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

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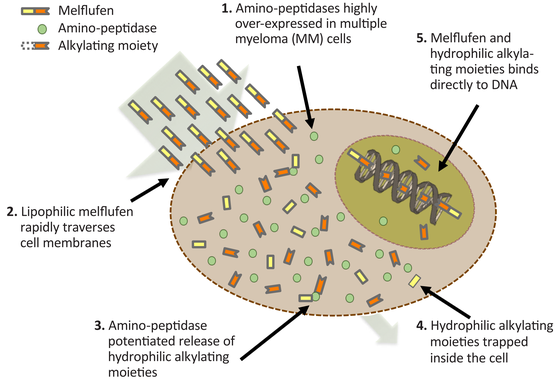
BACKGROUND

Following treatment and failure with IMIDs and PIs, patients refractory to pomalidomide and daratumumab have few remaining treatment options. Previously, melflufen has been studied in 45 relapsed-refractory multiple myeloma (RRMM) patients that had been exposed to IMiDs and PIs and progressed while on their last line of therapy or within 60 days of last dose, showing an ORR of 31%, a median PFS of 5.7 months and a median OS of 20.7 months (O-12-M1). Here we further evaluate the benefit of melflufen in heavily pretreated and highly refractory patients that have also become refractory to pomalidomide and/or daratumumab.

Melflufen is an alkylating peptide belonging to the novel class of Peptidase Enhanced Compounds (PEnCs) targeting the MM transformation process through aminopeptidase potentiation. Aminopeptidases are key for the transformation process in myeloma and are involved in tumor migration, cell proliferation and angiogenesis, and are heavily over-expressed in MM cells. Melflufen selectively targets MM cells through aminopeptidase-driven accumulation, where in vitro experiments show a 50-fold enrichment of alkylating metabolites in MM cells. The enrichment results in selective cytotoxicity (increased on-target cell potency and decreased off-target cell toxicity), overcomes resistance pathways of existing myeloma treatments (including alkylators) and demonstrates strong anti-angiogenic properties.

Figure 1. Melflufen is an alkylating peptide, targeting the MM transformation process



Peptidase enhanced activity in MM cells results in:

- Approx. 50-fold higher intra-cellular exposure in MM cells[1,5]
- Approx. 50-fold higher anti-MM potency[1,2,5]
- Alkylation of DNA with limited or no induction of DNA repair[3,5]
- Strong anti-angiogenic properties[1,4,5]
- Therapeutic index of 20x – 40x (MM cells compared with peripheral blood mononuclear cells)[1,5]

[1] Chauhan et al. (2013) Clin Cancer Res 19(11): 3019-303. [2] Wickstrom et al. (2008) Invest New Drugs 26(3): 195-204.
[3] Ray et al. (2016) Br J Hematol 174: 397-409. [4] Stresе et al. (2013) Biochem Pharmacol 86: 888–895.
[5] Wickström et al. (2017) Oncotarget, 2017, Vol 8. (No 39), PP: 66641-66655.

METHODS

Melflufen 40 mg is given i.v. over 30 minutes on Day 1 of each 28-day cycle, with dexamethasone 40 mg weekly, to RRMM patients refractory to pomalidomide or daratumumab or both. Patients must have measurable disease and at least 2 prior lines of therapy, including an IMiD and a PI (NCT02963493). Response is investigator assessed at each cycle by IMWG criteria. The primary objective is overall response rate (ORR). Patients receive treatment until there is documented disease progression, unacceptable toxicity or consent withdrawal.

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BASELINE CHARACTERISTICS AND DISPOSITION

62 patients were included at data cut-off May 10, 2018. The median follow-up time was short at 4.3 months. Median time since initial diagnosis was 6.1 years (0.7–16). The median number of prior therapies was 5.5 (2–12). 46% of patients were ISS stage 3 and 54% had high-risk cytogenetics (including 15% with deletion 17p). 55 (89%) patients were double-refractory (1 IMiD+1 PI), 62 (100%) patients were refractory to pomalidomide or daratumumab and 35 (56%) were refractory to pomalidomide and daratumumab. Almost 60% of the patients were refractory to an alkylator.

