THE OP-104 ANCHOR STUDY:

A phase 1/2 study of safety and efficacy of melflufen and dexamethasone in combination with either bortezomib or daratumumab in patients with RRMM; first report on phase 1 data

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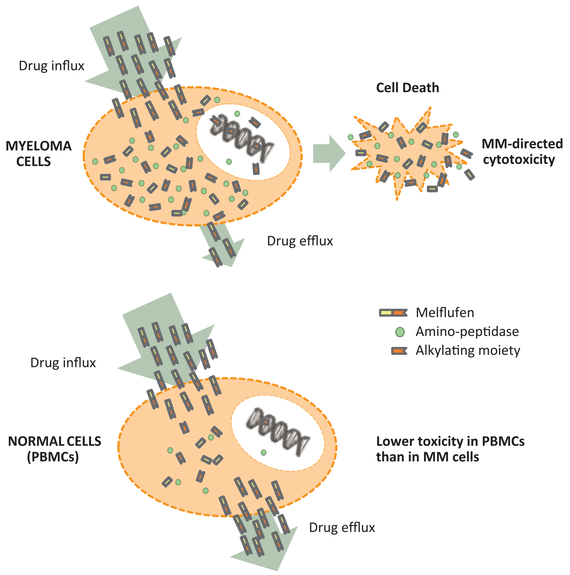
INTRODUCTION

Melflufen is a peptide conjugated alkylator and first in class peptidase enhanced compound that selectively targets multiple myeloma (MM). Melflufen in combination with dexamethasone (dex) has previously demonstrated encouraging activity in MM (Mateos *et al.* 2018*, Richardson *et al.* 2017**). Daratumumab and bortezomib are two drugs that are commonly used in the treatment of patients with MM. The phase 1/2 trial Anchor investigates the safety and efficacy of melflufen and dexamethasone in combination with either bortezomib or daratumumab in patients with relapsed-refractory multiple myeloma (RRMM).

BACKGROUND

Aminopeptidases are overexpressed in several cancers including multiple myeloma[1,2,3]. Melflufen acts as a substrate to aminopeptidases thus increasing the exposure of alkylating metabolites after melflufen treatment more than 50-fold compared to melphalan in MM[4]. The increase in cytotoxicity is selectively directed to MM cells and not to non-transformed cells such as peripheral blood mononuclear cells (PBMCs)[4,5,6]. In addition, resistance pathways associated with common alkylators are overcome by the increase in intracellular alkylator exposure after melflufen treatment[4,6].

Figure 1. By acting as a substrate for aminopeptidases, melflufen selectively targets MM cells



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* Mateos et al., The OP-106 Horizon Study: A preliminary report on efficacy and safety of melflufen in late stage relapsed-refractory myeloma patients refractory to pomalidomide and/or daratumumab, EHA 2018.
** Richardson et al., First report on OS and improved PFS in a completed phase 2 study (O-12-M1) of melflufen in advanced RRMM, ASH 2017.

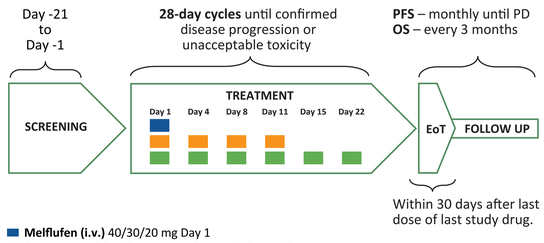
STUDY DESIGN

This is a phase 1/2 trial of melflufen and dex in combination with either bortezomib or daratumumab (NCT03481556). All patients must have had 1-4 prior lines of therapy and be refractory (or intolerant) to an immunomodulary agent (IMiD) or a proteasome inhibitor (PI) or both. In combination with bortezomib patients cannot be refractory to a PI and in combination with daratumumab patients cannot be previously exposed to any anti-CD38 monoclonocal antibody. Patients will be treated until documented disease progression or unacceptable toxicity. 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 where the primary objective is ORR (investigator assessed according to IMWG criteria).

Up to three 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 given i.v. on Day 1 of each 28-day cycle in the 2 different combinations.

Each regimen is evaluated separately.

