OP-106 Melflufen therapy for RRMM patients refractory to daratumumab and/or pomalidomide

Updated Results and First Report on PFS

Paul G. Richardson, MD[1], Enrique M. Ocio, MD[16], Albert Oriol, MD[2], Alessandra Larocca, MD[3], Paula Rodríguez Otero, MD[4], Jan S. 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], Nashat Gabrail, MD[13], Jeffrey Zonder, MD[15], Dharminder Chauhan, PhD[1], Johan Harmenberg, MD[15], Sara Thuresson, MSc[15], Hanan Zubair, MSc[15] and María-Victoria Mateos, MD[16]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA [2]ICO Badalona – 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]UF Health Shands Cancer Hospital, Gainesville, FL, USA; [6]Hospital Clínica de Barcelona, Servicio de Onco-Hematología, Barcelona, Spain; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Policlinico S. Orsola Malphigi, Bologna, Italy; [9]Hospital Universitario La Princesa, Madrid, Spain; [10]The Oncology Institute of Hope and Innovation, Glendale, CA, USA; [11]Baylor Scott & White Charles A Sammons Cancer Center, Dallas, TX, USA; [12]Rush University Medical Center, Chicago, IL, USA; [13]Gabrail Cancer Center Research, Canton, OH, USA; [14]Karmanos Cancer Institute, Detroit, MI, USA; [15]Oncopeptides AB, Stockholm, Sweden; [16]Hospital Clínico Universitario de Salamanca, Salamanca, Spain

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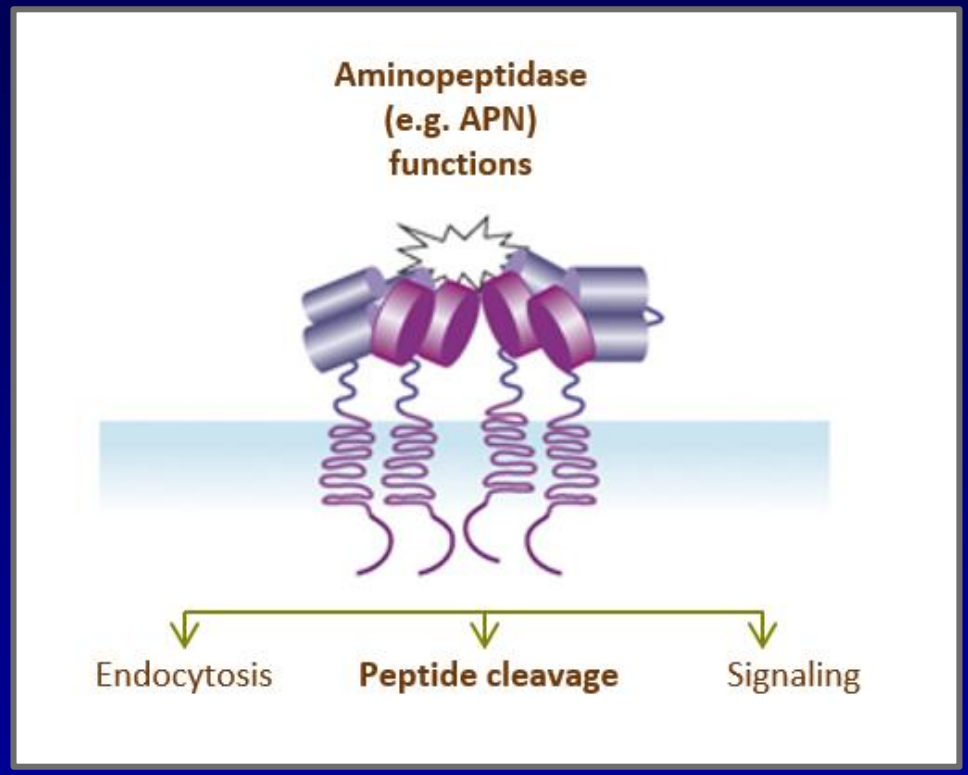
Aminopeptidases in MM
Key Functional Role in Multiple Myeloma

- Aminopeptidases (APs) are Zn2+ metalloenzymes that catalyze the cleavage of amino acids at the N-terminus of peptides and proteins by hydrolysis of peptide bonds
- APs operate downstream of ubiquitin-proteasome pathway and play a key role in protein homeostasis
- APs are also involved in key processes such as DNA repair, cell-cycle progression, signal transduction, transcriptional regulation, gene expression essential for immune response, development and programmed cell death

