

ANCHOR (OP-104): Melflufen Plus Dexamethasone and Bortezomib in Relapsed/Refractory Multiple Myeloma—Optimal Dose, Updated Efficacy and Safety Results

Poster
MM-169



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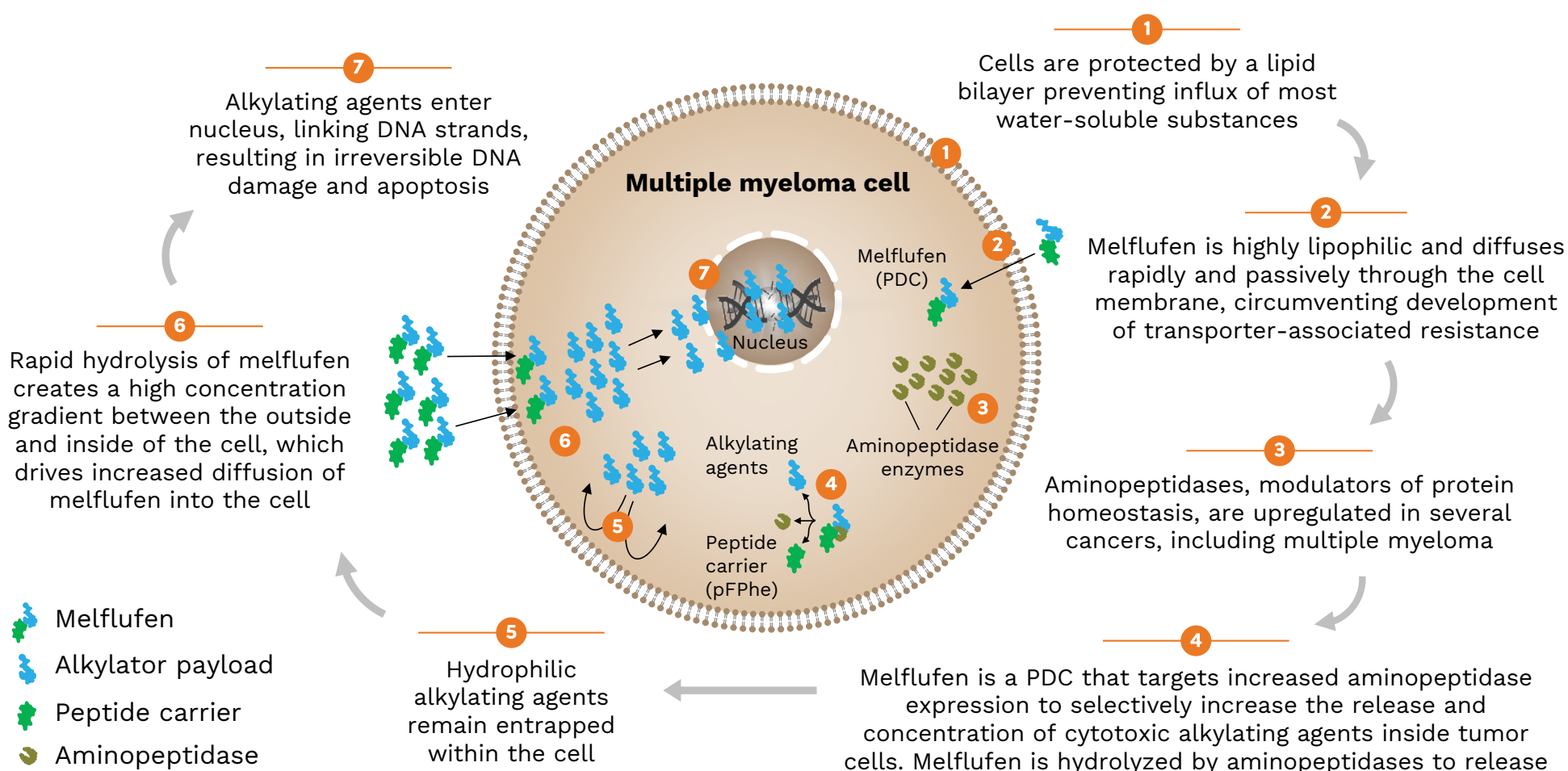
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BACKGROUND

