First report on OS and improved PFS in a completed Phase 2 Study (O-12-M1) of melflufen in advanced RRMM

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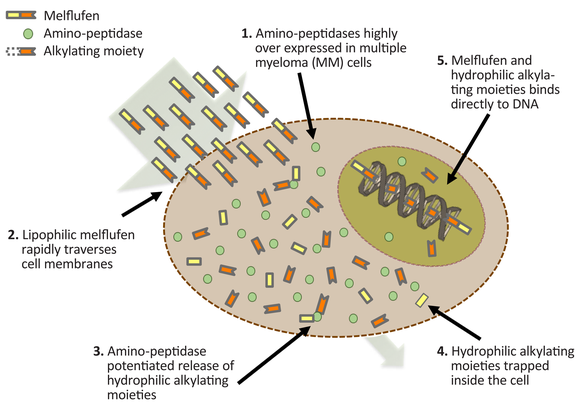
BACKGROUND

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 (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 potentiated therapy with an alkylating payload



Peptidase potentiated 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 20–40 (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.] Strese et al. (2013) Biochem Pharmacol 86: 888–895.
[5.] Wickström et al. (2017) Oncotarget E-pub June 08.

METHODS

Melflufen 40 mg was given i.v. on Day 1 of each 28-day cycle with dexamethasone 40 mg weekly for up to 8 cycles, or longer at the discretion of PI and sponsor. Patients had relapsed-refractory MM (RRMM) with measurable disease and ≥2 prior lines of therapy including lenalidomide and bortezomib and PD on or within 60 days of completion of last therapy (NCT01897714). Response was investigator assessed at each cycle by IMWG criteria. After disease progression (PD) or start of subsequent therapy, patients were followed for survival every 3 months for up to 24 months.

ASH abstract no. 3150

BASELINE CHARACTERISTICS AND DISPOSITION

Enrollment was closed in Dec 2016. Forty-five patients were included with data cut-off of 9 Nov 2017. Patient characteristics are described in Table 1.

Table 1. Baseline characteristics

	N = 45
Median age, years (range)	66 (47-78)
Years since diagnosis, median (range)	5.1 (1.4 – 21.2)
Number of previous lines of therapy, median (range)	4 (2-14)
ISS, stage at study entry, n (%)	
I	15 (33)
II or III	27 (60)
Unknown	3 (7)
ECOG performance status, n (%)	
0	23 (51)
1	22 (49)
2	0
High-risk cytogenetic risk factors by FISH, n (%)*	17 (38)
Double-refractory, n (%) (IMiD +PI)	29 (64)
Last line refractory, n (%)**	42 (93)
Pomalidomide refractory, n (%)	20 (44)
Refractory to an alkylator (melphalan, cyclophosphamide or bendamustine), n (%)	24 (53)

* t(4;14), t(14;16), t(14;20), del(17/17p) or gain(1q)
** 3 patients had PR or better in the last line of therapy and PD within 180 days of last dose

At the time of data cut-off, one patient was ongoing and 44 patients had discontinued therapy; 18 discontinued due to AEs, 13 due to PD, 2 died, and 9 completed treatment as planned (8 cycles). Two patients were discontinued due to other reasons (Table 2).

Table 2. Disposition

		DISCONTINUED TREATMENT				
	ONGOING	AEs	PD	DEATH	OTHER	COMPLETED PLANNED 8 CYCLES
N = 45	1	18	13	2	2	9

RESULTS – TREATMENT

To date, a total of 227 doses of melflufen were administered with a median of 5 cycles (1–14). Median treatment duration was 16 weeks (2–57). Fourteen (31%) patients had a dose reduction and 23 (51%) patients had a dose delay of 7 days or more.

Table 3. Treatment overview

	MEDIAN NUMBER OF CYCLES*	DOSE REDUCTIONS	DOSE INTERRUPTIONS (≥1 WEEK DELAY)	PLATELET TRANSFUSION	RBC** TRANS-FUSION	G-CSF**
n of patients (%)	5	14 (31)	23 (51)	20 (44)	25 (56)	15 (33)

* One patient is still ongoing on treatment
** RBC = red blood cell, G-CSF = Granulocyte colony-stimulating factor

RESULTS – EFFICACY

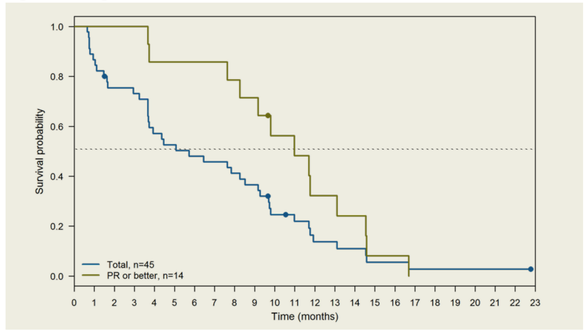
Patient responses were assessed by the investigators and the overall response rate (ORR) was 41% among 34 efficacy evaluable patients (≥2 doses of melflufen with baseline and follow-up assessments) including very good partial response (VGPR) in 4 (12%) patients and partial response (PR) in 10 (29%). Seven (21%) additional patients achieved minimal response (MR) for a clinical benefit rate (CBR) of 62%. ORR in all treated patients (ITT) was 31% and CBR 49%.

