THE HORIZON (OP-106) STUDY

Melflufen in patients with relapsed and refractory multiple myeloma refractory to daratumumab and/or pomalidomide

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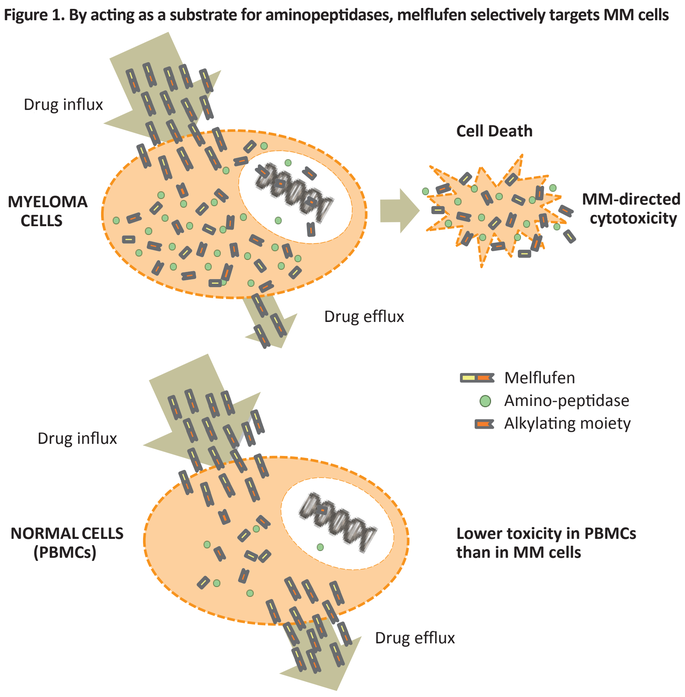
INTRODUCTION AND BACKGROUND

- Melflufen is a peptide conjugated alkylator and first in class peptidase-enhanced cytotoxic (PEnC) that selectively targets multiple myeloma (MM) cells (Figure 1)
- Aminopeptidases are overexpressed in several cancers including multiple myeloma[1,2,3]
- Melflufen acts as a substrate to aminopeptidases thus increasing the exposure of alkylating metabolites more than 50-fold compared to melphalan in MM cells[4]
- The increase in cytotoxicity is selectively directed to MM cells and not to peripheral blood mononuclear cells (PBMCs)[4,5,6]
- In addition, resistance pathways associated with common alkylators are overcome by the increase in intracellular alkylator exposure after melflufen treatment[4,6].
- In the phase 1/2 study O-12-M1, melflufen showed activity in patients with RRMM (overall response rate [ORR], 31%; median progression-free survival [PFS], 5.7 months; median overall survival, 20.7 months), with a favorable safety profile[7]
- The ongoing phase 2 HORIZON study evaluates melflufen in patients that are refractory to pomalidomide (pom) and/or daratumumab (dara), and that are exposed to immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs)
- The HORIZON study will recruit approximately 150 patients (including Quality of Life data for 50 patients)

Figure 1. By acting as a substrate for aminopeptidases, melflufen selectively targets MM cells



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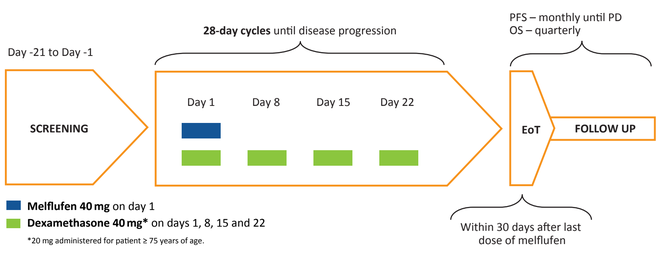
STUDY DESIGN

- Phase 2 study in relapsed and refractory (RRMM) patients (NCT02963493)
- ≥2 prior lines of therapy including IMiDs and PIs as well as refractory to pom and/or dara (refractory defined as relapsed while on therapy or within 60 days of last dose)
- Measurable disease (serum M protein ≥0.5 g/dL and/or urine M protein ≥200 mg/24h and/or involved free light chain (FLC) ≥10 mg/dL and abnormal FLC ratio (<0.26 or >1.65)
- Sufficient cell blood counts i.e. absolute neutrophil count (ANC) ≥1000 cells/mm^3, platelets ≥75.000 cells/mm^3)
- Primary endpoint: Overall Response Rate (ORR; ≥ partial response; investigator assessed per International Myeloma Working Group criteria)
- Secondary endpoints include clinical benefit rate (CBR; ≥ minimal response), PFS, and safety
- Treatment until progressive disease (PD), unacceptable toxicity or withdrawal of consent

