FINAL PHASE 2 STUDY DATA OF MELFLUFEN AND DEXAMETHASONE FOR PATIENTS WITH RELAPSED-REFRACTORY MULTIPLE MYELOMA (RRMM)

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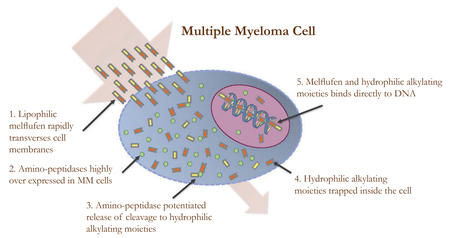
Background

- Melflufen is a peptidase potentiated therapy with an alkylating payload, designed for efficient targeting of tumor cells with a unique mechanism of action
- As a highly potent anti-angiogenic compound, melflufen triggers rapid, robust and irreversible DNA damage and exerts its cytotoxicity through alkylation of DNA
- 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 a 50-fold enrichment of these metabolites in multiple myeloma (MM) cells

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[1,2]
- Alkylation of DNA with limited or no induction of DNA repair[3]
- Highly potent anti-angiogenic activity[1,4]
- Therapeutic index of 20 - 40 (MM cells compared with peripheral blood mononuclear cells)[1]

Aim and Methods

- **Aim:** To study the efficacy and safety of melflufen in combination with dexamethasone (dex) in patients (pts) with RRMM
- **Methods:** Melflufen 40 mg was given in 28-day cycles in combination with 40 mg weekly dex in RRMM pts with ≥2 prior lines of therapy, including lenalidomide and bortezomib, and who progressed on or within 60 days of last therapy
- This poster presents the final Phase 2 data for the 40 mg melflufen + 40 mg weekly dex cohort as of 25 April 2016

Results - Baseline Characteristics (N=40)

- Fourty patients were treated at the melflufen 40 mg + dex dose level, with a median age of 65 years (47-78)
- Median time since diagnosis was 5 years (1-15) with a median of 4 (2-9) prior lines of therapy
- 63% of the patients were double-refractory at baseline to at least one IMiD and one PI, and 55% were refractory to an alkylator
- 65% of the patients had ISS stage II-III prior to study entry and 30% had high risk cytogenetic risk factors by FISH (Table 1)

Table 1. Patient Characteristics

Characteristics	Total N = 40
Median age, years (range)	64.5 (47-78)
≥75 years, n (%)	3 (7.5)
Years since diagnosis, median (range)	5.3 (1-15)*
Number of previous lines of therapy, median (range)	4.0 (2-13)
ISS stage at study entry, n (%)	
I	12 (30)
II or III	26 (65)
Unknown	2 (5.0)
ECOG performance status, n (%)	
0	17 (43)
1	21 (53)
2	0
Not done	2 (5.0)
Cytogenetic risk factor by FISH, n (%)	
High-risk**	12 (30)
del(13)	12 (30)
amp(1q)	11 (28)
Abnormal karyotype (excluding hyperdiploid pts)	14 (35)
Other	6 (15)
Unknown	2 (5)
Double-refractory (IMiD and PI), n (%)	25 (63)
Refractory to an alkylator (melphalan, cyclophosphamide or bendamustine), n (%)	22 (55)

*Missing information on two patients **Defined as del(17), t(4;14) or t(14;16)[5]

Table 2. Disposition (N=40)

	Number of patients	Reported reason for discontinuation	n
Ongoing on treatment	1	--	--
Completed study (≥ 8 cycles of therapy)	7	--	--
Discontinued treatment	32	Adverse Events*	17
		Thrombocytopenia	12
		Neutropenia/Febrile neutropenia	3
		Anemia	2
		Fever	2
		Hypercalcemia	1
		Unrelated infection	1
		Death	2
		Progressive disease	12
		Other	1

*Some patients discontinued due to more than one adverse event and are therefore included in more than one subcategory

Results - Treatment and Disposition

- As of 25 April 2016, 40 patients had received 188 doses of melflufen 40 mg + weekly dex. The median number of cycles initiated in an individual patient was 4 (1-14) and the median duration of treatment was 15 weeks (2-57)
- Of the 40 patients treated, 7 had completed the planned 8 cycles or more of treatment, and one is ongoing. Thirty-two patients discontinued from treatment (17 due to AEs, 12 due to PD, 2 deaths and 1 for other reasons), see Table 2