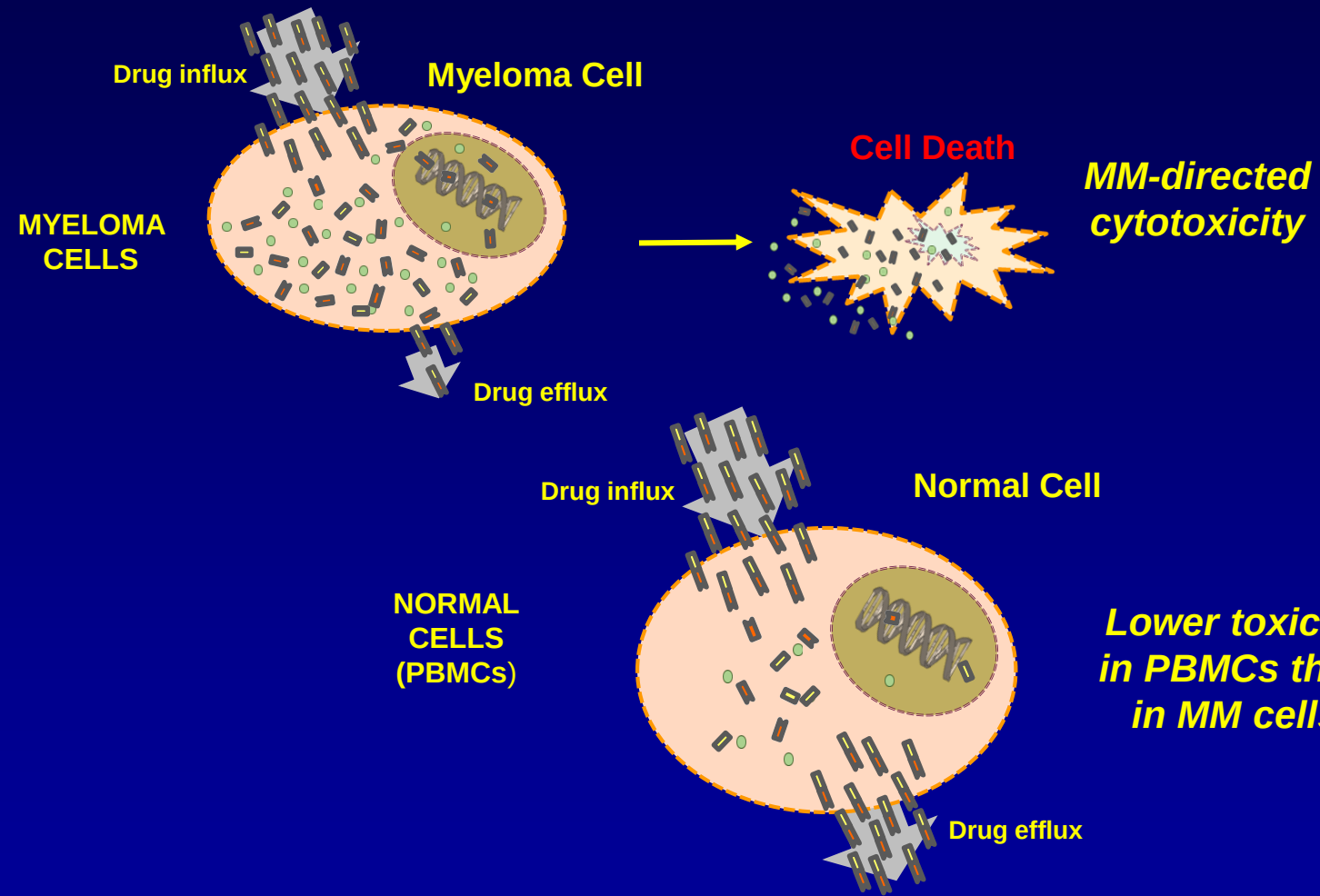


Dubowchik GM, Walker MA. Receptor-mediated and enzyme-dependent targeting of cytotoxic anticancer drugs. Pharmacol Ther 1999;83:67-123. DeClerck YA, Mercurio AM, Stack MS, et al. Proteases, extracellular matrix, and cancer: a workshop of the path B study section. Am J Pathol 2004;164:1131-39. Mina-Osorio P. The moonlighting enzyme CD13: old and new functions to target. Trends Mol Med 2008;14:361-71. Wickstrom M, Larsson R, Nygren P, Gullbo J. Aminopeptidase N (CD13) as a target for cancer chemotherapy. Cancer Sci 2011;102:501-8. Moore HE, Davenport EL, Smith EM, et al. Aminopeptidase inhibition as a targeted treatment strategy in myeloma. Mol Cancer Ther 2009; 8:762–70. Hitzerd SM, Verbrugge SE, Ossenkoppele G, et al. Positioning of aminopeptidase inhibitors in next generation cancer therapy. Amino Acids 2014; 46:793-808.

