Determination of the MTD and Preliminary Results in an Ongoing Open-Label Phase I/IIa Study of the Safety and Efficacy of Melflufen and Dexamethasone in Combination for Patients with Relapsed and Relapsed-Refractory Multiple Myeloma (RRMM)

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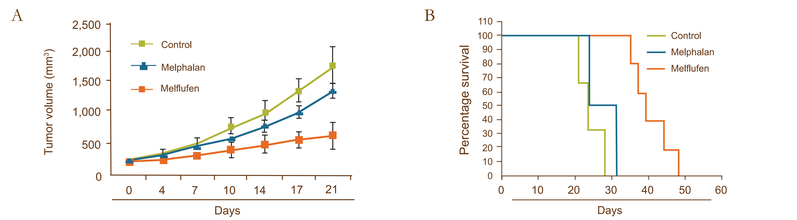
Background

- Alkylators are widely used in the treatment of multiple myeloma (MM), both as low dose agents in elderly patients, and as conditioning myeloablative regimen supported by autologous stem cell transplantation. However, alkylator treatment can be associated with significant toxicities, and the development of drug-resistance. Current therapies with novel agents have improved outcomes, but alkylators still play a significant role in the treatment of MM.
- Melflufen is an active, highly lipophilic alkylator, the mechanism of action being targeted alkylation of tumor cell DNA.
- Chemically, melflufen may be described as the ethyl ester of a dipeptide, consisting of melphalan and 4-fluoro-L-phenylalanine. Tissue distribution of melflufen is rapid due its lipophilicity. Intracellular peptidases that are overexpressed in most malignant cells, will rapidly cleave melflufen releasing the hydrophilic, active metabolite melphalan.
- *In vitro*, equimolar treatment of tumor cells with melphalan and melflufen, results in a 10-20 fold higher intracellular concentration of melphalan after melflufen treatment. In studies of 20 different human cancers in cell culture, including MM, melflufen showed a 50- to 100-fold higher cytotoxicity as measured by IC_{50} compared with that of melphalan. In efficacy studies conducted in mice and rats carrying different human tumors, including MM, superior antitumor activity of melflufen over equimolar dosage of melphalan was observed at seemingly comparable toxicity. (Figure 1)[1,2]
- Consequently, the peptidase dependent distribution profile of melflufen gives rise to a unique set of properties among alkylators as to both efficacy and potential side-effects.
- Here we present the preliminary results of a PhI/IIa dose escalation/expansion trial with melflufen and dexamethasone in heavily pre-treated patients with relapsed and relapsed- refractory MM (RRMM) *(Clinicaltrials.gov NCT01897714)*.

Figure 1. Pre-clinically meflufen is Superior to Melphalan



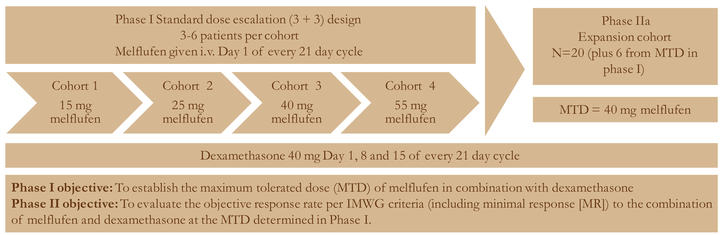
A. Tumor-bearing mice (human plasmacytoma xenograft model) were intravenously treated with vehicle, melflufen (2mg/kg) or equimolar dose of melphalan.

B. Survival in mice receiving melflufen vs melphalan ($p<0.05$).

Methods

- Fixed doses of melflufen are evaluated in combination with low dose dexamethasone (dex) in a Phase I/IIa study.
- Patients with relapsed or relapsed-refractory MM with measurable disease and at least two prior lines of therapy are eligible.

Figure 2. Study Design



Results

The Phase I component of the study has been finalized and the MTD is established at 40 mg melflufen in combination with dexamethasone. As of 17 November 2014, 29 patients had been dosed with melflufen, 23 in Phase I and 6 in the ongoing Phase IIa (Table 1).

- The median time from initial diagnosis to first dose of melflufen was 6 years (1-16).
- The median number of prior therapies was 4 (2-11).
- All patients to date were relapsed or relapsed-refractory to both immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) and 18 patients had received melphalan (62%).
- 9/29 patients (31%) were still receiving treatment at the time of data cutoff.