Results - Efficacy

- Thirty patients were evaluable for response (protocol defined as ≥2 doses of melflufen with baseline and follow-up response assessments)
- Four patients achieved very good partial response (VGPR) and 8 achieved partial response (PR) for an ORR of 40%. Seven additional patients achieved minimal response (MR) for a clinical benefit rate (CBR) of 63%. In the ITT population, the ORR was 30% and CBR 50% (Figure 1)
- Similar ORR were seen in various subgroups including those with >3 prior lines of therapy (53%), high-risk cytogenetics (44%) and ISS stage II or III (35%). It should be noted that ORR was also similar in alkylator-refractory (53%) and double-refractory (33%) patients (Table 4)
- The median duration of response (DOR) was 7.7 months (95% CI: 4.6 to ∞) based on 11 events in 12 responding (≥PR) patients
- The median progression-free survival (PFS-50%) was 4.3 months (95% CI: 3.7 to 8.5), and the PFS-25% was 9.7 months (95% CI: 7.9 to 14) based on 37 events in all 40 treated patients. Seventeen patients (43%) were progression-free at 6 months and 5 patients (12.5%) at 12 months (Figure 2)
- Ten patients were not evaluable for response due to rapid early progression (4), early termination due to adverse events (4) or death (2)

Table 3. Overall Response Rate (Efficacy evaluable and all treated patients)

	n	VGPR	PR	MR	SD	PD	ORR	CBR
Evaluable (≥2 doses of melflufen)	30	4	8	7	10	1	40%	63%
All treated (ITT)	40	4	8	8	11	9	30%	50%

Figure 1. Swim-lane plot for patients in the ITT population with ≥MR (N=20)

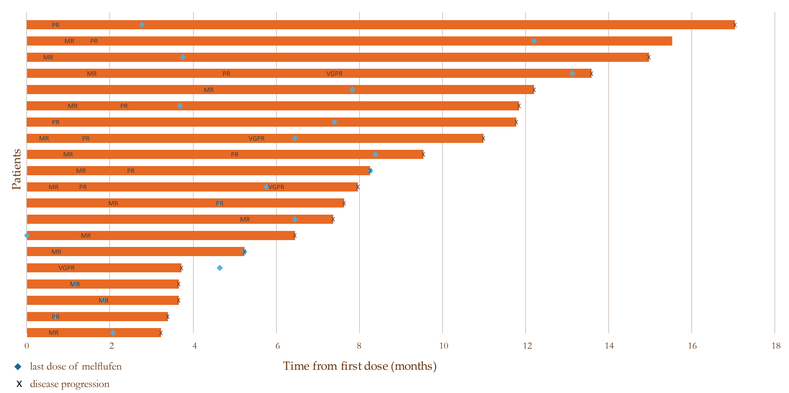


Figure 2. Melflufen PFS in ITT population (N=40) and efficacy evaluable (PP) population (N=30)

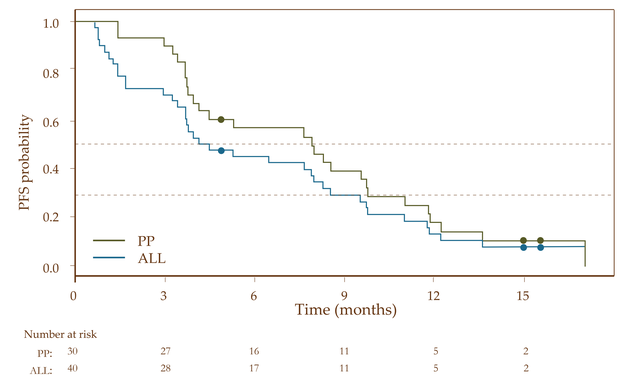


Table 4. ORR and CBR based on different stratification factors in efficacy evaluable patients (N=30)