- The development of resistance to standard treatments in patients with relapsed/refractory multiple myeloma (RRMM) often leads to poor outcomes and almost all patients relapse^{1,2}
- Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that targets aminopeptidases and thereby rapidly releases alkylating agents inside tumor cells (**Figure 1**)³⁻⁷
- In the pivotal phase 2 HORIZON study (OP-106), the activity of melflufen plus dexamethasone in patients with heavily pretreated RRMM refractory to pomalidomide and/or anti-CD38 monoclonal antibody therapy demonstrated clinical efficacy and acceptable safety⁸
 - Overall response rate (ORR) was 29%, median progression-free survival (PFS) was 4.2 months, and median overall survival (OS) was 11.6 months at a median follow-up of 14 months
 - Refractory to (or intolerant of) an immunomodulatory agent
 - Grade 3/4 hematologic treatment-emergent adverse events (TEAEs) were common (mainly neutropenia [79%], thrombocytopenia [76%], and anemia [43%]) but clinically manageable; nonhematologic AEs were infrequent
- ANCHOR is a phase 1/2a study of melflufen and dexamethasone in triplet combination with bortezomib or daratumumab. The study aims to establish the dose of melflufen in each triplet combination and to investigate their safety and efficacy
 - Results for the daratumumab arm have been previously reported, with melflufen 30 mg established as the recommended dose for this triplet combination in future studies⁹
 - Updated results for the bortezomib triplet combination are reported herein

Figure 1. Melflufen Mechanism of Action



PDC, peptide-drug conjugate; pFPhe, p-Fluoro-DL-phenylalanine.

OBJECTIVE

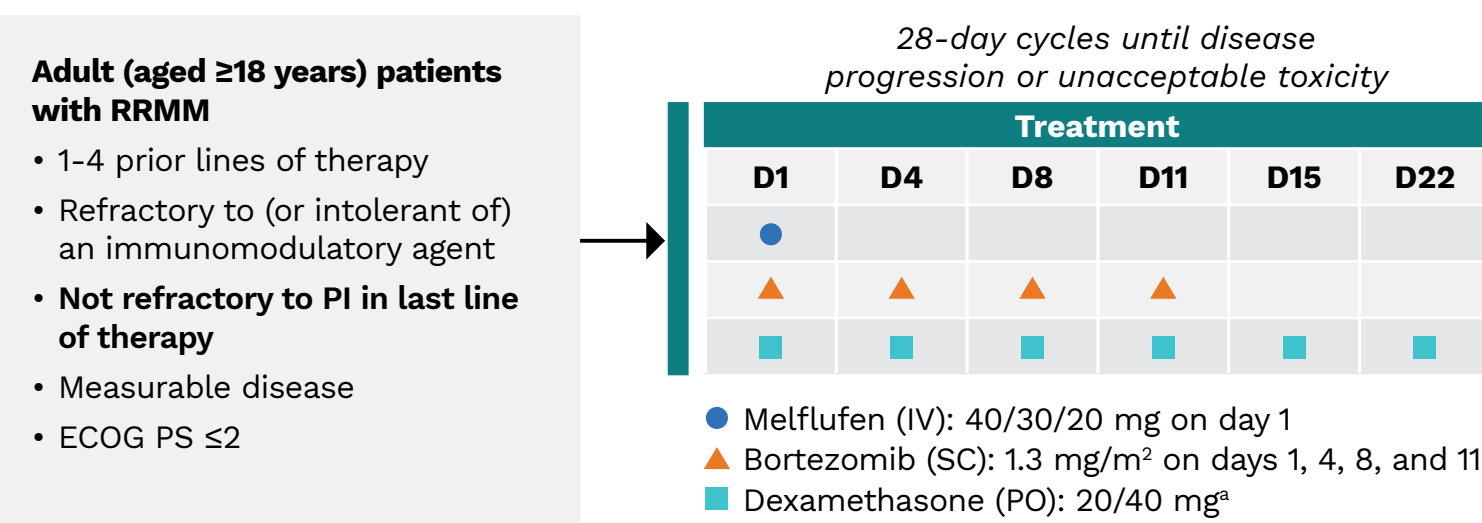
- The primary objective of phase 1 is to determine the optimal phase 2 dose of melflufen in combination with dexamethasone and bortezomib
- The objective of the phase 2 portion of the study is to evaluate the ORR, assessed by the investigator, per International Myeloma Working Group response criteria¹⁰