Melflufen – a Novel Targeted Alkylating Peptide: Mechanism of Action

Selectively targeting Myeloma as a first in class Aminopeptidase Enhanced Compound

- Aminopeptidases are overexpressed in several cancers including MM[1,2,3]
- Aminopeptidases enrich alkylating metabolites of melflufen in MM more than 50-fold compared to melphalan[4]
- Increase in cytotoxicity is selectively directed to MM cells and not to peripheral blood mononuclear cells (PBMCs) e.g. T cells, B cells[4,5,6]



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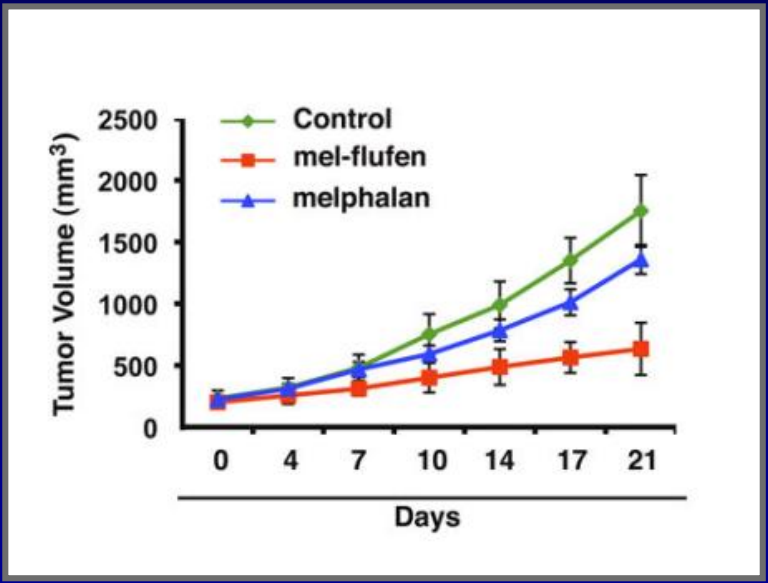
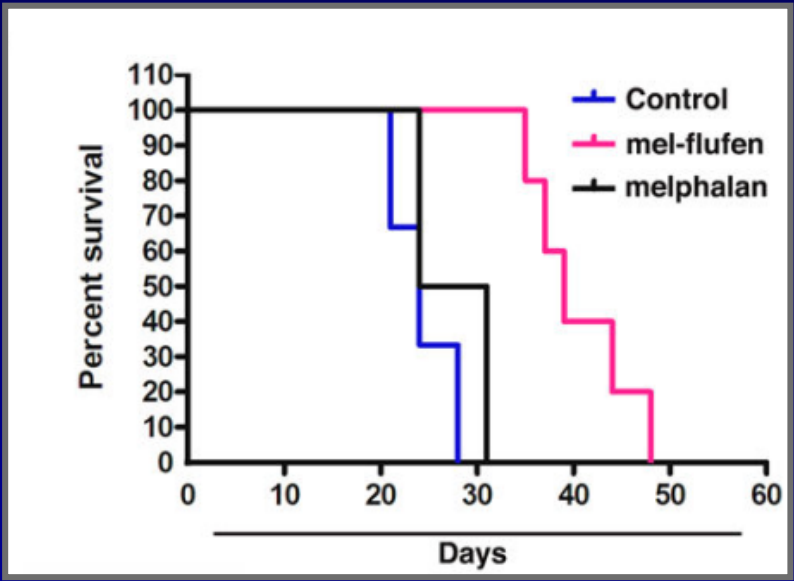
Melflufen Selective Cytotoxicity:
In vivo Efficacy

- *In vivo* human xenograft mouse models treated with melflufen showed
  - Higher inhibition of tumor growth
  - Prolonged survival than those treated with alkylators such as melphalan alone