	n (%)	ORR (≥PR) n (%)	CBR (≥MR) n (%)
Refractory status			
Non refractory	1 (3)	1 (100)	1 (100)
PI	20 (67)	7 (35)	13 (65)
IMiD	25 (83)	9 (36)	15 (60)
Alkylator	15 (50)	8 (53)	11 (73)
Double refractory (PI + IMiD)	18 (60)	6 (33)	11 (61)
Triple refractory (2 PI/IMiD + 1 IMiD/PI)	10 (33)	3 (30)	7 (70)
Pomalidomide refractory	11 (37)	4 (36)	7 (64)
Cytogenetic risk factor by FISH			
High-risk	9 (30)	4 (44)	7 (78)
Standard	19 (63)	7 (37)	10 (53)
Not done	2 (7)	1 (50)	1 (50)
ISS stage at study entry*			
I	12 (40)	5 (42)	7 (58)
II or III	17 (57)	6 (35)	10 (59)
Prior number of therapies			
≤3	13 (43)	3 (23)	6 (46)
>3	17 (57)	9 (53)	12 (70)

*Unknown for one patient

Results - Safety and Tolerability

- All 40 patients experienced treatment emergent adverse events (TEAEs) of any grade.Thirty-seven patients (92%) experienced Grade 3 or 4 TEAEs, 34 patients (85%) experienced treatment-related Grade 3 TEAEs and 20 patients (50%) Grade 4 TEAEs (Table 5)
- Dose-related, reversible and clinically manageable thrombocytopenias and neutropenias were the most frequent related Grade 3/4 adverse events
- Sixteen patients (40%) experienced serious TEAEs (SAE) and and 12 patients (30%) experienced treatment-related SAEs (Table 6)
- Eighteen patients (45%) experienced any TEAE that led to treatment discontinuation

Table 5. Any treatment-related Grade 3 and 4 AE in ≥5% of patients (N=40)

	Treatment related Grade 3 n (%)	Treatment related Grade 4 n (%)
Any treatment-related AE	34 (85)	20 (50)
Blood and lymphatic system disorders	32 (80)	20 (50)
Thrombocytopenia	24 (60)	17 (42)
Neutropenia	21 (53)	12 (30)
Anemia	17 (43)	0
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
Investigations	5 (13)	0
Neutrophil count decreased	4 (10)	0
White blood cell count decreased	2 (5)	0
Infections and infestations	2 (5)	0
Pneumonia	2 (5)	0

Table 6. Treatment-related SAEs (N=40)

Adverse Event Term	Number of patients (%)
Pneumonia	4 (10)
Febrile Neutropenia	2 (5)
Pyrexia	2 (5)
Diarrhoea	2 (5)
Neutropenia	2 (5)
Escherichia coli sepsis	1 (3)
Myelodysplastic syndrome	1 (3)
Subdural hematoma	1 (3)
Thrombocytopenia	1 (3)

Conclusion

- Melflufen has promising activity in heavily pre-treated RRMM patients where conventional therapies have failed
- The ORR is 40% and CBR is 63% in the efficacy evaluable population. Similar results were seen across patient populations regardless of refractory status
- The effect seems long-lasting with median DOR of 7.7 months and median PFS (PFS-50%) of 4.3 months. Of note, is that 43% were progression-free at 6 months and 12.5% at 12 months, with a PFS-25% of 9.7 months
- The most common related AEs were, as expected, reversible and clinically manageable thrombocytopenia and neutropenia. Non-hematological related AEs were infrequent
- Current data suggests that the activity of melflufen in RRMM is higher or on par with second generation PIs and IMiDs, and novel antibodies without sharing the same resistance mechanisms. This warrants that melflufen should be further evaluated and characterized in refractory myeloma patients

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References

1. Chauhan et al. (2013). "In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells." Clin Cancer Res 19(11): 3019-3031
2. Chauhan (2013) and Wickstrom et al. (2008). "The novel alkylating prodrug J1: diagnosis directed activity profile ex vivo and combination analyses in vitro." Invest New Drugs 26(3): 195-204
3. Chauhan 2016. A novel alkylating agent Melflufen induces irreversible DNA damage and cytotoxicity in multiple myeloma cells. British Journal of Haematology: 20 APR 2016. DOI: 10.1111/bjh.14065
4. Sirese et. al. The novel alkylating prodrug melflufen (J1) inhibits angiogenesis in vitro and in vivo. Biochemical Pharmacology 86 (2013) 888–895
5. Palumbo et. al. (2015) Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. Journal od Clinical. 2015.61.2267

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