Figure 2. Study Design



BASELINE CHARACTERISTICS AND DISPOSITION

- 83 patients treated; 82 evaluable for response (80 with M-protein data) at data cutoff (22 Oct 2018)
- 19 of the 83 patients were active on treatment
- 64 patients discontinued treatment: 73% due to PD, 17% due to AE, 9% due to other reason
- Median treatment time was 9 weeks (0-61)
- Late stage, highly refractory RRMM patients enrolled (table 1 and 2)

Table 1. Patient Characteristics at Study Entry (n=83)

		RANGE
Age (median)	63 yrs	(35-86)
Male / Female	59 / 41%	
Median time since diagnosis	6.5 yrs	(0.7-25)
Median prior lines of therapy	5	(2-13)
ISS stage I / II / III*	33 / 29 / 36%	
ECOG 0 / 1 / 2	27 / 58 / 16%	
High-risk cytogenetics** / 2 or more high risk abnormalities	61 / 20%	
Received ASCT*** / Relapsed within 1 year after ASCT	69 / 17%	
Albumin < 3.5 g/dl	35%	
Baseline β2 microglobulin > 3.5 mg/l	50%	

*ISS at study entry unknown for 3 pts **High-Risk status data pending/missing in 23 pts ***ASCT: Autologous Stem Cell Transplant

Table 2. Prior Treatment and Refractory Characteristics (n=83)

	%
Refractory status	
Pom or dara	100
Pom and dara	60
Double (PI+IMiD)	86
Double + anti-CD38 (triple-class)	65
Monoclonal antibody (mAb)	80
Alkylator exposed	84
Alkylator refractory	55
Received 1 ASCT / 2 ASCT	69 / 25
Refractory in last line	93

- 100% received prior PIs + IMiDs
- 46% exposed to ≥3 regimens in the last 12 months
- IMiDs include lenalidomide, thalidomide and pomalidomide
- PIs include bortezomib, carfilzomib and ixazomib
- mAbs include daratumumab, elotuzumab and isatuximab

RESULTS

- Promising activity in highly refractory patient population (table 3 and 4)

Table 3. Response Rates

	OVERALL RESPONSE RATE, ORR (≥PR)	CLINICAL BENEFIT RATE, CBR (≥MR)	DISEASE STABILIZATION (≥SD)
N (%)	27 (32)	32 (39)	69 (84)

Table 4. Response Depths

	sCR	CR	VGPR	PR	MR	SD	PD	TOTAL ASSESSABLE	DATA PENDING
N (%)	1 (1)	0 (0%)	9 (11)	17 (21)	5 (6)	37 (45)	12 (15)	82* (100)	1 (1)

* Includes 1 patient with unknown response

Figure 3. Best M-Protein Response (n=80)

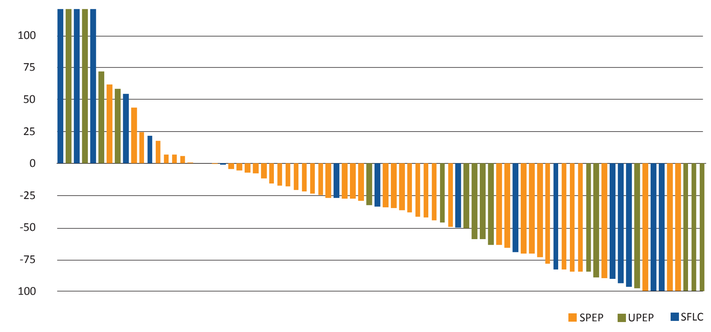
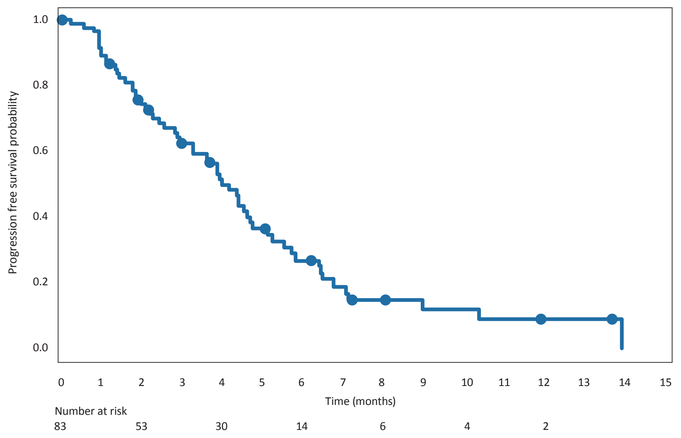