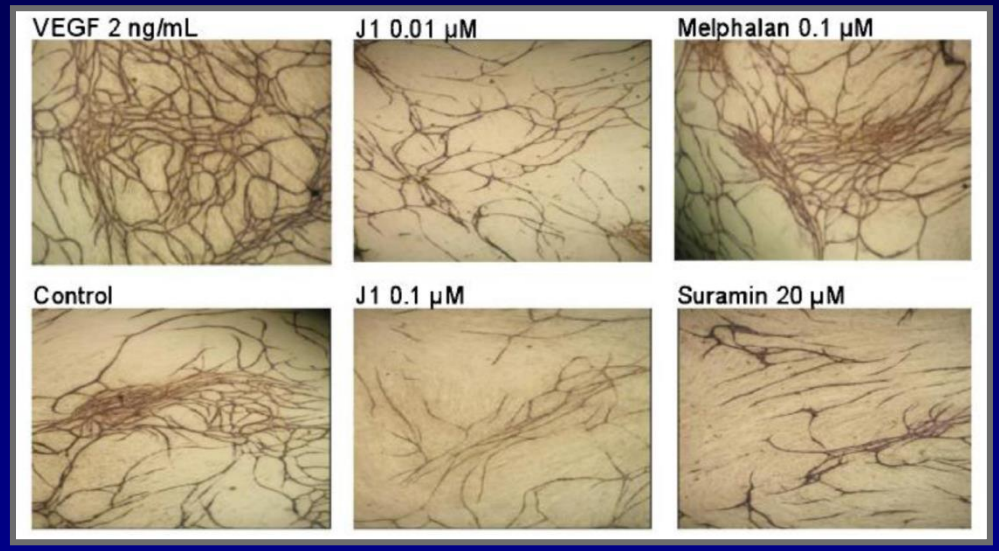


In vivo efficacy of melflufen shown using a human plasmacytoma MM.1S xenograft mouse model. Treatment of tumor-bearing mice with melflufen intravenously significantly inhibited A) MM tumor growth ($P = 0.001$) and B) prolonged survival ($P < 0.001$) of these mice

Chauhan D, Ray A, Viktorsson K, et al. 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.

Selective Cytotoxicity of Melflufen:
Anti-angiogenesis

- Melflufen is cleaved by aminopeptidases such as APN which is also known to be overexpressed in angiogenic endothelial cells in the tumor microenvironment
- Melflufen itself is shown to have strong anti-angiogenic properties
- In xenografted mice models, melflufen not only showed cytotoxic effects but also decreased vasculature within the tumors
- Melflufen showed pronounced anti-angiogenic activity (> 100-fold in some assays) at lower doses than the existing alkylator, melphalan alone



Decrease in both tubule length and vessel junctions shown for melflufen and melphalan in a dose response manner compared to the positive control VEGF (2 ng/ml)

Strese S, Wickstrom M, Fuchs PF, et al. The novel alkylating prodrug melflufen (J1) inhibits angiogenesis in vitro and in vivo. Biochem Pharmacol 2013;86:888-95.

Melflufen/dex in RRMM O-12-M1 Study Summary (n=45)

HORIZON

- Melflufen 40 mg every 28 days with 40 mg dex weekly identified as recommended dose and schedule
- Melflufen/dex demonstrated high response rate and durable response activity in heavily pretreated RRMM patients with a median of 4 prior lines (IMiD- and PI-exposed and disease progression while on therapy or within 60 days of last dose in their last line of therapy)
- ORR was 31% and CBR 49% in ITT population: similar results were seen across patient subgroups, regardless of refractory status
- Benefit of treatment durable, with median DOR of 8.4 months, median PFS of 5.7 months, and median OS of 20.7 months
- Favorable tolerability - hematologic toxicity, mostly thrombocytopenia was common but clinically manageable; non-hematologic AEs were infrequent

Richardson PG, Bringhen S, Voorhees P et al., First report on OS and improved PFS in a completed phase 2 study (O-12-M1) of melflufen in advanced RRMM. Presented at the 2017 American Society of Hematology Annual Meeting, Atlanta, December 9-12, 2017.

Response in Alkylator Refractory pts (O-12-M1)

Time of progression on alkylator treatment in relationship to melflufen	ORR on melflufen + dex
Within 12 months	42%
Within 60 days	38%

Richardson PG, Bringhen S, Voorhees P et al., First report on OS and improved PFS in a completed phase 2 study (O-12-M1) of melflufen in advanced RRMM.

Presented at the 2017 American Society of Hematology Annual Meeting, Atlanta, December 9-12, 2017.

