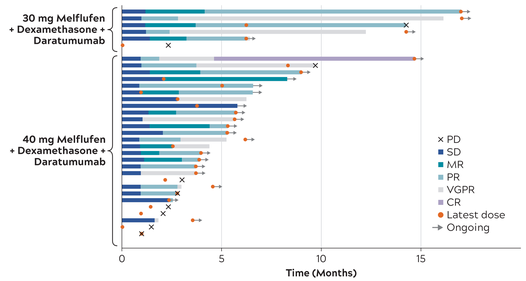
- Median follow-up time was 6.6 months
- Median duration of treatment was 6.2 months (range, 0.9-18.0), with 22 of 33 patients (67%) still ongoing at the time of data cutoff (4 patients on melflufen 30 mg and 18 patients on melflufen 40 mg)
  - 6 Patients discontinued melflufen and have continued daratumumab plus dexamethasone, for a median duration of treatment of 3.6 months (range, 0.7-8.7)
- Of the 33 patients, 26 responded to treatment, with an ORR of 76% and a CBR of 79% (**Table 2** and **Figure 4**)
- Most patients were progression-free at the time of the data cutoff, with 10 events in 33 patients (**Figure 6**)
  - Median PFS was 14.3 months (95% CI, 9.7-not reached)
  - Patients were censored on their latest progression-free observation

Table 2. Response Assessment

Subgroup	Patients, n							Patients (%)	
	sCR	CR	VGPR	PR	MR	SD	PD	ORR	CBR
Total (n=33)	1	0	11	13	1	2	5	76	79
Melflufen 30 mg (n=6)	0	0	3[a]	2	0	0	1	83	83
Melflufen 40 mg (n=27)	1	0	8[b]	11	1	2	4	74	78

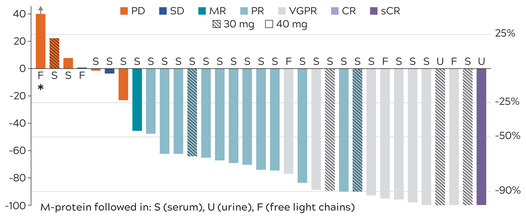
[a]Includes 1 unconfirmed VGPR.
[b]Includes 2 unconfirmed VGPRs.
CBR, clinical benefit rate; CR, complete response; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

Figure 4. Swim-Lane Plot[a]



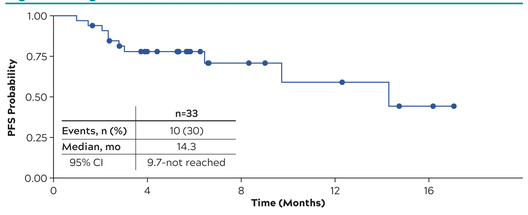
[a]The swim-lane plot is based on response assessments reported by the investigators. Gaps between the bar and latest dose indicate there were no response data available for that time.
CR, complete response; EoT, end of treatment; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 5. Waterfall Plot (Best M-Protein Change)



*Measurable disease by UPEP at baseline but not evaluated at response assessment.
CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease; UPEP, urine protein electrophoresis; VGPR, very good PR.

Figure 6. Progression-Free Survival[a]



[a]These data are immature since 23 patients are still in PFS follow-up
PFS, progression-free survival.

SAFETY

- No DLTs were observed at any dose level in the phase 1 part of the study
- The combination of melflufen, dexamethasone, and daratumumab was well tolerated, with clinically manageable grade 3/4 hematologic AEs (**Table 3**), and the low number of nonhematologic AEs was noteworthy
- 3 Patients died, all with myeloma progression (one detected at autopsy)
  - 1 Patient had grade 5 sepsis and pneumonia while in progression (considered study treatment-related)

Table 3. Treatment-Related Grade 3/4 AEs (n=33)[a]

Preferred Term	Treatment-Related Grade 3/4 AEs	
	30 mg (n=6) Patients, n (%)	40 mg (n=27) Patients, n (%)
Any Grade 3/4 AE	5 (83)	22 (81)
Thrombocytopenia[b]	3 (50)	18 (67)
Neutropenia[b]	5 (83)	15 (56)
Anemia	3 (50)	2 (7)
Febrile neutropenia	1 (17)	1 (4)