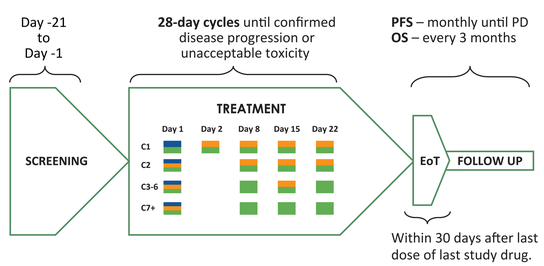
Figure 2. Melflufen and dexamethasone in combination with bortezomib



- **Melflufen (i.v.)** 40/30/20 mg Day 1
- **Bortezomib (SQ)** 1.3 mg/m^2 on Days 1, 4, 8 and 11
- **Dexamethasone (p.o)** 20* mg Days 1, 4, 8, 11 and 40** mg on Days 15 and 22

*12 mg and **20 mg for patients ≥ 75 years

Figure 3. Melflufen and dexamethasone in combination with daratumumab



- **Melflufen (i.v.)** 40/30/20 mg Day 1
- **Daratumumab (i.v.)** 16 mg/kg on Days 2, 8, 15 and 22 for C1, Days 1, 8, 15 and 22 for C2, Days 1 and 15 for cycles 3-6 and on Day 1 for C7+
- **Dexamethasone (p.o.*)** 40 mg p.o. weekly (20 mg p.o for ≥ 75 years)

*Oral dex may be substituted with i.v. dex prior to dara infusion only

MELFLUFEN AND DEX IN COMBINATION WITH BORTEZOMIB

At the time of the data cut-off (12 Nov 2018), 3 patients had been treated with 30 mg melflufen and dex in combination with bortezomib. Median age was 81 years with a median of 3 prior lines of therapy. All patients were relapsed-refractory and 2 out of 3 patients were last line refractory (disease progression while on therapy). All patients were ongoing with a median of 7 cycles on treatment.

Table 1. Patient characteristics

CHARACTERISTICS	MELFLUFEN+BORTEZOMIB+DEX (N=3)
Median age, years (range)	81 (70-82)
Median time since diagnosis, years (range)	6.9 (5.7-7.3)
Number of previous lines (range)	3 (2-4)
ISS at study entry, n (%)	
I	3 (100)
II	0
III	0
High-risk, cytogenetic risk factor by FISH*, n(%)	0
Median albumin, n (range)	3.9 (3.6-4.2)
High LDH (1.5 x UNL), n (%)	2 (67)
IMiD refractory, n (%)	3 (100)
Dara refractory, n (%)	1 (33)
Alkylator refractory, n (%)	1 (33)
Last line refractory, n (%)	2 (67)

*t(4;14), t(14;16), t(14;20), del(17/17p) or gain(1q)
Note: PI refractory status was an exclusion criterion in this trial arm.

SAFETY

No DLTs were observed at the 30 mg melflufen dose level. The regimen was well tolerated with clinically manageable G3/4 hematological AEs and the low number of non-hematological AEs was noteworthy. The highest cohort of melflufen 40 mg has been opened for enrolment.

Table 2. Treatment-related (possible/probable) G3/G4 AEs

CHARACTERISTICS	MELFLUFEN + DEX + BORTEZOMIB (N=3) GRADE 3 n (%)	GRADE 4 n (%)
Any treatment-related AE	2 (67)	0
Neutropenia	2 (67)	0
Thrombocytopenia	2 (67)	0
Pneumonia pneumococcal	1 (33)	0

One patient experienced 3 treatment-related SAEs (G2 pneumonia, G3 neutropenia, G3 pneumonia pneumococcal).

EFFICACY

All 3 patients were still ongoing with a median treatment duration of 5.8 months (2.3-6.1). The patients received a total of 17 cycles of treatment with a median of 7 (3-7). All 3 patients achieved partial response (PR) (Table 3).

Table 3. Response assessment

	ORR	CR	VGPR	PR	MR	SD	PD
Total (N=3)	100%	0	0	3*	0	0	0

* 1 unconfirmed PR

Figure 4. Swim-lane plot

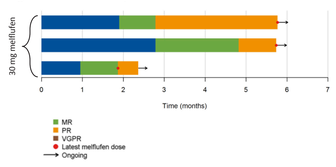
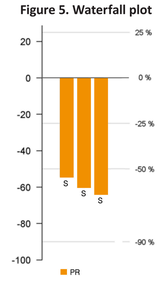


Figure 5. Waterfall plot



MELFLUFEN AND DEX IN COMBINATION WITH DARATUMUMAB

At the time of the data cut-off (12 Nov 2018), 9 patients had been treated with melflufen and dex in combination with daratumumab. Median age was 63 years with a median of 2 prior lines of therapy. No patient had achieved CR in any previous line of therapy, 67% were IMiD refractory and 56% were last line refractory (disease progression while on therapy). All patients were ongoing with a median of 4 cycles on treatment.