Table 1. Baseline characteristics (N=62)

CHARACTERISTICS	
Median age, years (range)	62.5 (41-82)
Median time since diagnosis, years (range)	6.1 (0.7-16)
Number of previous lines (range)	5.5 (2-12)
ISS at study entry, n (%)*	
I	16 (28)
II	15 (26)
III	26 (46)
ECOG performance status, n (%)	
0	15 (24)
1	38 (61)
2	9 (15)
High-risk, cytogenetic risk factor by FISH**, n (%)	25 (54)

* Missing data for 5 patients
** {t(4;14), t(14;16), t(14;20), del(17/17p) or gain(1q)}; missing data for 16 patients

Table 2. Characteristics of prior lines of therapy (N=62)

CHARACTERISTICS	n (%)
Pomalidomide or daratumumab refractory	62 (100)
Pomalidomide and daratumumab refractory	35 (56)
Double refractory (1 IMiD+1 PI)	55 (89)
Last line refractory	60 (98)
Received triple combination therapy in last line	28 (46)
Received regimens containing antibodies (CD38/BCMA/CS-1), carfilzomib or pomalidomide in last line	47 (77)
Double + daratumumab + last line refractory	36 (58)
Alkylator refractory	36 (58)

The trial is still accruing patients. Treatment was ongoing in 21 (34%) patients. Main reason for treatment discontinuation was progression of disease (47%), adverse events (15%) or physician decision (3%). One patient discontinued treatment at their own request.

Table 3. Patient disposition (N=62)

		DISCONTINUED TREATMENT			
	ON TREATMENT	PD	AEs	PHYSICIAN'S DECISION	PATIENT'S REQUEST
n (%)	21 (34)	29 (47)	9 (15)	2 (3)	1 (2)

RESULTS – EFFICACY

At the cut-off date, a total of 188 doses of melflufen had been given. 49 (79%) patients had completed at least two cycles of melflufen. Median number of cycles was 2 (1–11).

56 patients had received at least one dose of melflufen and were evaluable for response. Preliminary ORR was 32% and clinical benefit rate, MR or better, was 39%. One patient had achieved a CR. Responses were observed in all the subgroups of the patients. Of note is that 84% of the patients achieved disease stabilization (SD or better). Subgroup analysis suggests that response does not vary across refractory subsets.

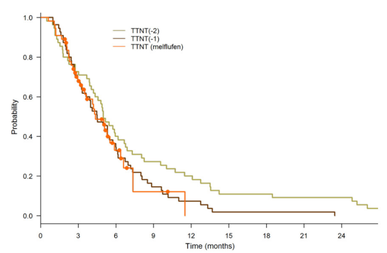
RESULTS – EFFICACY

Table 4. Overall response rate (N=56)

N	ORR	CBR	CR	VGPR	PR	MR	SD	PD
Total, N=56	32.1%	39.3%	2%	9%	21%	7%	45%	16%
ISS stage III, N=24	25.0%	29.2%	4%	4%	17%	4%	50%	21%
HR cytogenetics, N=22	27.3%	27.3%	5%	9%	14%	0%	55%	18%
Pom but not dara refractory, N=20	40.0%	55.0%	5%	5%	30%	15%	40%	5%
Dara but not pom refractory, N=6	66.7%	66.7%	0%	17%	50%	0%	33%	0%
Pom + dara refractory, N=30	20.0%	23.3%	0%	10%	10%	3%	50%	27%
ISS stage I + II, N=13	38.5%	38.5%	0%	15%	23%	0%	54%	8%

In the time-to-next-treatment (TTNT) graph (Figure 2) the same patient group is followed across two previous lines of therapy as well as the line of therapy with melflufen; TTNT(-2), TTNT(-1) and TTNT(melflufen) respectively. Myeloma patients usually see a deterioration of TTNT (and PFS) from one line to the next with a shorter duration of treatment and remission[1,2,3]. Analyzing the two previous lines of therapy for these patients show an increase of 45 % of the relative risk to get to a new treatment from TTNT(-2) to TTNT(-1). Time to next treatment between the most recent previous line and melflufen are similar, suggesting that patients will stay at least as long on treatment with melflufen compared to the last prior treatment. In TTNT(-1), 46% of patients were treated with triplet or quadruplet combination therapies and 77% of patients received anti-CD38, anti-CS-1, anti-BCMA, pomalidomide or carfilzomib.