Figure 4. Progression-Free Survival (PFS) (n=83)



- Median PFS was 4.0 months (95% CI: 3.3-5.1)

PROGNOSTIC FACTORS

- Influence on ORR by baseline factors were analysed (table 5)

Table 5. ORR by Albumin and Albumin + Beta2Microglobulin (β2M)

		OVERALL RESPONSE RATE		
	N	ALL	ALBUMIN ≥3.5 g/dL	ALBUMIN ≥3.5 g/dL AND β2M <3.5 mg/L
ITT	82	33%	42%	49%
Pom refractory	74	30%	38%	43%
Dara refractory	57	25%	34%	40%
Pom + Dara refractory	49	19%	28%	29%
Dara + double refractory	48	19%	28%	36%

- ORR increased with high albumin, and increased even further with low β2M in the total population and in all investigated subgroups
- However, in an exploratory multivariable logistic regression model, only baseline albumin emerged as a possible prognostic factor for ORR (table 6)

Table 6. Serum Albumin was the Strongest Predictor of ORR

	N	ODDS RATIO	95% CI	P-VALUE
Albumin	79	2.62	(0.91-7.56)	0.075
β2M	79	0.92	(0.73-1.15)	0.460
LDH	79	0.96	(0.80-1.15)	0.648
ISS at study entry	79	0.95	(0.49-1.84)	0.872

- Baselines lactate dehydrogenase (LDH), β2M and ISS at study entry did not add additional information.
- Further verified after a stepwise logistic regression model, albumin remained as the only independent factor (table 7)

Table 7. Albumin level a Prognostic Factor of ORR

	N	ODDS RATIO	95% CI	P-VALUE
Albumin	79	3.21	(1.19-8.69)	0.021

- Further evaluation ongoing, but caution warranted given relatively low number of events and analysis not prespecified

SAFETY AND TOLERABILITY

- Adverse event profile dominated by reversible bone marrow toxicity (table 8)
- Low overall incidence of non-hematologic adverse events
- 7.2% incidence of G3/G4 treatment-related infection (all G3)

Table 8. Overview of Treatment-Related Adverse Events in >2 patients (n=83)

	G3/G4 N (%)	G4 N (%)
Any treatment-related grade 3-4 AEs in ≥2 pts	62 (75)	42 (51)
Blood and lymphatic system disorders	61 (73)	41 (49)
Neutropenia	51 (61)	29 (35)
Thrombocytopenia	49 (59)	30 (36)
Anaemia	21 (25)	1 (1)
Febrile neutropenia	5 (6)	2 (2)
Leukopenia	4 (5)	3 (4)
Lymphopenia	4 (5)	1 (1)
Infections and infestations	6 (7)	0 (0)
Pneumonia	2 (2)	0 (0)

- 13 patients stopped treatment due to AE
- 14 patients experienced a treatment-related SAE of G3/G4
  - Most frequent: febrile neutropenia (5 of 14), neutropenia (3 och 14) and thrombocytopenia (2 of 14)
- 5 patients experienced a treatment-related SAE of G4
- 8 patients discontinued treatment due to thrombocytopenia
- 3 patients experienced a treatment-related bleeding (G1 in 2 patients and G3 in 1 patient)

CONCLUSIONS AND FUTURE DIRECTIONS

- Melflufen/dexamethasone has promising activity in RRMM patients with advanced disease and multiple lines of treatment in this interim data analysis: ORR (>PR) 33%, CBR (>MR) 39%, disease stabilization (>SD) in 84% and a PFS of 4.0 months
- Activity was seen regardless of underlying refractory status, though higher serum albumin levels predicted higher ORR
- Favorable safety profile dominated by reversible bone marrow toxicity
- Non-hematologic toxicity was infrequent
- Melflufen also investigated in:
  - Randomized controlled Phase 3 study (NCT03151811) comparing melflufen/dexamethasone and pomalidomide/dexamethasone in RRMM patients (OCEAN)
  - Phase 1/2 combination study (NCT03481556) in RRMM patients with melflufen/dexamethasone combined with either daratumumab or bortezomib (ANCHOR)

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DISCLOSURES

Albert Oriol, Paul G. Richardson, Alessandra Larocca, Paula Rodriguez Otero, Joan Bladé, Hani Hassoun, Michele Cavo, Adrián Alegre, Amitabha Mazumder, Christopher Maisel, Agne Paner, Xavier Leleu, Jeffrey A. Zonder and Maria-Victoria Mateos are investigators in the Horizon trial. Johan Harmenberg and Sara Thuresson are working for Oncopeptides AB.