Abstract PF608

ANCHOR (OP-104): A Phase 1 Study Update of Melflufen and Dexamethasone Plus Bortezomib or Daratumumab in Relapsed/Refractory Multiple Myeloma Patients Refractory to an IMiD or a Proteasome Inhibitor

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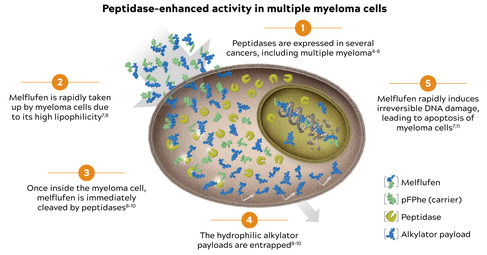
BACKGROUND

- Despite recent advances in therapy, multiple myeloma (MM) remains incurable, showing the need for novel therapies[1]
- Melflufen is a lipophilic peptide-conjugated alkylator that rapidly delivers a highly cytotoxic payload into myeloma cells through peptidase activity (**Figure 1**)
- Melflufen in combination with dexamethasone (dex) has previously shown encouraging activity in relapsed/refractory MM (RRMM)[2,3]
- Daratumumab and bortezomib are 2 drugs with different mechanisms (anti-CD38 monoclonal antibody [aCD38 mAb] and proteasome inhibitor [PI], respectively) that are approved and commonly used in the treatment of patients with MM
- The phase 1/2 trial OP-104 ANCHOR investigates the safety and efficacy of melflufen and dex in combination with either bortezomib or daratumumab in patients with RRMM

Figure 1. Melflufen Mechanism of Action



Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to increased intracellular alkylator activity[7,8]

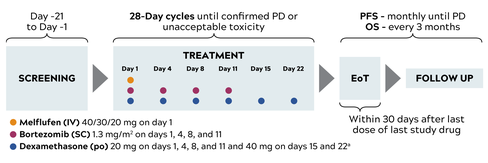
OBJECTIVES

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

METHODS

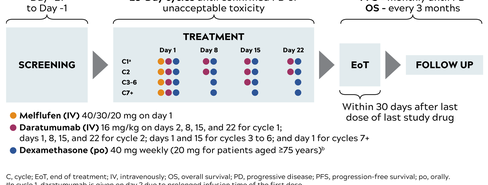
- This is a phase 1/2 trial (NCT03481556) of melflufen and dex in combination with either bortezomib (regimen A; **Figure 2**) or daratumumab (regimen B; **Figure 3**)
- All patients must have had 1 to 4 prior lines of therapy and be refractory (or intolerant) to an IMiD or PI or both
- For the combination with bortezomib, patients cannot be refractory to a PI
- For the combination with daratumumab, patients must be aCD38 mAb naive
- Patients will be treated until documented progressive disease (PD) or unacceptable toxicity

Figure 2. Melflufen and Dexamethasone in Combination With Bortezomib



EoT, end of treatment; IV, intravenously; OS, overall survival; PD, progressive disease; PFS, progression-free survival; po, orally; SC, subcutaneously.
[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.

Figure 3. Melflufen and Dexamethasone in Combination With Daratumumab



C, cycle; EoT, end of treatment; IV, intravenously; OS, overall survival; PD, progressive disease; PFS, progression-free survival; po, orally.
[a]In cycle 1, daratumumab is given 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.