Figure 2. Time-to-next-treatment (N=55)



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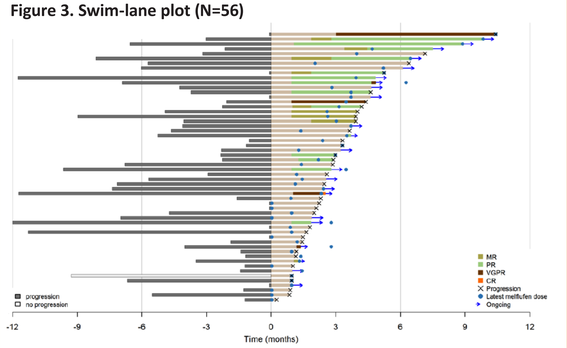
2 Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia 2012; 26: 149–157.
3 Kumar SK, Therneau TM, Gertz MA, Lacy MQ, Dispenzieri A, Rajkumar SV et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc 2004; 79: 867–874.

The swim-lane graph (Figure 3) represents at left axis duration on treatment of the last line of therapy prior to melflufen treatment and on right axis duration on melflufen treatment with responses, level of response and time of progression (if present) by patient. Preliminary data suggest longer treatment is associated with deeper response.

Figure 3. Swim-lane plot (N=56)



RESULTS – SAFETY AND TOLERABILITY

Treatment-emergent AEs, regardless of grade and relationship, were reported in 60 (97%) patients. Treatment-related grade 3/4 AEs were reported in 48 (77%) patients with the majority being hematologic (Table 5). Treatment-related non-hematologic grade 3/4 events were rare, with infections in only 6% of patients. Of those, no single AE was reported in more than 1 patient each. Only one case of treatment-related bleeding has been reported (grade 3). No treatment-related deaths have been reported.

Table 5. Treatment-related G3/4 AEs occurring in ≥ 2 patients (N=62)

	GRADE 3 OR 4, n (%)	GRADE 4, n (%)
Any treatment-related AE	**48 (77)**	**32 (52)**
Blood and lymphatic system disorders	**46 (74)**	**31 (50)**
Neutropenia	37 (60)	21 (34)
Thrombocytopenia	37 (60)	25 (40)
Anemia	19 (31)	1 (2)
Leukopenia	4 (6)	3 (5)
Lymphopenia	4 (6)	1 (2)
Febrile neutropenia	4 (6)	1 (2)

The proportion of patients with at least one melflufen-related SAE was 13 (21%). The most frequently occurring SAEs were febrile neutropenia in 4 (6%) patients and pneumonia in 2 (3%) patients.

CONCLUSION

Patients refractory to pomalidomide and daratumumab after failing IMiDs and PIs have few remaining treatment options.

- Analysis of the preliminary efficacy results showed an ORR of 32% and a CBR of 39% in a population with a median of 5.5 prior lines of therapy, 54% with high-risk cytogenetic and 46% of ISS stage III.
  - Subgroup analysis suggests that response does not vary across refractory subsets but rather with the underlying disease and health status of the patient (in line with the observation made in the O-12-M1 study).
- Time-to-next-treatment was maintained compared to the previous line of therapy without the deterioration normally seen in myeloma patients.
  - In the previous line of therapy, 75% of the patients were treated with antibody-based therapies or 2nd/3rd generation PIs and IMiDs, and 46% received triple combination therapies.
- Melflufen showed an acceptable safety profile. Thrombocytopenia and neutropenia were the most frequent AEs and non-hematologic AEs were infrequent.

Melflufen is currently evaluated in OP-103 OCEAN, a phase 3 head-to-head comparison of melflufen+dex against pomalidomide+dex (NCT03151811). Additionally, melflufen+dex in combination with either bortezomib or daratumumab is investigated in OP-104 ANCHOR phase 1/2 trial (NCT03481556).

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DISCLOSURES

María-Victoria Mateos, Albert Oriol, Alessandra Larocca, Paula Rodríguez Otero, Jan S. Moreb, Joan Bladé, Hani Hassoun, Michele Cavo, Adrián Alegre, Amitabha Mazumder, Christopher Maisel, Agne Paner, Nashat Gabrail, Kathleen Halka, Jeffrey Zonder, Enrique M. Ocio and Paul G. Richardson are investigators in the Horizon trial. Paul G. Richardson and María-Victoria Mateos are expert advisors to Oncopeptides AB. Catriona Byrne, Johan Harmenberg, Eva Nordström, Sara Thuresson and Hanan Zubair are working for Oncopeptides AB.