METHODS

- ANCHOR is a phase 1/2a, 3+3 design, dose-escalation study (NCT03481556) of melflufen plus dexamethasone in combination with either bortezomib or daratumumab
 - This presentation is an update on the bortezomib triplet combination (**Figure 2**)
- 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 toxicities (DLTs)
 - Melflufen is administered via central vein infusion on day 1 of each 28-day treatment cycle
- Once the optimal dose has been established, an additional 20 efficacy evaluable patients per regimen will be recruited into the phase 2 portion of the study
- All eligible patients must have received 1-4 prior lines of therapy and been intolerant of or refractory to a prior immunomodulatory agent
- Prior treatment with a proteasome inhibitor (PI) is allowed, but patients cannot be refractory to PIs in the last line of therapy
- Patients will be treated until disease progression or unacceptable toxicity
- Median follow-up for duration of response (DOR), PFS, and OS was obtained via reverse Kaplan-Meier estimation

METHODS (continued)

Figure 2. Melflufen Plus Dexamethasone in Combination With Bortezomib



Primary objectives

- Phase 1: Optimal dose of melflufen in combination
- Phase 2: ORR

Secondary objectives

- Best response
- DOR
- TTR
- PFS
- OS
- Safety

¹Dexamethasone 20-mg is administered on days 1, 4, 8, and 11 of each cycle and 40-mg on days 15 and 22 of each cycle; for patients aged ≥75 years, a 12-mg dose is administered on days 1, 4, 8, and 11 and 20 mg on days 15 and 22.
D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PO, orally; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; TTR, time to response.

RESULTS

PATIENTS

- As of the data cutoff date (February 6, 2021), 14 patients had been treated with melflufen (30 mg, n=7; 40 mg, n=7) plus dexamethasone and bortezomib
 - Data set includes 13 patients enrolled in phase 1 (30 mg, n=6; 40 mg, n=7) and 1 patient enrolled in phase 2 (30 mg)
 - One patient was replaced at the 40-mg dose level in the DLT analysis but was included in the safety and efficacy analyses
- At the 30-mg and 40-mg dose levels, respectively, 5 patients (71%) and 3 patients (43%) remained on treatment, and 2 patients (29%) and 4 patients (57%) discontinued treatment (**Table 1**)
- Baseline characteristics are shown in **Table 2**
- The median treatment duration was 6.1 months (range, 0.8–32.7) at the 30-mg dose level and 11.4 months (range, 2.1–23.9) at the 40-mg dose level (**Table 3**)

Table 1. Patient Disposition

Patient Disposition at Data Cutoff	Melflufen 30 mg (n=7)	Melflufen 40 mg (n=7) ^a
Treated, n (%)	7 (100)	7 (100)
Ongoing at the data cutoff date	5 (71)	3 (43)
Discontinued treatment, n (%)	2 (29)	4 (57)
Adverse event	0	2 (29)
Progressive disease	1 (14)	1 (14)
Lack of efficacy	0	1 (14)
Other	1 (14)	0
Alive, n (%)	5 (71)	5 (71)

Data cutoff date: February 6, 2021.

^aOne patient was replaced at the 40-mg dose level in the DLT analysis but was included in the safety and efficacy analyses.

RESULTS (continued)

Table 2. Baseline Patient Characteristics

Characteristics	Melflufen 30 mg (n=7)	Melflufen 40 mg (n=7)
Age, median (range), years	76 (70–82)	70 (61–76)
Sex (men / women), n (%)	5 (71) / 2 (29)	7 (100) / 0 (0)
Time since diagnosis, median (range), years	5.0 (1.4–7.4)	1.9 (1.2–8.0)
No. prior lines of therapy, median (range)	3.0 (2–4)	2.0 (1–4)
ISS at study entry, I / II / III, n (%)	4 (57) / 2 (29) / 1 (14)	4 (57) / 3 (43) / 0 (0)
High-risk cytogenetics by FISH, ^a n/N (%)	2/5 (40)	3/6 (50)
ECOG PS 0 / 1 / 2, n (%)	3 (43) / 3 (43) / 1 (14)	2 (29) / 5 (71) / 0 (0)
Prior ASCT / exposed to alkylator, n (%)	0 (0) / 7 (100)	3 (43) / 4 (57)
Refractory to alkylator, n (%)	2 (29)	0 (0)
Refractory to immunomodulatory agent, n (%)	7 (100)	5 (71)
Exposed to prior PI, n (%)	7 (100)	6 (86)
Refractory to PI, n (%)	2 (29)	1 (14)
Exposed to prior anti-CD38 mAb, n (%)	2 (29)	2 (29)
Refractory to anti-CD38 mAb, n (%)	2 (29)	2 (29)
Refractory to last line of therapy, n (%)	6 (86)	5 (71)
Refractory to immunomodulatory agent + PI, n (%)	2 (29)	1 (14)

