EFFICACY OF MELFLUFEN, A PEPTIDASE POTENTIATED THERAPY, AND DEXAMETHASONE IN AN ONGOING OPEN-LABEL PHASE 2 STUDY IN PATIENTS WITH RELAPSED AND RELAPSED-REFRACTORY MULTIPLE MYELOMA (RRMM)

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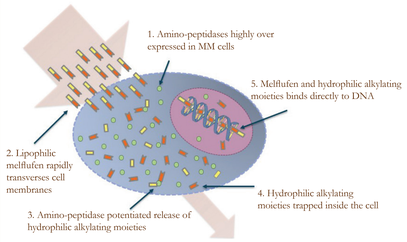
Background

- Melflufen is a peptidase potentiated therapy with an alkylating payload designed for efficient targeting of tumor cells. Melflufen is a highly potent anti-angiogenic compound, triggers rapid, robust, and irreversible DNA damage and exerts it cytotoxicity through alkylation of DNA[1,2,3,4]
- The lipophilicity of melflufen leads to rapid and extensive distribution into tissues and cells, where it binds directly to DNA or is readily metabolized by intracellular peptidases (often over-expressed in malignant cells) into hydrophilic alkylating metabolites
- The delivery of alkylating metabolites - potentiated by peptidase activity - to tumor cells in cell culture, results in that melflufen exerts a 50-fold higher anti-tumor potency as well as a 50-fold higher intra-cellular concentration of alkylating moieties compared to melphalan, but with a similar safety profile[1,2]

Melflufen - Mechanism of Action



Peptidase potentiated activity in multiple myeloma (MM) cells results in:

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

Methods

- Melflufen is evaluated in combination with dexamethasone (dex) 40 mg weekly in an ongoing Phase 2 study (NCT01897714)
- RRMM patients with measurable disease and at least 2 prior lines of therapy, including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of last therapy are eligible
- Phase 1 established the maximum tolerated dose (MTD) of melflufen to be 40 mg every 3 weeks in combination with weekly 40 mg dex
- The primary objective of Phase 2 is the overall response rate (ORR) and safety of the MTD in a total of 55 evaluable patients. Response is investigator assessed at the end of each cycle by IMWG criteria
- This poster presents the Phase 2 data as of 23 October 2015

Results - Baseline Characteristics

- Thirty-eight patients included in the trial with a median age of 65 years (47-76)
- Median 5 years (1-15) since diagnosis and a median of 4 (2-9) prior lines of therapy
- 62% were double-refractory to an IMiD and PI and 57% were refractory to an alkylator
- 66% had ISS stage II-III and 26% had high risk cytogenetic risk factors by FISH, 47% standard risk and 27% were not done/unknown

Table 1. Baseline Characteristics

Characteristics	Total	Efficacy evaluable (n=27)	
	N = 38	Responders (n=11)	Non-responder (n=16)
Median age, years (range)	65 (47-76)	68 (48-74)	63 (47-73)
≥75 years, n (%)	2 (5)	0	0
Years since diagnosis, median (range)	5** (1-15)	7 (4-15)*	5 (1-14)
Number of previous lines of therapy, median (range)	4 (2-9)	4 (3-7)	3 (2-6)
ISS stage, n (%)			
I	11 (29)	5 (45)	6 (38)
II or III	25 (66)	5 (45)	10 (63)
Unknown	2 (5)	1 (9)	0
ECOG performance status, n (%)			
0	16 (42)	6 (55)	8 (50)
1	20 (53)	5 (45)	6 (38)
Not done	2 (5)	0	2 (13)
Cytogenetic risk factor by FISH, n (%)			
High [del(17)p13, t(4;14)(p16;q32) or t(14;16)(q32;q23)]	10 (26)	2 (18)	5 (31)
Standard	18 (47)	5 (45)	8 (50)
Not done	9 (24)	3 (27)	3 (19)
Unknown	1 (3)	1 (9)	0
Double-refractory (IMiD and PI)*, n (%)**	23* (62)	5 (45)	11 (69)
Refractory to melphalan, cyclophosphamide or bendamustine, n (%)	21* (57)	8 (73)	5 (55)

*Missing information on one patient **Missing information on two patients ***16 patients (59%) were double-refractory in the efficacy evaluable population (N=27)

Table 2. Disposition (N=38)

	Number of patients	Reported reason for discontinuation	n
Ongoing on treatment	10		
Discontinued treatment	28	Completed study (≥ 8 cycles of therapy)	2
		Adverse Events*	15
		Death	2
		Progressive disease	8
		Cachexia in progressive disease	1
Discontinued study in follow-up	11	Lost to follow-up	1
		Progressive disease	1
		Withdrew consent	1
		Death	8
Remain alive in follow-up	17		

*Some patients have discontinued due to more than one adverse event and are therefore included in more than one subcategory: thromobcytopenia 9, neutropenia/febrile neutropenia 3, fever 2, anemia 2, hypercalcemia/renal insufficiency 1, unrelated infection 1, unknown 2.

