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ENCOURAGING PRELIMINARY DATA IN ONGOING PHASE I/II STUDY OF SAFETY AND EFFICACY OF MELFLUFEN AND DEXAMETHASONE FOR PATIENTS WITH RELAPSED AND RELAPSED-REFRACTORY MULTIPLE MYELOMA

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Background

Melflufen is a peptidase targeted therapy designed for efficient targeting of tumor cells. Melflufen is a highly potent anti-angiogenetic compound, triggers rapid, robust, and irreversible DNA damage and exerts it cytotoxicity through alkylation of DNA [1,2].

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 into hydrophilic alkylkating metabolites. With targeted delivery of alkylating metabolites to tumor cells (such as multiple myeloma) in cell culture, melflufen exerts a 20-100 fold higher anti-tumor potency as well as a 20-fold higher intra-cellular concentration of alkylating moieties compared with melphalan, but with a similar safety profile [1, 3].

Aims

To study the safety and efficacy of melflufen and dexamethasone (dex) in combination for the treatment of patients with relapsed or relapsed-refractory multiple myeloma (RRMM).

Methods

Melflufen is evaluated in combination with low dose dex in an ongoing Phase I/II study in RRMM (NCT01897714).

The primary objectives are to determine the maximum tolerated dose (MTD) in Phase I and the objective response rate in Phase II.

Phase I evaluated 4 dose levels of melflufen on day 1 with 40 mg dex on days 1, 8 and 15 of 21-day cycles in a standard 3+3 design, with an additional 55 planned patients added at the MTD in Phase II.

Adult patients with measureable disease, ≥2 lines of prior therapy, life expectancy ≥6 months, ECOG ≤2, absolute neutrophil count ≥1.0x10^9/L, platelet count ≥75x10^9/L, hemoglobin ≥8.0 g/dl, total bilirubin ≤ 1.5 x ULN (Upper Limit of Normal), estimated creatinine clearance ≥45 ml/min, serum creatinine ≤2.5 mg/dL and AST/ALT ≤ 3.0 x ULN are eligible. All patients are required to provide signed informed consent.

Patients are treated for a maximum of 8 planned cycles or until unacceptable toxicity, investigator/patient decision or progression of disease. Patients could continue beyond 8 cycles if experiencing clinical benefit in the investigator's opinion.

Data cut for the poster was 20 May 2015.

Phase I Results

Phase I was completed in September 2014. No dose limiting toxicities (DLTs) were observed in the first three dose cohorts (15, 25 and 40 mg melflufen). 4 of 6 patients at the highest dose of 55 mg experienced DLTs of prolonged and severe neutropenia and thrombocytopenia, manageable with dose delays or reductions and appropriate treatment. The MTD was established at 40 mg of melflufen every 21 days combined with 40 mg dex weekly.

Phase II Baseline Characteristics

29 patients had received 103 doses (range 1-10 per patient) of melflufen at the MTD of 40 mg in the ongoing Phase II. Median time from initial diagnosis to first dose of melflufen was 5.5 years (range 1-15) and median number of prior therapies was 4 (range 2-11). All patients had been exposed to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and alkylators and 19 were at least single-refractory (IMiD or PI), 10 were double-refractory (IMiD and PI), 5 were triple refractory (IMiD, PI and alkylator) and 11 were alkylator-refractory (Table 4).

Phase II Safety Results

- The safety profile for melflufen 40 mg was similar to that for other alkylators, with neutropenia and thrombocytopenia as the most common adverse events.
- Treatment-related Grade 3 and 4 adverse events (AEs) were reported in 22 of the 29 patients, with thrombocytopenia reported in 59% and neutropenia in 48% of the patients, respectively (Table 2).
- The dose intensity was 89% and 41 out of 89 (46%) completed cycles were delayed ≥1 week.
- Fifteen (15) patients had discontinued from therapy while 14 patients were still ongoing in the study. One patient completed all (8+2) cycles. Eight (8) patients discontinued study treatment due to adverse events, equally divided between responders (defined as PR or better) and non-responders. Six (6) patients discontinued due to progression, whereof 5 progressed rapidly and one after 5 cycles (Table 1).
- A total of 12 serious adverse events have occurred in 8 patients of the Phase II population of 29 patients. 3 events in 3 patients were assessed as related to melflufen treatment and are all well-known from previous treatment with alkylators (2 Febrile neutropenia and 1 Pyrexia).

Table 1. Treatment Discontinuations Related to Cycle Length and Response

Reason for discontinuation	Number of patients	Cycles received median (range)	Best response
Completed therapy	1	10	PR
Adverse events	8	5 (2-6)	4 PR, 4 SD
Progressive disease	6	1 (1-5)	1 SD, 5 PD

Phase II Efficacy Results

- 21 patients were evaluable for efficacy according to the protocol (defined as having received ≥2 cycles of therapy and completed response assessments after cycle 2). 4 patients withdrew from treatment after only one cycle due to rapid disease progression and are included in a second response assessment (n = 25). 4 patients had only recently initiated cycle 1 or 2 and are too early to evaluate so are excluded from any response assessments.
- Among the 21 protocol defined evaluable patients 11 patients achieved Partial Response (PR) and 3 Minimal Response (MR). Six patients had Stable Disease (SD) and one Progressive Disease (PD). The overall response rate [ORR (≥PR)] was 52% and the clinical benefit rate [CBR (≥MR)] was 67% . In the 25 evaluable patients with ≥ 1 cycle the ORR was 44% and CBR was 56% (Table 3 and Figure 1).
- The PFS was 7.6 months (3.4 -∞) based on 11 events in all 25 patients. 56% of patients had not yet progressed in their disease at time of data-cut (Figure 2).
- Time to initial clinical benefit and response was rapid with 86% of patients with clinical benefit achieving ≥ MR after only 1-2 cycles, and 82% of responding patients achieving PR after 1-3 cycles.
- Dose intensity was 89% and dose delays did not affect level of response to treatment.
- Refractory status did not affect level of response. 5 of 7 patients refractory to an alkylator in last previous line responded with a PR or better (Table 4).