[a]Treatment-related grade 3/4 AEs reported occurred in at least 1 patient in the 40-mg cohort.
Additional treatment-related grade 3/4 AEs that occurred in 1 (4%) patient each in the 40-mg cohort included pancytopenia, upper respiratory tract infection, fatigue, pyrexia, infusion-related reaction, respiratory failure and sepsis (grade 4 events both occurring in 1 patient; events later worsened to grade 5 pneumonia and sepsis), agitation, muscular weakness, increased blood alkaline phosphatase, hypertension.
[b]Event terms include platelet count decreased and neutrophil count decreased, respectively.
AE, adverse event.

Table 4. Overview of SAEs (n=33)

	n=33 Patients, n (%)
Any Grade SAE	12 (36)
Treatment-related SAE	6 (18)

SAE, serious adverse event.

Table 5. Treatment-Related SAEs (n=33)

Preferred Term	Treatment-Related SAEs n=33 Patients, n (%)
Febrile neutropenia	2 (6)
Abdominal pain	1 (3)
Pancytopenia	1 (3)
Pyrexia	1 (3)
Respiratory failure	1 (3)
Sepsis	1 (3)
Upper respiratory tract infection	1 (3)

SAE, serious adverse event.

Melflufen plus dexamethasone in combination with bortezomib

PATIENTS

- At the time of data cutoff (8 October 2019), 6 patients had been treated with melflufen (3 patients with melflufen 30 mg, 3 patients with melflufen 40 mg) plus dexamethasone in combination with bortezomib
- Median age was 71.5 years, with a median of 2.5 prior lines (range, 2-4) and a median time since diagnosis of 3.9 years (1.2-7.4)
- All patients had relapsed/refractory disease, and 3 of the 6 patients (50%) were last-line refractory
- All patients had previously received a PI and 5 patients an alkylating agent
- 2 Patients out of 6 had high-risk cytogenetics; 1 of the patients had unknown cytogenetics status

EFFICACY

- Median follow-up time was 13.4 months
- Median treatment duration was 9.3 months (range, 2.1-16.1)
- Median number of treatment cycles was 9 (range, 2-16)
- 3 Patients (50%) remain on treatment at the time of data cutoff
  - 1 Patient discontinued treatment because of PD after 10 months
- ORR was 67%, and clinical benefit rate (CBR) was 83%
  - 2 Patients achieved VGPR, 2 achieved PR, 1 achieved MR, and 1 progressed

SAFETY

- No DLTs were observed at any dose level
- The regimen was well tolerated, with clinically manageable grade 3/4 hematologic adverse events (AEs); the low number of nonhematologic AEs is noteworthy
  - Treatment-related grade 3/4 AEs included thrombocytopenia (n=5), neutropenia (n=3), anemia (n=1), and pneumonia (n=1)
- 5 Patients experienced serious adverse events (SAEs); 1 experienced treatment-related SAEs (pneumonia and neutropenia)
- 2 Patients died after discontinuation of study treatment, both due to myeloma progression

CONCLUSIONS

- Based on interim data from ANCHOR, the combination of melflufen plus dexamethasone with either bortezomib or daratumumab showed encouraging activity with a median follow-up time of 6.8 months and 64% of patients still on treatment
  - ORR was 76% in combination with daratumumab and 67% in combination with bortezomib
  - Median PFS was 14.3 months in combination with daratumumab and not reached in combination with bortezomib
- Both combinations were well tolerated
  - Grade 3/4 treatment-related AEs were mostly hematologic
  - No DLTs have been observed across both regimens and melflufen dose levels

Additional Ongoing Studies

- HORIZON (OP-106) is an ongoing pivotal, single-arm, multicenter, phase 2 study evaluating the efficacy and safety of melflufen plus dexamethasone in heavily pretreated and poor-risk patients with MM refractory to pomalidomide or anti-CD38 monoclonal antibody, or both (NCT02963493)
- OCEAN (OP-103) is a randomized, head-to-head, superiority, open-label, global, phase 3 study evaluating the efficacy and safety of melflufen plus dexamethasone vs pomalidomide plus dexamethasone in 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

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