Results - Treatment and Disposition

- As of 23 October 2015, 38 patients had received 162 doses of melflufen 40 mg
- The median number of cycles initiated was 3 (range 1-13) and the median duration of treatment was 13 weeks (2-51)
- The mean dose intensity was 96% (range 77-100)
- Ten patients were still in treatment, 2 had completed treatment and 26 patients discontinued from treatment (15 due to AEs, 8 due to PD, 2 deaths and 1 for other reasons), see Table 2
- Twenty-seven patients were still in the study (10 patients on treatment and 17 in follow-up), while 11 patients were off study (8 patients due to death, 1 due to PD, 1 withdrew consent and 1 lost in follow-up)

Results - Efficacy

- Twenty-seven patients were evaluable for response (protocol defined as ≥2 doses of melflufen with baseline and follow-up response assessments)
- Two patients achieved very good partial response (VGPR) and 9 achieved partial response (PR) for an ORR of 41%. Four additional patients achieved minimal response (MR) for a clinical benefit rate (CBR) of 56% (Figure 1 and Table 3)
- Similar ORR were seen in PI-refractory (35%), IMiD-refractory (35%), alkylator-refractory (57%), double-refractory (31%) and triple-refractory (40%) patients. (Table 4)
- The median progression free survival (PFS) was 9.4 months (95% CI: 3.7 to ∞) based on 13 events in 27 patients. For all treated patients the PFS is 4.5 months (95% CI: 3.7 to ∞) (Figure 2)
- The median duration of response (DOR) was 9.6 months (95% CI: 7.1 to ∞) based on 4 events in 11 patients (Figure 3)
- Eleven patients were not evaluable for response due to rapid early progression (7), early termination due to adverse events (3) or too early to assess (1), but are presented in Table 3 for transparency

Table 3. Response Rate (Response evaluable patients)

Status 23 October	n	VGPR	PR	MR	SD	PD	ORR	CBR
Evaluable ≥ 2 cycles	27	2	9	4	11	1	41%	56%
All treated	38	2	9	6	12	9	29%	45%

Figure 1. Best change from baseline in para-protein in efficacy evaluable patients (n=27)

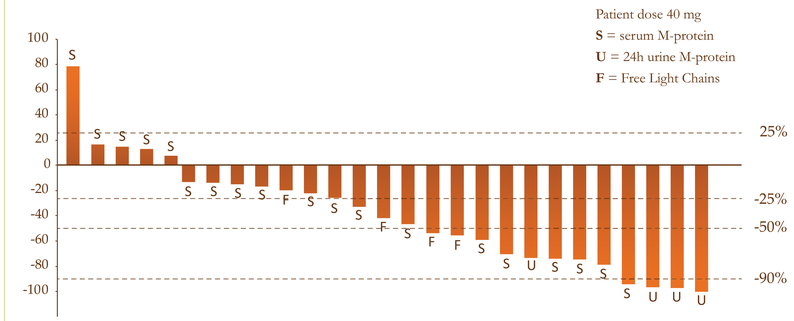


Figure 2. Kaplan-Meier plot of Progression Free Survival N=38 (n=27)

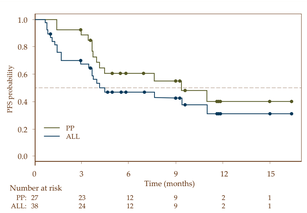


Figure 3. Kaplan-Meier plot of Duration of Response (n=11)

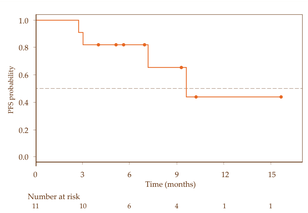


Table 4. ORR and CBR based on Refractory Status in efficacy evaluable patients (n=27)

Refractory status	n (%)	Overall Response Rate (≥ PR) 11 of 27 (41%)	Clinical Benefit Rate (≥ MR) 15 of 27 (56%)
Non refractory	1 (4)	1 (100)	1 (100)
PI	17 (63)	6 (35)	8 (47)
IMiD	23 (85)	8 (35)	12 (52)
Alkylator	14 (52)	8 (57)	9 (64)
Low dose melphalan	4	2	3
High dose melphalan	3	2	3
Cyclophosphamide	9	6	6
Double refractory (PI + IMiD)	16 (59)	5 (31)	7 (44)
Double + Alkylator refractory	9 (33)	3 (33)	4 (44)
Triple refractory (2 PI/IMiD + 1 IMiD/PI)	10 (37)	4 (40)	6 (60)
Pomalidomide refractory	10 (37)	3 (30)	5 (50)

Table 5. ORR and CBR based on number of prior refractory agents in efficacy evaluable patients (n=27)

Number of refractory agents*	n (%)	Overall Response Rate (≥ PR) 11 of 27 (41%)	Clinical Benefit Rate (≥ MR) Total 15 of 27 (56%)
0	1 (4)	1 (100)	1 (100)
≥1	26 (96)	10 (38)	14 (54)
≥2	21 (78)	9 (43)	12 (57)
≥3	16 (59)	7 (44)	10 (63)
≥4	7 (26)	3 (43)	5 (71)