Table 3. Investigators' Response Assessments According to IMWG in Phase II

	n	PR	MR	SD	PD	ORR	CBR
Evaluable patients with ≥2 cycles	21	11	3	6	1	52%	67%
Evaluable patients with ≥1 cycle	25	11	3	6	5	44%	56%

Figure 1. Best Change from Baseline in Para-protein in Evaluable Patients in Phase II (n=21)

The main measurable para-protein per patient is presented. Patients without reduction are shown with the smallest increase reported. Dotted lines show IMWG criteria for PD (+25%), MR (-25%), PR (-50%) and VGPR (-90%).

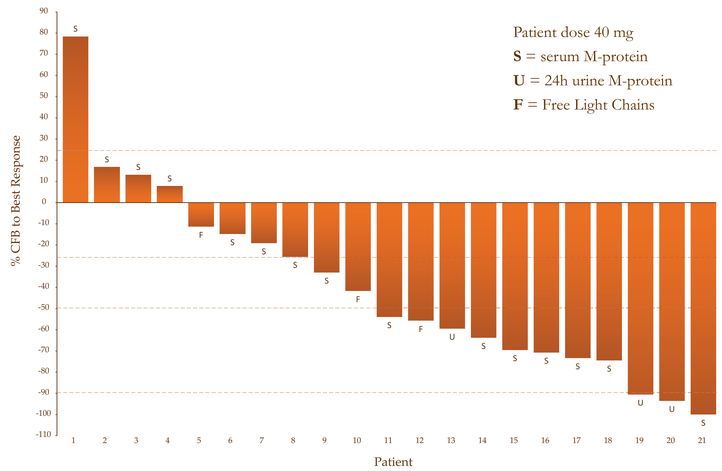

Table 2. Treatment Related Grade 3 and Grade 4 Adverse Events Reported in >5% of Patients in Phase II (N=29)

Preferred term	Number of patients (number of events)	% of patients
Any treatment related grade 3 or 4 AE	22 (135)	76
Thrombocytopenia	17 (51)	59
Neutropenia	14 (32)	48
Anemia	9 (13)	31
Leukopenia	6 (20)	21
Asthenia	2 (2)	7
Fatigue	2 (2)	7
Hyperglycemia	2 (10)	7
Pyrexia/Fever	2 (2)	7

Figure 2. Kaplan-Meier Plot of Progression Free Survival in Phase II

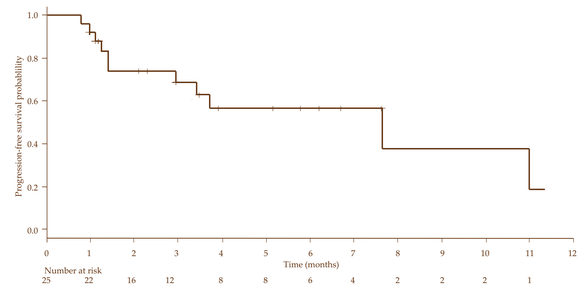

Table 4. Refractory Status in Relation to Response in Evaluable Patients in Phase II (n=21)

		n (%)	ORR (≥PR) 52% (11 of 21)
Refractory status	None	1 (5)	100% (1 of 1)
	PI	12 (57)	58% (7 of 12)
	IMiD	17 (81)	41% (7 of 17)
	Alkylator	11 (52)	73% (8 of 11)
	Low dose melphalan	3 (14)	67% (2 of 3)
	High dose melphalan	2 (10)	100% (2 of 2)
	Cyclophosphamide	8 (38)	75% (6 of 8)
	PI + IMiD	10 (48)	50% (5 of 10)
	PI + IMiD + Alkylator	5 (24)	60% (3 of 5)
Refractory last line	None	7 (33)	43% (3 of 7)
	PI	6 (29)	50% (3 of 6)
	IMiD	8 (38)	50% (4 of 8)
	Alkylator	7 (33)	71% (5 of 7)
	Low dose melphalan	0	0
	High dose melphalan	2 (10)	100% (2 of 2)
	Cyclophosphamide	6 (29)	67% (4 of 6)
	PI + IMiD	2 (10)	0% (0 of 2)
	PI+IMiD+Alkylator	0	0

Conclusion

- Melflufen has promising activity in RRMM patients (median 4 prior lines of therapy) where conventional therapies have failed, and is well tolerated.
- The ORR was 52% and CBR 67% in the 21 protocol evaluable patients, with 11 PR and 3 MR.
- The PFS was 7.6 months in the total population.
- Similar response rates were seen across patient groups with different refractory status (single-, double- and triple-refractory) including those refractory to alkylators in their last line of therapy.
- Only 3 out of 29 patients treated in Phase II experienced treatment-related SAEs.
- Thrombocytopenia and neutropenia were as expected the primary toxicities. The few SAEs reported suggest that the thrombocytopenias and neutropenias were monitorable, manageable and of limited clinical concern.
- Recruitment continues towards a total of 55 patients in Phase II to further characterize safety and efficacy of melflufen.

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References

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