- 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 (IV) is administered on day 1 of each 28-day cycle in each regimen
- Each regimen is evaluated separately

RESULTS

REGIMEN A: Melflufen and dex in combination with bortezomib

- At the time of data cutoff (8 May 2019), 5 patients had been treated with melflufen (3 with 30 mg, 2 with 40 mg) (**Table 1**)
- Median age was 73 years, with a median of 2 prior lines (range, 2-4), and no patient had achieved CR in any previous line
- All patients had relapsed/refractory disease, and 2 of the 5 patients were last-line refractory (PD while on therapy)

Table 1. Patient Characteristics: Regimen A

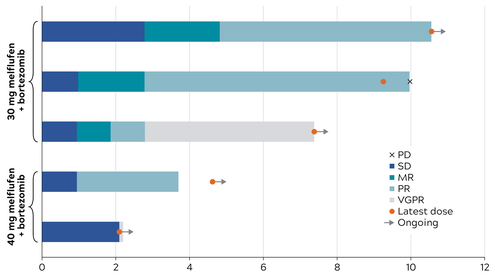
Characteristics	n=5[a]
Median age, years (range)	73.0 (63-82)
Gender, n (%) Male/female	3 (60)/2 (40)
Median time since diagnosis, years (range)	5.8 (1.2-7.4)
Median number of previous lines (range)	2 (2-4)
Prior ASCT/alkylator exposed, n (%)	1 (20)/4 (80)
Alkylator refractory, n (%)	1 (25)
PI exposed, n (%)	5 (100)
IMiD refractory, n (%)	3 (75)
Daratumumab refractory, n (%)	1 (25)
Last-line refractory, n (%)	2 (50)
ISS stage at study entry, n (%) I/II/III	5 (100)/0/0
High-risk genetic by FISH[b], n (%)	0

ASCT, autologous stem cell transplantation; FISH, fluorescence in situ hybridization; ISS, International Staging System; PI, proteasome inhibitor.
[a]One patient with missing refractory status.
[b]High-risk defined as: t(4;14), t(14;16), t(14;20), del(17/17p), or gain(1q).

EFFICACY

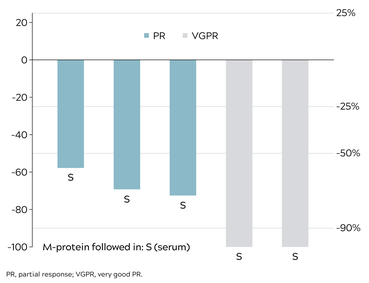
- Median treatment duration was 7.4 months (range, 2-11 months)
- Four patients were ongoing (**Figure 4**)
  - One discontinued treatment due to PD after 10 months
- Two patients achieved VGPR and 3 patients achieved PR (**Figure 5**) for an **ORR of 100%**

Figure 4. Swim-Lane Plot



CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

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



PR, partial response; VGPR, very good PR.

SAFETY

- No DLTs were observed at any dose level
- The regimen was well tolerated with clinically manageable grade 3/4 hematologic adverse events (AEs; **Table 2**), and the low number of nonhematologic AEs is noteworthy
- One patient experienced treatment-related serious AEs (**Table 3**)
- No deaths on study were reported

Table 2. Treatment-Related Grade 3/4 AEs (n=5)

Preferred Term	No. of Patients (%) 30 mg (n=3)	40 mg (n=2)
Any AE	2 (67)	1 (50)
Thrombocytopenia[a]	2 (67)	1 (50)
Neutropenia[a]	2 (67)	0
Pneumonia[a]	1 (33)	0

AE, adverse event.
[a]Event terms include "platelet count decreased," "neutrophil count decreased," and "pneumonia pneumococcal," respectively.

Table 3. Serious AEs (n=5)

Preferred Term	SAEs (Total n=5) No. of Patients (%) All	Treatment-Related
Any SAE	4 (80)	1 (20)
Pneumonia[a]	1 (20)	1 (20)
Bronchitis	1 (20)	0
Deep vein thrombosis	1 (20)	0
Humerus fracture	1 (20)	0
Neutropenia	1 (20)	1 (20)

[a]Event term includes "pneumonia pneumococcal."
AE, adverse event; SAE, serious AE.