*not counting steroids

Results - Safety and tolerability

- All 38 patients experienced drug related TEAEs of any grade (Table 6)
- 34 patients (90%) experienced grade 3-4 TEAEs, and 33 (87%) patients experienced treatment-related grade 3-4 TEAEs (Table 7)
- Thrombocytopenia and neutropenia were the most commont grade 3-4 TEAEs, however no event of bleeding was reported in connection with thrombocytopenia and the neutropenia only developed into febrile neutropenia in 2 patients. GI related symptoms such as nausea, vomiting and mucositis were infrequent and none reported as related grade 3-4
- Thirteen patients (34%) experienced Serious TEAEs and 8 patients (21%) experienced treatment-related Serious TEAEs (Table 8)
- Seven patients (18%) had TEAEs leading to dose reduction of melflufen and 15 patients (39%) had TEAEs leading to treatment discontinuations
- Supportive care use (such as transfusions and G-CSF) was in line with other studies in this late-stage patient population
- Dose interruptions occurred in 67% of patients and dose reductions in 33% of patients (Table 9)
- DSMC has decided to increase the cycle length from 21 days to 28 days to allow sufficient recovery

Table 6. TEAEs, irrespective of grade or relationship occuring in ≥15% of patients (N=38)

TEAE	n (%)
Any TEAE	38 (100)
Blood and lymphatic system disorders	35 (92)
Thrombocytopenia	34 (90)
Anaemia	29 (76)
Neutropenia	22 (58)
Leukopenia	16 (42)
General disorders and administration site conditions	28 (74)
Pyrexia	16 (42)
Asthenia	13 (34)
Fatigue	9 (24)
Gastrointestinal disorders	24 (63)
Nausea	11 (29)
Diarrhoea	8 (21)
Constipation	6 (16)
Infections and infestations	22 (58)
Pneumonia	8 (21)
Upper respiratory tract infection	6 (16)
Musculoskeletal and connective tissue disorders	17 (45)
Bone pain	6 (16)
Respiratory, thoracic and mediastinal disorders	13 (34)
Cough	7 (18)

Table 7. Treatment Related ≥ Grade 3 TEAEs reported in >5% of patients (N=38)

	Treatment related ≥grade 3 n (%)	Treatment related grade 4 n (%)
Any treatment-related grade 3 and/or grade 4	33 (87)	19 (50)
Blood and lymphatic system disorders	29 (76)	18 (47)
Thrombocytopenia	26 (68)	13 (34)
Neutropenia	20 (53)	10 (26)
Anemia	15 (40)	0
Leukopenia	13 (34)	5 (13)
Febrile neutropenia	2 (5)	0
General disorders and administration site conditions	7 (18)	0
Asthenia	2 (5)	0
Fatigue	2 (5)	0
Pyrexia	2 (5)	0
Infections and infestations	3 (8)	0
Pneumonia	3 (8)	0
Investigations	4 (10)	0
Neutrophil count decreased	4 (10)	0
Metabolism and nutrition disorders	3 (8)	1 (3)
Hyperglycemia	3 (8)	1 (3)

Table 8. SAEs Related to Melflufen 40 mg (N=38)

Adverse Event Term	Number of patients (%)
Pneumonia	3 (8)
Febrile Neutropenia	2 (5)
Pyrexia	2 (5)
Diarrhoea	1 (3)
Escherichia coli sepsis	1 (3)
Neutropenia	1 (3)

*Fatal events in a total of 3 patients with disease progression where contribution from treatment with melflufen cannot be excluded

Table 9. Dose interruptions and reductions of melflufen (N=38)*

Event	Patients with an event n (% of 27)	Median time to first event (weeks)
Dose interruption	18 (67)	7.9
Dose reduction	9 (33)	16.9

*11 patients only received one dose due to early PD and have by definition no dose interruptions or reductions. These patients were excluded from the analysis.

Note: The 28 day cycle per protocol cannot be evaluated separately since it only includes 3 patients at data cut.

Conclusion

- Melflufen has promising activity in heavily pre-treated RRMM patients where conventional therapies have failed
- The current ORR is 41% and CBR is 56%. Similar results were seen across patient populations regardless of refractory status
- The median PFS is encouraging at 9.4 months and DOR is currently at 9.6 months
- Hematologic toxicity was common, but managable with cycle prolongations, dose modifications and supportive therapy
- Non-hematologic TEAEs were infrequent

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5. Derived from Chauhan (2013)

Disclosures:

Mellqvist, Paba-Prada, Palumbo, Plesner, Sonneveld and Voorhees are Principal Investigators in the trial
Richardson is senior medical advisor to Oncopeptides AB
Byrne and Harmenberg are consultants of Oncopeptides AB. Nordstrom is employed by Oncopeptides AB

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