THE OP-106 HORIZON STUDY:

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

HORIZON

Paul G. Richardson, MD[1] Albert Oriol, MD[2] Alessandra Larocca, MD[3] Paula Rodriguez Otero, MD[4] Jan Moreb, MD[5] Joan Bladé, MD[6] Hani Hassoun, MD[7] Michele Cavo, MD[8] Adrián Alegre, MD[9] Amitabha Mazumder, MD[10] Christopher Maisel, MD[11] Agne Paner, MD[12] Xavier Leleu, MD[13] Jeffrey A. Zonder, MD[14] Johan Harmenberg, MD[15] Sara Thuresson, MSc[15] Hanan Zubair, MSc[15] and Maria-Victoria Mateos, MD[16]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA [2]Hospital Germans Trias i Pujol, Badalona, Spain [3]A.O.U. Città della Salute e della Scienza di Torino - S.C. Ematologia U, Torino, Italy [4]Clínica Universidad de Navarra, Pamplona, Spain [5]University of Florida Health Cancer Center, Gainesville, FL, USA [6]Hospital Clínica de Barcelona - Servicio de Onco-Hematología, Barcelona, Spain [7]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA [8]Policlinico S. Orsola Malpighi, Bologna, Italy [9]Hospital Universitario La Princesa, Madrid, Spain [10]Innovative Clinical Research Institute, Whittier, CA, USA [11]Baylor Scott & White Charles A. Sammons Cancer Center, Dallas, TX, USA [12]Rush University Medical Center, Chicago, IL, USA [13]CHU de Poitiers, Poitiers, France [14]Karmanos Cancer Institute, Detroit, MI, USA [15]Oncopeptides AB, Stockholm, Sweden [16]Hospital Clínico Universitario de Salamanca, Salamanca, Spain

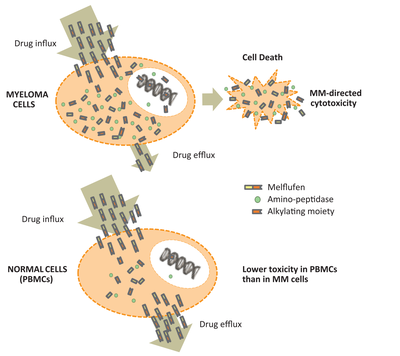
INTRODUCTION

- Melflufen is a peptide conjugated alkylator and first in class peptidase enhanced compound that selectively targets multiple myeloma (MM) cells
- Aminopeptidases are heavily overexpressed in MM cells
- Melflufen selectively targets MM cells through aminopeptidase-driven accumulation, leading to a 50-fold enrichment of alkylating metabolites vs melphalan[4]
- In the phase 1/2 study O-12-M1, melflufen showed activity in pts with RRMM (overall response rate [ORR], 31%; median progression-free survival [PFS], 5.7 mo; median overall survival, 20.7 mo), with a favorable safety profile*
- The phase 2 HORIZON study evaluates melflufen in pts exposed to immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) as well as refractory to pom and/or dara

BACKGROUND

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 after melflufen treatment more than 50-fold compared to melphalan in MM cells[4]. The increase in cyto-toxicity is selectively directed to MM cells and not to non-transformed cells such as peripheral blood mononuclear cells (PBMCs)[4,5,6]. In addition, resistance pathways associated with common alkyla-tors are overcome by the increase in intracellular alkylator exposure after melflufen treatment[4,6].

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

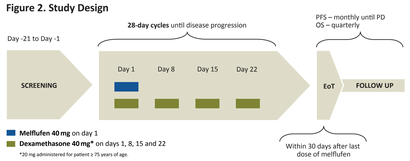


1. Dubowchik GM, Walker MA. Receptor-mediated and enzyme-dependent targeting of cytotoxic anticancer drugs. Pharmacol Ther. 1999; 83: 67-123.
2. Moore HE, Davenport EL, Smith EM, Muralikrishnan S, Dunlop AS, Walker BA, Krige D, Drummond AH, Hoofman L, Morgan GJ, Davies FE (2009) Aminopeptidase inhibition as a targeted treatment strategy in myeloma. Mol Cancer Ther 8:762–770.
3. Wickstrom M, Larsson R, Nygren P, Gullbo J. Aminopeptidase N (CD13) as a target for cancer chemotherapy. Cancer Sci. 2011; 102: 501-8.
4. Chauhan D, Ray A, Viktorsson K, Spira J, Paba-Prada C, Munshi N, Richardson P, Lewensohn R, Anderson KC. In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. Clin Cancer Res. 2013; 19: 3019-31.
5. Chauhan D et al., In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. EHA 2013 Poster
6. Ray A, Das DS, Song Y, Richardson P, Gullbo J, Richardson PG, Chauhan D, Anderson KC. A novel alkylating agent Melflufen induces irreversible DNA damage and cytotoxicity in multiple myeloma cells. Br J Haematol.2016; 174: 397-409
* Richardson et al., First report on OS and improved PFS in a completed phase 2 study (O-12-M1) of melflufen in advanced RRMM, ASH 2018 poster of abstract # 3150

