Melflufen therapy for Relapsed Refractory Multiple Myeloma (RRMM) patients Refractory to Daratumumab and/or Pomalidomide; an early report on efficacy

HORIZON

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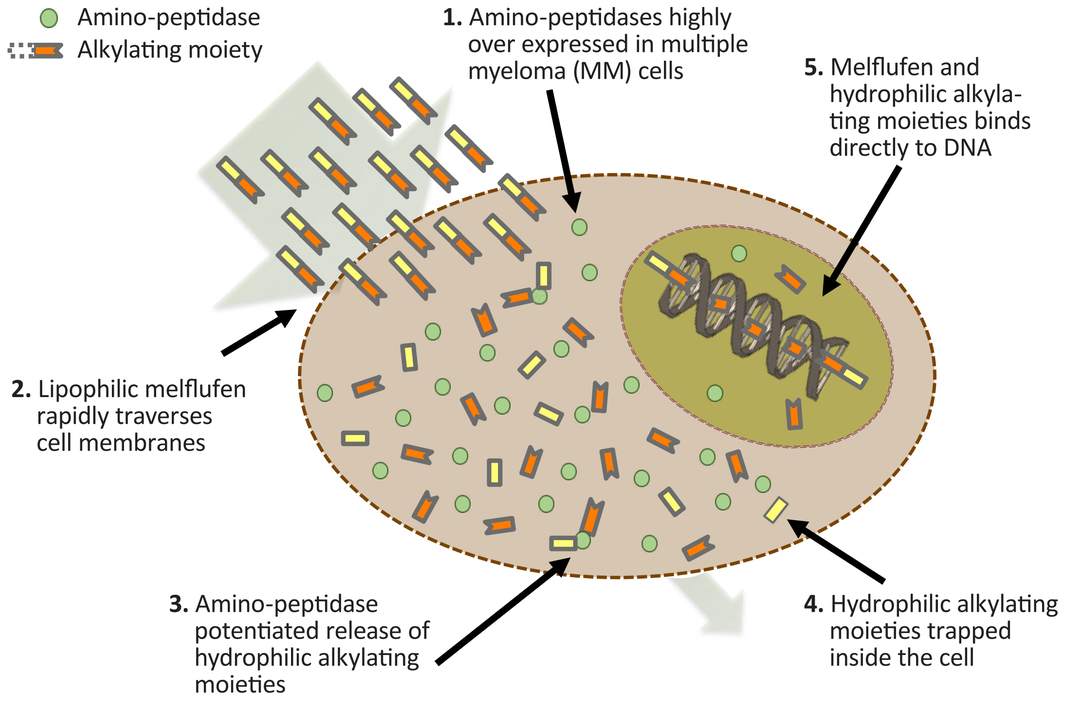
BACKGROUND

Melflufen is a next generation alkylator, belonging to the novel class of Peptidase Enhanced Cytotoxics (PEnCs), designed for efficient targeting of tumor cells with a unique mechanism of action. Melflufen provides a peptidase enhanced therapy with an alkylating payload and triggers fast, robust and irreversible DNA damage. The lipophilicity of melflufen leads to rapid and extensive distribution into cells where it is readily metabolized by intracellular peptidases (often over-expressed in malignant cells) into hydrophilic alkylating metabolites leading to 50-fold enrichment of these metabolites in multiple myeloma (MM) cells. In addition, melflufen has potent anti-angiogenic properties.

Melflufen is a peptidase enhanced therapy with an alkylating payload



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. Wickström et al. (2008) Invest New Drugs 26(3): 195-204.
3. Ray et al. (2016) Br J Hematol 174: 397-409.
4. Strese et al. (2013) Biochem Pharmacol 86: 888–895.
5. Wickström et al. (2017) Oncotarget E-pub June 08.

METHODS

Melflufen 40 mg is given i.v. on Day 1 of each 28-day cycle, with dexamethasone 40 mg weekly, in relapsed-refractory multiple myeloma (RRMM) patients refractory to pomalidomide and/or daratumumab with 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 or unacceptable toxicity.

BASELINE CHARACTERISTICS AND DISPOSITION

The study was initiated in Dec 2016. 47 patients were included at data cut-off 6 Feb 2018. The median time from initial diagnosis was 6.6 years (0.7–16). The median number of prior therapies was 6 (3–12). 37 (86%) patients were double-refractory (IMiD + PI), 27 (60%) were refractory to pomalidomide and daratumumab.

Table 1. Baseline characteristics (N=47)

CHARACTERISTICS	
Median age, years (range)	62 (41-82)
Median years since diagnosis, years (range)	6.6 (0.7–16)
Number of previous lines (range)	6 (3-12)
ISS at study entry, n (%)	
I	9 (19)
II	10 (21)
III	22 (47)
Unknown	3 (6)
Missing	3 (6)
ECOG performance status, n (%)*	3 (6)
0	10 (21)
1	29 (62)
2	6 (13)
High risk, cytogenetic risk factor by FISH**, n (%)	11 (23)

* 1 unknown
* * t(4;14), t(14;16), del(17/17p)

Table 2. Characteristics of prior lines of therapy (N=45)*

CHARACTERISTICS	n (%)
Double-refractory (IMiD + PI)	37 (82)
Alkylator exposed	41 (91)
Alkylator refractory	25 (56)
Last line refractory (progressed while on therapy or within 60 days of last dose)	44 (98)
Pomalidomide refractory	43 (96)
Daratumumab refractory	31 (69)
Pomalidomide and Daratumumab refractory	27 (60)

* Data missing for 2 patients

Treatment was ongoing in 16 (34%) patients. 4 (9%) patients discontinued treatment due to adverse events (AEs), 23 (49%) due to disease progression, 2 (4%) patients due to physician´s decision and 2 (4%) patients due to other reasons.