REGIMEN B: Melflufen and dex in combination with daratumumab

- At the time of data cutoff (8 May 2019), 24 patients had been treated with melflufen (6 with 30 mg, 18 with 40 mg)
- Baseline characteristics were as expected in RRMM and similar between the dose levels (**Table 4**)

Table 4. Patient Characteristics: Regimen B

Characteristics	30 mg[a] (n=6)	40 mg (n=18)
Median age, years (range)	57.0 (49-78)	62.0 (35-77)
Gender, n (%) Male/female	3 (50)/3 (50)	13 (72)/5 (27)
Median time since diagnosis, years (range)	3.1 (1.9-8.0)	4.4 (0.7-8.2)
Median number of previous lines (range)	2.5 (1-3)	2 (1-4)
Prior ASCT/ alkylator exposed, n (%)	5 (83)/ 3 (50)	14 (78)/ 10 (56)
Alkylator refractory, n (%)	1 (17)	4 (22)
IMiD refractory, n (%)	3 (50)	11 (61)
PI refractory, n (%)	0	10 (56)
Last-line refractory, n (%)	2 (33)	10 (56)
IMiD + PI refractory, n (%)	0	8 (44)
ISS at study entry,[b] n (%) I/II/III	6 (100)/0/0	13 (76)/2 (12)/2 (12)
High-risk cytogenetic by FISH,[c] n (%)	2 (40)	5 (36)
Median albumin level, g/dL (range)	4.1 (3.1-4.5)	3.9 (3.1-4.9)

ASCT, autologous stem cell transplant; FISH, fluorescence in situ hybridization; ISS, International Staging System; PI, proteasome inhibitor.
[a]Three patients erroneously dosed with 30-mg melflufen instead of the assigned 40 mg.
[b]Missing data for 1 patient.
[c]High-risk defined as: t(4;14), t(14;16), t(14;20), del(17/17p), or gain(1q). Missing data for 5 patients.

EFFICACY

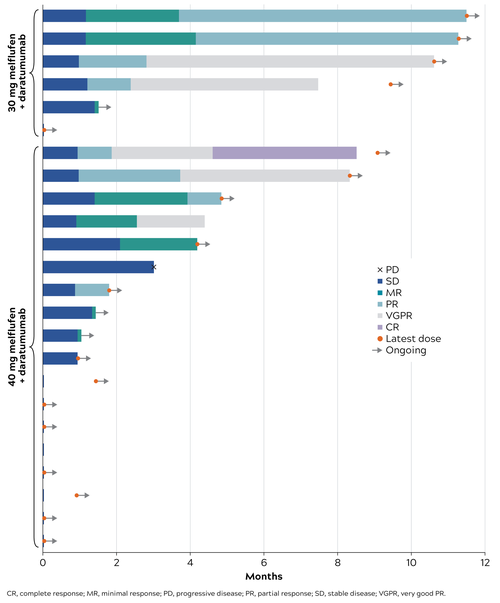
- All 6 patients on 30 mg and 16 of the 18 patients on 40 mg were still ongoing (**Figure 6**)
  - Two discontinued treatment due to physician's decision (1 due to lack of response)
- Median treatment duration was 7.9 months (range, 0-11 months) and 1.2 months (range, 0-9 months) on 30 mg and 40 mg, respectively
- One patient achieved CR and 2 patients achieved VGPR (**Table 5** and **Figure 7**)
- Median progression-free survival was not reached with only 1 event in 24 patients; patients were censored on their latest progression-free observation (**Figure 8**)

Table 5. Response Assessment

Subgroup	No. of Patients sCR	CR	VGPR	PR	MR	SD	PD	NA	Percentage of Patients ORR	CBR
Total (n=24)	0	1	4	4	4[a]	2	0	9	60	87
Patients with ≥2 completed cycles of therapy (n=11)	0	1	4	4	1[a]	1	0	0	82	91

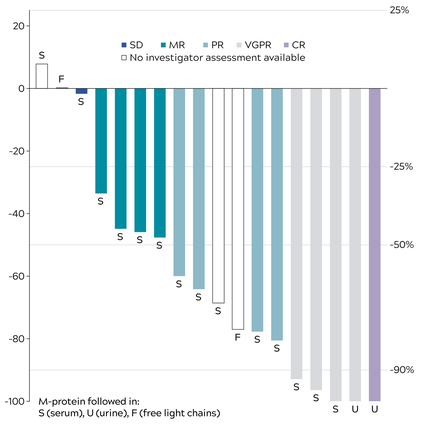
CBR, clinical benefit rate; CR, complete response; MR, minimal response; NA, no assessment at time of data cutoff; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.
[a]Including 3 and 1 unconfirmed MR, respectively.