Data cutoff date: February 6, 2021.

^aHigh-risk defined as t(4;14), t(14;16), t(14;20), del(17;17)p, or gain(1q). FISH at study entry missing for 2 patients at the 30-mg dose level, and for 1 patient at the 40-mg dose level.

ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor.

Table 3. Treatment Exposure

	Melflufen 30 mg (n=7)	Melflufen 40 mg (n=7)
Follow-up, ^a median, mo	6.1	15.1
No. of treatment cycles, median (range)	7 (1–32)	10 (2–21)
Treatment duration, median (range), mo	6.1 (0.8–32.7)	11.4 (2.1–23.9)
Total cumulative doses administered, median (range), mg		
Melflufen	210 (30–920)	240 (80–840)
Bortezomib	74.8 (10.2–247.8)	56.5 (12.3–128.7)
Dexamethasone	528 (20–4060)	1000 (180–2760)

Data cutoff date: February 6, 2021.

^aFollow-up from cycle 1, day 1 to data cutoff or study end.

SAFETY

- No DLTs were observed at either dose level
- Grade ≥3 nonhematologic treatment-related TEAEs were uncommon (**Table 4**)
- Serious TEAEs occurred in 4 patients (57%) at the 30-mg dose level and 4 patients (57%) at the 40-mg dose level and were considered treatment related in 2 patients (29%) at the 30-mg dose level (pneumonia and neutropenia; syncope [1 patient each]) and 1 patient (14%) at the 40-mg dose level (thrombocytopenia and neutropenia)
- TEAEs led to melflufen dose reductions in 3 patients (43%) at the 30-mg dose level and 4 patients (57%) at the 40-mg dose level (**Table 5**)
- Two patients experienced a TEAE with a fatal outcome <30 days after last dose of study drug (cardiac failure chronic at the 30-mg dose level and COVID-19 pneumonia at the 40-mg dose level)
 - Both events were considered unrelated to study drug

Table 4. Grade ≥3 Treatment-Related TEAE

Characteristics	Melflufen 30 mg (n=7)	Melflufen 40 mg (n=7)
Any grade ≥3 treatment-related TEAE, n (%)	6 (86)	7 (100)
Thrombocytopenia ^a	4 (57)	7 (100)
Neutropenia ^a	2 (29)	5 (71)
Anemia	2 (29)	4 (57)
Fatigue	1 (14)	0 (0)
Hypotension	1 (14)	0 (0)
Pneumonia pneumococcal	1 (14)	0 (0)
Syncope	1 (14)	0 (0)
Hemorrhage	0 (0)	1 (14)

Data cutoff date: February 6, 2021.

^aThrombocytopenia includes the preferred terms 'thrombocytopenia' and 'platelet count decreased'.

^bNeutropenia includes the preferred terms 'neutropenia' and 'neutrophil count decreased'.

TEAE, treatment-emergent adverse event.

Table 5. TEAEs Leading to Melflufen Dose Reductions, Delays, and Discontinuations