Table 4. Patient characteristics

CHARACTERISTICS	MELFLUFEN + DEX + DARA (N=9)
Median age, years (range)	63 (35-78)
Median time since diagnosis, years (range)	4.0 (1.8-6.6)
Number of previous lines (range)	2.0 (1-3)
ISS at study entry, n (%)	
I	8 (89)
II	0
III	1 (11)
High-risk cytogenetic risk factor by FISH*, n(%)	3 (33)
Median albumin (range)	4.1 (3.1-4.5)
High LDH (1.5 x UNL)	3 (33)
IMiD refractory, n (%)	6 (67)
PI refractory, n (%)	2 (22)
IMiD + PI refractory, n (%)	1 (11)
Alkylator, n (%)	2 (22)
Last line refractory, n (%)	5 (56)

*t(4;14), t(14;16), t(14;20), del(17/17p) or gain(1q)
Note: Daratumumab refractory status was an exclusion criterion in this trial arm.

SAFETY

Four* patients were treated with 30 mg melflufen and no DLTs were observed. Five patients were treated with 40 mg melflufen with no DLTs observed (6 patients on 40 mg melflufen required to confirm dose level). The combination of melflufen, dexamethasone and daratumumab was well tolerated with clinically manageable G3/4 hematological AEs and the low number of non-hematological AEs was noteworthy.

* First patient in the 40 mg cohort erroneously received 30 mg.

Table 5. Treatment-related (possible/probable) G3/G4 AEs

CHARACTERISTICS	MELFLUFEN+BORTEZOMIB+DEX (N=9) GRADE 3/4 n (%)	GRADE 4 n (%)
Any treatment-related AE	7 (78)	4 (44)
Neutropenia	6 (67)	0
Thrombocytopenia	3 (33)	1 (11)
Lymphocyte count decrease	3 (33)	3 (33)
White blood cell count decrease	1 (11)	1 (11)

No treatment-related SAEs were reported.

EFFICACY

All 9 patients were still ongoing with a median treatment duration of 3.9 months (0-6.9). They received a total of 39 cycles of treatment with a median of 4 (1-8). Best response for the 9 treated patients is described in Table 6.

Table 6. Response assessment

	ORR	CR	VGPR	PR	MR	SD	PD	N/A**
Total (N=9)	86%	0	4*	2	0	1	0	2

* 1 unconfirmed VGPR ** 2 pts were still in their first cycle of treatment and were therefore not evaluable for response

Figure 6. Swim-lane plot

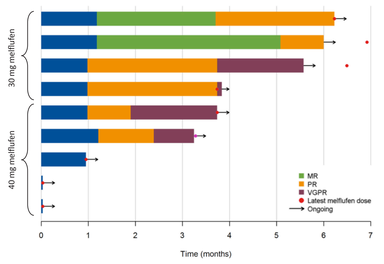
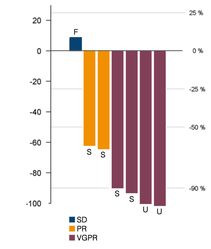


Figure 7. Waterfall plot



CONCLUSION

Based on interim data from Anchor in RRMM patients, the combination of melflufen and dexamethasone with either bortezomib or daratumumab is well tolerated. Early signs of efficacy are encouraging in both combinations with all patients still on treatment. The response rate was 100% in combination with bortezomib and 86% in combination with daratumumab with a median treatment duration of 5.8 and 3.9 months respectively. No DLTs have been observed across both regimens and dose levels. The 40 mg dose level is still recruiting. Grade 3/4 AEs were mostly hematological and all were clinically manageable. All patients across the two regimens responded to treatment but 1 (achieved SD after 1 cycle, still ongoing). All 3 patients treated with melflufen and dexamethasone in combination with bortezomib achieved PR. Out of the 9 patients treated with melflufen and dexamethasone in combination with daratumumab, 4 patients achieved VGPR, 2 PR, 1 SD and 2 patients were not yet evaluable for response at the time of the data cut-off. The study is ongoing.

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DISCLOSURES

Ludek Pour, Yvonne Efebera, Miquel Granell, Roman Hajek, Albert Oriol, Jacques Delaunay, Katell Le Du, Jean-Richard Eveillard, Lionel Karlin, Vladimir Maisnar, Joaquín Martinez-Lopez, María-Victoria Mateos, Jan Moreb, Vincent Ribrag, Paul G. Richardson, Jan Straub and Enrique M. Ocio are investigators in the Anchor trial. Paul G. Richardson and María-Victoria Mateos are expert advisors to Oncopeptides AB. Catriona Byrne, Christian Jacques and Hanan Zubair are working for Oncopeptides AB.