STUDY DESIGN

- Phase 2 study in relapsed/refractory (RRMM) patients (pts) (NCT02963493)
- ≥2 prior lines of therapy including IMiDs and PIs as well as refractory to pomalidomide (pom) and/or daratumumab (dara) (refractory is 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 FLC >10 mg/dL and abnormal FLC ratio (<0.26 or >1.65)
- Sufficient cell blood counts (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 pts treated; 82 evaluable for response (80 with M-protein data) at data cutoff 22 Oct 2018
  - 19 pts ongoing at treatment
  - 64 pts discontinued treatment: 73% due to PD, 17% due to AE, 9% due to other reason
- Study is ongoing and will recruit up to approximately 150 pts (including Quality of Life data for 50 pts)
- Late stage RRMM pts enrolled (table 1)

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 ***Autologous Stem Cell Transplant

- Heavily pre-treated patient population (table 2)

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% used ≥3 treatment 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

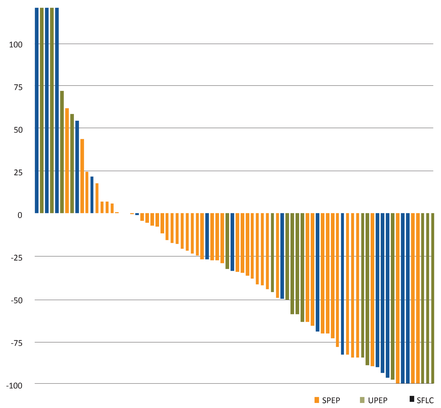
- Promising activity in this highly refractory pt population (table 3)
- Overall response rate (>PR) 33%
- Clinical Benefit Rate (>MR) 39%
- Disease stabilization (≥SD) 84%

Table 3. ORR in Multi-Refractory RRMM patients (n=83)

	N	%
Overall response	27	33
sCR	1	1
CR	0	0
VGPR	9	11
PR	17	21
MR	5	6
SD	37	45
PD	12	15
Not evaluable	1	1
Data pending	1	1

- Majority of patients show disease stabilization and/or reduction of tumor burden (n=80)

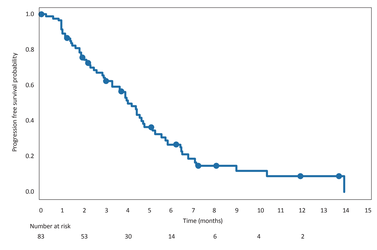
Figure 2. Best M-Protein Response (n=80)



RESULTS

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

Figure 3. Progression-Free Survival (PFS) (n=83)



PROGNOSTIC FACTORS

- Influence on ORR by baseline factors were analysed (table 4)

Table 4. Prognostic Factors Associated with ORR

		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%

- The ORR was found to increase with high albumin, and further increase with low beta 2 microgluline (β2M)
- This effect was found in all investigated refractory subgroups
- However, in an exploratory multivariable logistic regression model, only baseline albumin emerged as a possible prognostic factor for ORR (table 5)

Table 5. Serum Albumin: 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 6)

Table 6. 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

- Favorable safety profile (table 7)
- No treatment-related deaths
- 4% of cycles with G4 lab thrombocytopenia at Day 29
- 3 pts (4%) experienced treatment-related bleeding: G1 in 2 pts, and G3 in 1 patient
- Low overall Incidence of non-hematologic adverse events - Incidence of infections: 7.2%
- 14 pts experienced a treatment-related SAE G3/G4. Most frequent: febrile neutropenia (5 of 14), neutropenia (3 of 14) and thrombocytopenia (2 of 14)
- 5 pts experienced a treatment-related SAE G4
- 13% discontinuation rate due to AE (8 of 11 due to thrombocytopenia)

Table 7. Overview of Safety and Tolerability (n=83)

	G3/G4	G4
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)

CONCLUSIONS AND FUTURE DIRECTIONS

- Melflufen/dexamethasone has promising activity in multi-resistant RRMM patients, with an ORR of 33% (>PR), CBR of 39% (>MR), disease stabilization (>SD) in 84% and PFS of 4.0 months
- Activity regardless of underlying refractory status, but serum albumin was found as a predictor of ORR
- Treatment was generally well tolerated with manageable toxicity
  - Non-hematological adverse events were infrequent
  - Infection rate 7.2%
- Phase 3 study (NCT03151811) comparing melflufen/dexametha-sone and pomalidomide/dexamethasone in RRMM ongoing (OCEAN)
- Phase 1/2 combination study (NCT03481556) in RRMM of melflufen/dexamethasone combined with either daratumumab or bortezomib ongoing (ANCHOR) (AACR 2019 abstract CT080)

ACKNOWLEDGEMENTS AND THANK YOU

The authors would like to thank the patients who volunteered to participate in the study, the staff and the study sites who cares for them, and the CROs involved in data gathering and analysis.

DISCLOSURES

Paul G. Richardson, Albert Oriol, Alessandra Larocca, Paula Rodriguez Otero, Jan Moreb, 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, Sara Thuresson and Hanan Zubair are working for Oncopeptides AB.