	Melflufen 30 mg (n=7)	Melflufen 40 mg (n=7)
Any TEAE leading to dose reduction of any study drug, n (%)	5 (71)	5 (71)
Any TEAE leading to melflufen dose reduction, n (%)	3 (43)	4 (57)
Thrombocytopenia ^a	2 (29)	4 (57)
Anemia	1 (14)	1 (14)
Neutropenia ^a	0 (0)	1 (14)
Hemorrhage	0 (0)	1 (14)
Any TEAE leading to melflufen dose delay, n (%)	3 (43)	7 (100)
Most common (occurring in ≥3 patients overall), n (%)		
Thrombocytopenia ^a	1 (14)	6 (86)
Neutropenia ^a	2 (29)	2 (29)
Upper respiratory tract infection	2 (29)	2 (29)
Infection	1 (14)	2 (29)
Any TEAE leading to discontinuation of any study drug, n (%)	2 (29)	2 (29)
Any TEAE leading to melflufen discontinuation, n (%)	2 (29)	2 (29)
COVID-19 pneumonia	0 (0)	1 (14)
Thrombocytopenia ^a	0 (0)	1 (14)
Cardiac failure chronic	1 (14)	0 (0)
Osteolysis	1 (14)	0 (0)

Data cutoff date: February 6, 2021.

^aThrombocytopenia grouped term includes the preferred terms 'thrombocytopenia' and 'platelet count decreased'.

^bNeutropenia grouped term includes the preferred terms 'neutropenia' and 'neutrophil count decreased'.

TEAE, treatment-emergent adverse event.

EFFICACY - RESPONSE

- At the 30-mg and 40-mg dose levels, respectively, the ORR was 57% and 71% and clinical benefit rate was 71% and 71% (**Table 6**)
- At a median DOR follow-up time of 26.7 months at the 30-mg dose level and 10.4 months at the 40-mg dose level, the median DOR data were immature

Table 6. Response Assessment

Response Category	Melflufen 30 mg (n=7)	Melflufen 40 mg (n=7)
Best confirmed response, n		
≥CR	1	1
VGPR	0	3
PR	3	1
MR	1	0
SD	1	1
PD	0	0
NA	1	1 ^a
ORR (95% CI), %	57.1 (18.4–90.1)	71.4 (29.0–96.3)
CBR (95% CI), %	71.4 (29.0–96.3)	71.4 (29.0–96.3)

Data cutoff date: February 6, 2021.

^aOne patient had an unconfirmed SD at the 40-mg dose level.

CR, complete response; PR, partial response; NA, not assessable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

EFFICACY - PFS AND OS

- PFS data were immature, with 2 of 7 patients at the 30-mg dose level and 3 of 7 patients at the 40-mg dose level experiencing an event
- OS data were immature, with 5 of 7 patients at the 30-mg dose level and 5 of 7 patients at the 40-mg dose level alive at the data cutoff date (median OS follow-up: 29.2 months and 15.9 months, respectively)

CONCLUSIONS

- Melflufen plus dexamethasone as a triplet regimen with bortezomib in patients with RRMM and poor prognostic factors was well tolerated, with a similar safety profile as when used as a doublet (melflufen plus dexamethasone)^{3,11}
 - Grade 3/4 treatment-related TEAEs were mostly hematologic
 - Grade 3/4 nonhematologic treatment-related TEAEs were infrequent
- Both dose levels demonstrated encouraging activity
 - ORR was 57% at the 30-mg dose level and 71% at the 40-mg dose level
- Phase 1 data in ANCHOR determined 30 mg of melflufen as the optimal dose in combination with bortezomib (1.3 mg/m² on days 1, 4, 8, and 11 of each 28-day cycle)
 - Efficacy outcomes were similar with 30 and 40 mg melflufen as the starting dose
 - However, fewer melflufen dose reductions and dose delays were reported at the 30-mg dose level
- Recruitment for phase 2 is currently ongoing with 1 patient enrolled thus far

REFERENCES

- Kumar SK, et al. *Leukemia*. 2017;31:2443–2448.
- Gandhi LH, et al. *Leukemia*. 2019;33:2286–2275.
- Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019–3031.
- Ray A, et al. *Br J Haematol*. 2016;174:397–409.
- Wickström M, et al. *Oncotarget*. 2017;8:6641–6655.
- Wickström M, et al. *Invest New Drugs*. 2008;26:195–204.
- Strese S, et al. *Biochem Pharmacol*. 2015;96:888–895.
- Richardson PG, et al. *J Clin Oncol*. 2012;30:757–767.
- Ocio EM, et al. *Blood*. 2020;136(Supplement 1): 9–10.
- Rajkumar SV, et al. *Blood*. 2011;117:4691–4695.
- Richardson P, et al. *Lancet Haematol*. 2020;7:e395–e407.

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DISCLOSURES

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