Safety

- In total, 86 doses of melflufen have been given (1-12 cycles).
- No DLTs were observed in the first three dose cohorts (15, 25 and 40 mg).
- The highest dose cohort (55 mg) exceeded the MTD as 4 out of 6 patients experienced dose limiting toxicities (DLTs). The DLTs were prolonged and severe thrombocytopenia and neutropenia but proved manageable with platelet transfusions and growth factor support.
- The most frequent treatment emerging adverse events (TEAEs) occurring at least once in a specific patient, all grades, regardless of relationship to study drug include thrombocytopenia (69%), anemia (59%), neutropenia (41%) and nausea (38%).
- Grade 3 and/or 4 TEAEs have been reported in 76% of patients (N =22); e.g. thrombocytopenia (48%) and neutropenia (38%).
- The most common related Grade 3/4 TEAEs were reversible thrombocytopenia and neutropenia, which occurred at least once in 41% and 38% of the patients respectively (Table 3).
- The dose intensity was less in the 55 mg dose group (1.28 mg/day) compared to the 40 mg dose group (1.73 mg/day) due to treatment delays (Table 4).

Table 1. Demographics and Baseline Characteristics

	15mg N=4	25mg N=7	40mg N=12	55mg N=6	Total N=29
Median age, years (range)	68 (49-68)	69 (59-82)	66 (48-73)	68 (44-72)	68 (44-82)
Median time since diagnosis, years (range)	5.5 (2.8-12.4)	7.2 (1.0-9.8)	6.1 (2.1-15.1)	6.4 (3.2-15.7)	6.1 (1.0-15.7)
Type of myeloma, n (%)					
IgG	3 (75)	3 (43)	8 (67)	5 (83)	19 (66)
IgA	2 (50)	3 (43)	0	0	5 (17)
Other		1 (14)	4 (33)	1 (17)	6 (21)
Kappa Light Chain	3	5	7	4	19
Lambda Light Chain	1	2	5	2	10
Multiple myeloma ISS at Diagnosis n (%)					
Stage I	0	3 (42.9)	3 (27.3)	2 (33.3)	8 (28.6)
Stage II	3 (75)	1 (14.3)	3 (27.3)	1 (16.7)	8 (28.6)
Stage III	1 (25)	3 (42.9)	1 (9.1)	0	5 (17.9)
Unknown	0	0	4 (36.4)	3 (50)	7 (25)
% Bone marrow plasma cells					
Mean (SD)	43.5 (13.5)	25.9 (23.6)	25.7 (17.9)	16.9 (9.3)	26.9 (18.5)
Median	47.5	25.7	18.3	16	22
Range	24-55	4.8-63.9	5-47	3.5-29.4	3.5-63.9
Median number of prior therapies (range)	5 (3-7)	5 (2-10)	4 (2-11)	5 (3-10)	4 (2-11)
Number of patients with prior therapy, n (%)					
Immunomodulatory drugs (IMiDs)	4 (100)	7 (100)	12 (100)	4 (100)	29 (100)
Proteazome inhibitors (PIs)	4 (100)	7 (100)	12 (100)	4 (100)	29 (100)
Melphalan	3 (75)	4 (57)	8 (75)	3 (50)	18 (62%)
Disease status, n (%)					
Relapsed	4 (100)	3 (43)	7 (58)	4 (67)	18 (62)
Relapsed-refractory		4 (57)	5 (42)	2 (33)	11 (38)

Table 2. Patient Disposition

	15mg (N=4)	25mg (N=7)	40mg (N=6)	55mg (N=6)	40 mg PH 2 MTD (N = 6)	Total N=29
Median number of weeks on therapy (range)	10 (5-36)	2.9 (1-18)	11.5 (1-29)	11 (2-24)	1 (1-1) (at data cutoff)	5 (1-36)
Ongoing treatment	0	0	1	2 (reduced dose)	6	9
DLT	0	0	0	4	NA	4
Discontinued treatment						20
Disease progression	3	3	1	2		9
Adverse event	0	2	3	2		7
Other	1	2	1			4

Table 3. Grade 3 and 4 Treatment Related Advers Events, Occuring in More Than One Patient