Table 3. Patient disposition (N=47)

	DISCONTINUED TREATMENT			
ON TREATMENT	AEs	PD	PHYSICIAN'S DECISION	OTHER
16	4	23	2	2

RESULTS – EFFICACY

At the time of data cut-off, a total of 126 doses of melflufen had been given. 35 (74%) patients had completed at least two cycles of melflufen. Median number of cycles was 2 (1–9).

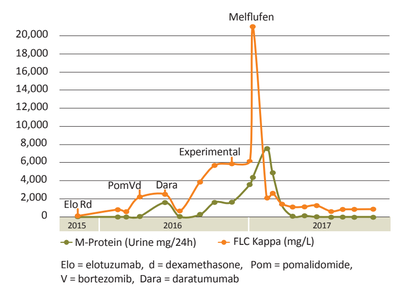
Patient responses were assessed by the investigators and the overall response rate (ORR) was 28% among 43 patients who had received at least one dose of melflufen and had an assessment of response (adjusted ITT). This includes 2 patients with a very good partial response (VGPR) and 10 patients with a partial response (PR). 3 additional patients achieved minimal response (MR) for a clinical benefit rate (CBR) of 35% (Table 4).

Table 4. Overall response rate (N=43)*

N	PD	SD	MR	PR	VGPR	ORR	CBR
Adjusted ITT, n (%)	8 (19)	20 (47)	3 (7)	10 (23)	2 (5)	28%	35%

* Myeloma response assessment available for 43 patients.

Figure 1. Patient case study

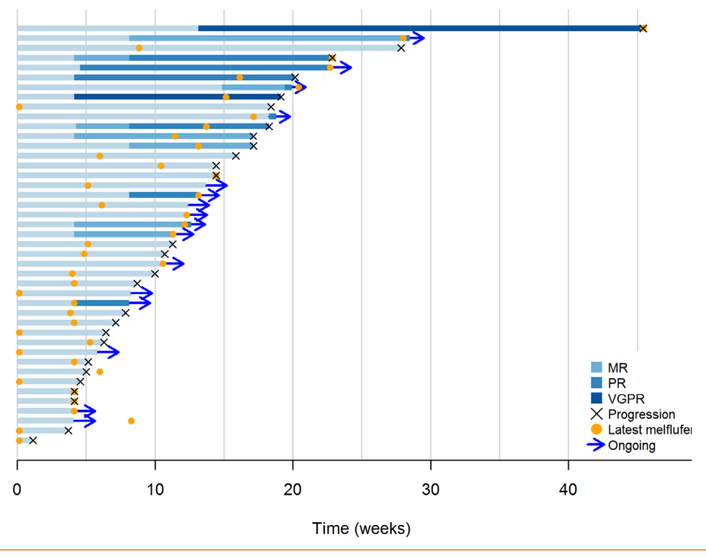


Elo = elotuzumab, d = dexamethasone, Pom = pomalidomide, V = bortezomib, Dara = daratumumab

42-year old man with ISS stage 3, MM diagnosed 2007. No detectable serum M-protein. Nine prior lines of therapy including ASCT X 2 and Allo-SCT. Refractory to R, Elo, V, Pom, Dara and an experimental drug. The patient only achieved PD to the last 4 lines of therapy.

Following 5 cycles of melflufen, the urinary M-protein was undetectable (Figure 1). The patient has received 9 cycles of melflufen and achieved VGPR.

Figure 2. Swim-lane plot (N=43)



RESULTS – SAFETY AND TOLERABILITY

Treatment-emergent AEs, regardless of grade, were reported in 41 patients (87%). Treatment-related grade 3/4 AEs were reported in 31 (66%) patients; with those occurring in ≥2 patients including thrombocytopenia in 25 (53%) patients, neutropenia in 21 (45%) and anemia in 10 (21%) (Table 5).

Table 5. Treatment-related G3/4 AEs occurring in ≥ 2 patients (N=47)

	GRADE 3 OR 4, n (%)	GRADE 4, n (%)
Any treatment-related AE	31 (66)	19 (40)
Blood and lymphatic system disorders	28 (60)	19 (40)
Thrombocytopenia	25 (53)	16 (34)
Neutropenia	21 (45)	10 (21)
Anemia	10 (21)	0
Lymphopenia	4 (9)	1 (2)
Leukopenia	3 (6)	3 (6)
Febrile neutropenia	2 (4)	0
Hemolytic anemia	2 (4)	0

Table 6. Melflufen-related SAEs (N=47)

	n (%)
Any melflufen-related SAE	8 (17)
Febrile neutropenia	3 (6)
Pyrexia	1 (2)
Hypercalcemia	1 (2)
Soft tissue infection	1 (2)
Resparatory tract infection	1 (2)
Sepsis	1 (2)

22 patients (47%) experienced a treatment-emergent SAE irrespective of relationship to study treatment. 8 patients experienced a melflufen-related SAE (Table 6).

CONCLUSION

Following treatment with IMiDs and PIs, patients refractory to pomalidomide and daratumumab have little to no treatment options. Melflufen, a peptidase enhanced therapy with an alkylating payload, demonstrates activity in a heavily refractory population with a median of 6 prior lines of therapy. The efficacy results in this interim analysis are encouraging with an ORR of 28% (including 2 VGPRs) and a CBR of 35%. Melflufen showed a good safety and tolerability profile. Thrombocytopenia and neutropenia were, as expected, the most common AEs, and non-hematologic AEs were infrequent. Melflufen is further evaluated in this ongoing study and the phase 3 study OCEAN (NCT03151811) and the phase 1/2 combination study ANCHOR (NCT03481556).

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DISCLOSURES

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

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