Figure 6. Swim-Lane Plot



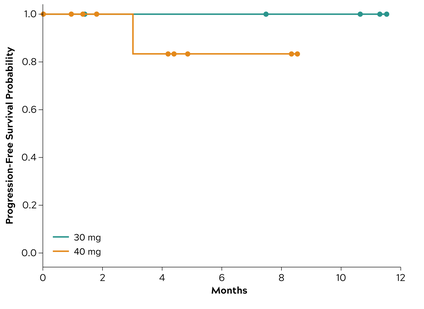
CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 7. Waterfall Plot (Best M-Protein Change)



CR, complete response; MR, minimal response; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 8. Progression-Free Survival



SAFETY

- No DLTs were observed at any dose level in the phase 1 part of the study
- The regimen was well tolerated with clinically manageable grade 3/4 hematologic AEs (**Table 6**), and the low number of nonhematologic AEs was noteworthy
- Four patients experienced treatment-related serious AEs (**Table 7**)

Table 6. Treatment-Related Grade 3/4 AEs

Preferred term	No. of Patients (%) 30 mg (n=6)	40 mg (n=18)
Any AE	5 (83)	14 (78)
Neutropenia[a]	5 (83)	10 (56)
Thrombocytopenia[a]	3 (50)	11 (61)
Anemia	2 (33)	1 (6)
Febrile neutropenia	1 (17)	0
Fatigue	0	1 (6)
Agitation	0	1 (6)
Muscular weakness	0	1 (6)

AE, adverse event.
[a]Event terms include "platelet count decreased" and "neutrophil count decreased," respectively.

Table 7. Serious AEs

Preferred Term	SAEs (Total n=24) No. of Patients (%) All	Treatment-Related
Any SAE	8 (33)	4 (17)
Influenza	1 (4)	0
Parainfluenza virus infection	1 (4)	0
Pneumonia	1 (4)	0
Febrile neutropenia	1 (4)	1 (4)
Neutropenia	1 (4)	1 (4)
Thrombocytopenia	1 (4)	1 (4)
Pyrexia	1 (4)	1 (4)
Chest pain	1 (4)	0
Abdominal pain	1 (4)	1 (4)

AE, adverse event; SAE, serious AE.

CONCLUSIONS

- Based on interim data from ANCHOR in patients with RRMM, the combination of melflufen and dexamethasone with either bortezomib or daratumumab is well tolerated
  - No DLTs have been observed across both regimens and dose levels
  - Grade 3/4 AEs were mostly hematologic, and all were clinically manageable
- Evolving efficacy is encouraging in both combinations, with 90% of patients still on treatment
  - In the ITT population, ORR was 100% for the bortezomib combination and 60% for the daratumumab combination (82% for patients that had completed 2 or more cycles of therapy). Responses with both combinations improved with continued therapy
- The ANCHOR study is ongoing, with active recruitment of patients to the 40-mg bortezomib dose level
- Additional studies with melflufen in RRMM include the following:
  - OP-106 HORIZON, an ongoing, open-label, phase 2 study evaluating efficacy and safety of melflufen plus dex in mainly patients with triple-class refractory RRMM (NCT02963493)
  - OP-103 OCEAN, an ongoing, phase 3, randomized, study evaluating efficacy and safety of melflufen plus dex versus pomalidomide plus dex in patients with RRMM refractory to lenalidomide (NCT03151811)

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DISCLOSURES

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