	15 mg (N=4) n(e)	25 mg (N=7) n(e)	40 mg (N=12) n(e)	55 mg (N=6) n(e)	Total (N=29) n(e)
Any event	2 (4)	5 (13)	7 (23)	6 (58)	20 (98)
Thrombocytopenia	1 (1)	2 (3)	4 (9)	5 (28)	12 (41)
Neutropenia	0 (0)	2 (6)	4 (8)	5 (17)	11 (31)
Anaemia	0 (0)	0 (0)	1 (1)	2 (4)	3 (5)
Febrile neutropenia	1 (1)	0 (0)	1 (2)	1 (1)	3 (4)
Pneumonia	1 (1)	0 (0)	0 (0)	2 (2)	3 (3)
Fatigue	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)
Lymphopenia	1 (1)	1 (1)	0 (0)	0 (0)	2 (2)

N = Total number of patients treated, **n=** Number of patients with at least one related TEAE in each category (patients with multiple TEAEs in each category are counted only once in each category), and **e =** Number of events in each category.

Table 4. Mean Cycle Length and Dose Intensity in 40 and 55 mg Dose Cohorts

	Mean dose	Mean cycle length	Dose intensity
40 mg (N=12)	40 mg	23.1 days	1.7 mg / day
55 mg (N=6)	47 mg	36.5 days	1.3 mg / day

Efficacy

- At the time of data cut off 18 patients were evaluable for clinical response (i.e. received ≥2 cycles) – summarized in Figure 3.
- Median Time on treatment was 5 weeks with a range of 0 – 36 weeks. One patient in the 15 mg dose level maintained stable disease for 36 weeks (Figure 4). For responding patients median time on treatment is 13 weeks.
- At the MTD of 40 mg the overall response rate (ORR, defined as partial response [PR] or better) was 60% and clinical benefit rate (CBR, defined as minimal response [MR] or better) was 100% (Figure 5).

Figure 3. Maximum Change in Paraprotein in Evaluable Patients

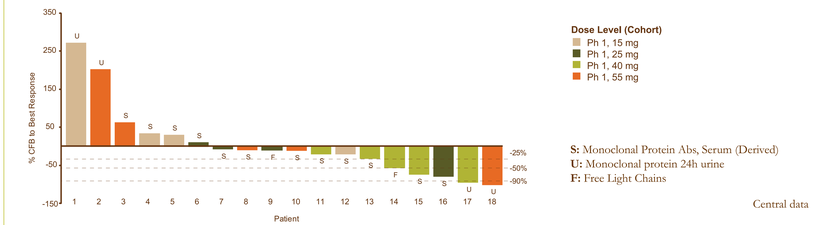


Figure 4. Median Time on Treatment - Evaluable Patients

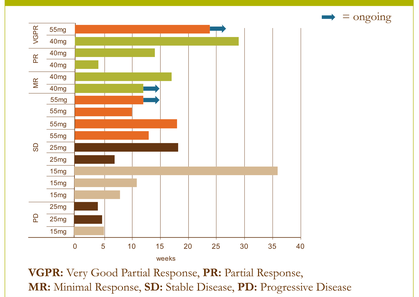
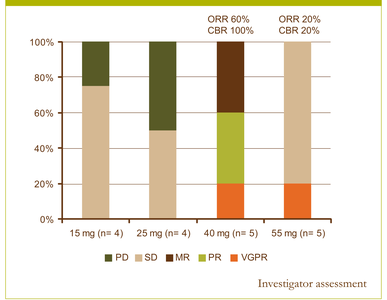


Figure 5. Clinial Response by IMWG Criteria - Evaluable Patients



Conclusion and Future Directions

Melflufen plus low dose dexamethasone appears, from early data, to be well tolerated and demonstrate activity in this advanced RRMM population. The MTD was exceeded at 55 mg due to myelosuppression, which was expected and manageable, and the MTD was established at the 40 mg dose level. Responses are seen in these heavily pre-treated patients, all being relapsed or relapsed refractory to both IMiDs and PIs. The ORR in the 5 evaluable patients in the 40 mg dose group was 60% and the CCBR was 100%, with median time on treatment of 13 weeks. The study is ongoing. Combination studies are warranted.

References

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2. M. Wickström *et al.*, Invest New Drugs (2008) 26:195–204; The novel alkylating prodrug J1: diagnosis directed activity profile *ex vivo* and combination analyses *in vitro*.

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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