Table 4. Overall response rate (efficacy evaluable and all treated patients)

N	PD	SD	MR	PR	VGPR	ORR	CBR
ITT (N = 45)*	7	12	8	9	5	31%	49%
Efficacy evaluable (N = 34)	1	11	8	9	5	41%	65%

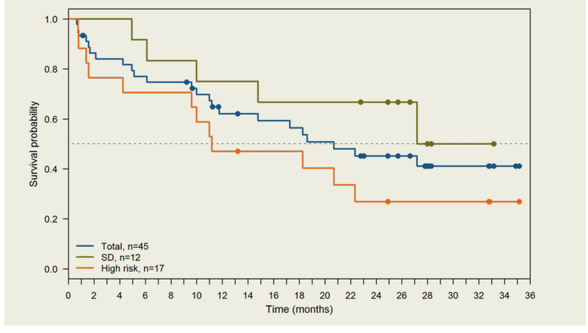
* 4 patients did not have a response assessment

Figure 1. Progression-free survival



The median progression free survival (PFS) in all treated patients was 5.7 months (95% CI:3.7 – 9.3) based on 41 events in 45 patients. In patients with ≥PR, the median PFS was 11.7 months (95% CI: 9.8 – ∞, event rate 93%) (Figure 1). The median DOR was 8.4 months (95% CI: 5.8 – ∞).

Figure 2. Overall survival



The median overall survival (OS) in all treated patients was 20.7 months (95% CI: 11.8 – ∞) based on 23 events in 45 patients. Of note, among the 12 patients that achieved stable disease (SD), the median OS was 30.2 months (95% CI: 14.8 – ∞, event rate 42%), and in patients with high-risk cytogenetics the median OS was 11.2 months (10.0 – ∞, event rate 71%) (Figure 2). Fourteen (31%) patients were alive 24 months after end of treatment, including 4 patients with high-risk cytogenetics.

RESULTS – SAFETY AND TOLERABILITY

All patients experienced an AE irrespective of grade and relationship to melflufen. Melflufen-related G3 or G4 AEs were experienced among 37 patients (82%). SAEs were experienced by 17 (38%) patients and were melflufen-related in 12 (27%) patients.

Table 5. Grade 3/4 melflufen-related AEs in at least 2 patients

	G3 n (%)	G4 n (%)
Any melflufen-related	**35 (78)**	**19 (42)**
Blood and lymphatic system disorders	**31 (69)**	**19 (42)**
Thrombocytopenia	9 (20)	17 (38)
Neutropenia	12 (27)	11 (24)
Anaemia	19 (42)	0
Lymphopenia	2 (4)	1 (2)
Febrile neutropenia	2 (4)	0
General disorders	**7 (16)**	**0**
Asthenia	2 (4)	0
Fatigue	2 (4)	0
Pyrexia	2 (4)	0
Investigations	**5 (11)**	**0**
Neutrophil count decreased	4 (9)	0
White blood cell count decreased	2 (4)	0
Infections and infestations	2 (4)	0
Pneumonia	2 (4)	0

Table 6. Melflufen-related SAEs

SAE TERM	NUMBER OF PATIENTS (%)
Any melflufen-related	**12 (27)**
Pneumonia	4 (9)
Neutropenia	2 (4)
Febrile neutropenia	2 (4)
Pyrexia	2 (4)
Diarrhoea	1 (2)
Escherichia sepsis	1 (2)
Myelodysplastic syndrome	1 (2)
Pneumonitis	1 (2)
Subdural haematoma	1 (2)
Thrombocytopenia	1 (2)

CONCLUSION

Treatment with melflufen, a peptidase enhanced alkylator, shows long-term benefit in late-stage RRMM patients where conventional therapies have failed. The median PFS of 5.7 months is encouraging in this heavily pre-treated population. The median OS of 20.7 months, along with the extended median OS of 30.2 months in patients only achieving SD as best response, warrants further investigation as it suggests benefit regardless of depth of response, and that treatment with melflufen in this advanced patient population enables subsequent treatments. The treatment was well tolerated with reversible and clinically manageable hematologic toxicity as the most common AE type. Non-hematologic AEs were infrequent. Melflufen is further evaluated in the ongoing studies OCEAN (phase 3, NCT03151811) and HORIZON (phase 2, abstract no. 1841).

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DISCLOSURES Paul G. Richardson, Sara Bringhen, Peter Voorhees, Torben Plesner, Claudia Paba-Prada, Jeffrey Zonder and Ulf-Henrik Mellqvist are investigators in the O-12-M1 trial. Paul G. Richardson is a member of the Oncopeptides AB advisory committee. Catriona Byrne, Johan Harmenberg, Jakob Lindberg, Eva Nordström and Hanan Zubair are working for Oncopeptides AB.