Patients that progressed while on alkylator therapy within 12m in O-12-M1

Alkylator regimen	Time on alkylator regimen treatment (mos)	Best response on regimen	Time between last dose of alkylator and first dose of melflufen (mos)	Best subsequent response to melflufen
CyKd	13	PR	0.7	VGPR
Cy	2	PD	1.1	NE
CyVD, CyP	16	VGPR	1.2	NE
CyVD	2	PD	1.4	SD
CyP	1	PD	1.5	PR
MP / Cy	1.5 / 6	SD / SD	1.5 / 5.5	SD
Mel200, Cy	ASCT/ 3	SD	1.6 / 2.9	PR
Cy	15	SD	1.7	SD
CyTD	12	SD	3.5	VGPR
MPR	5	PD	9.8	PR
CyRVdDox	4	PR	11.2	MR
Mel30	1	SD	11.3	SD

Efficacy in RRMM

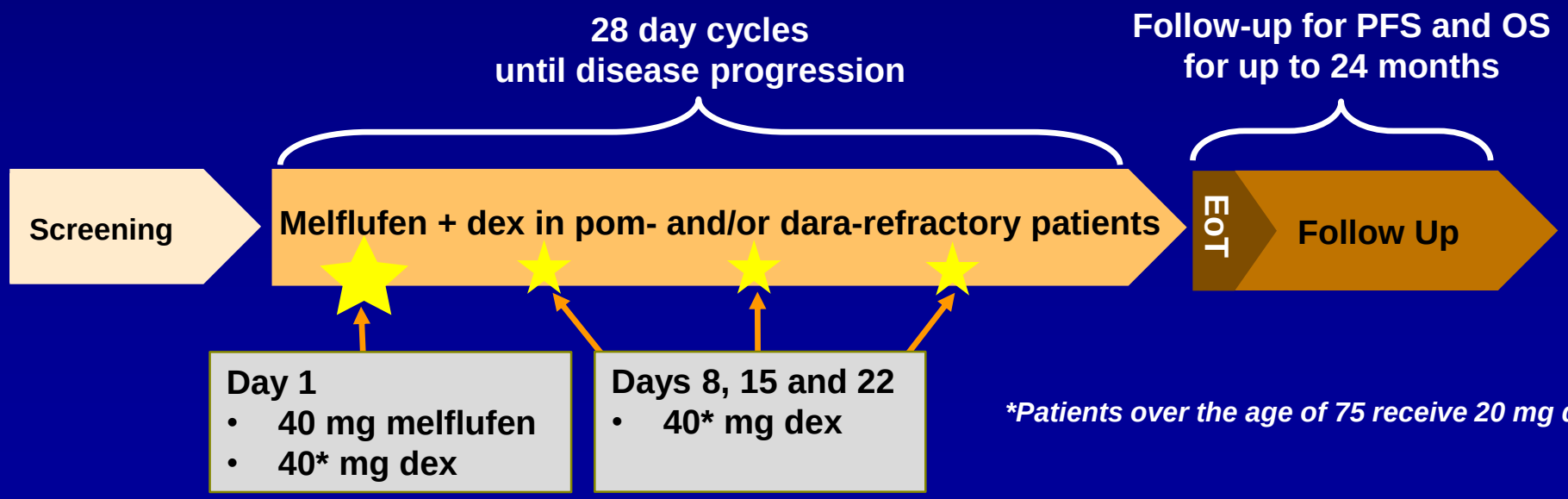
	Melflufen+Dex	Daratumumab	Pomalidomide+Dex	Carfilzomib	FOCUS (Cy+steroid)
N	45	106	113	266	158
Year	2017	2016	2013	2012	2016
Population	≥2 prior lines incl bortezomib and lenalidomide, refractory to last tx	≥3 prior lines incl PI and IMiD or double refractory (PI and IMiD)	≥2 prior lines incl lenalidomide and bortezomib, refractory to last tx	≥2 prior lines for relapsed disease incl bortezomib, thalidomide or lenalidomide, alkylator, or anthracycline	≥3 prior lines incl bortezomib, lenalidomide or thalidomide, alkylator, steroids, anthracycline and relapsed to last tx
Time from diag.	5.0 years	4.8 years	5.3 years	5.4 years	5.0 years
High risk Cytog.	44%	19%	27%	28%	18%
Median number of lines	4, 78% ≥3 lines	5, 82 % >3 lines	5, 95 % >2 lines	5, 82% ≥ 4 lines	5, 100% ≥ 3 lines
Refract. to last	87%	97%	100%	95%	99%
ORR	31.1%	29.2%	33.0%	23.7%	11.0%
ORR high risk	25.0%	20.0%	-	29.6%	-
Med duration treat	3.7 months	-	-	3.0 months	2.5 months
Med. Dur response	8.4 months	7.4 months	8.3 months	7.8 months	9.4 months
Median PFS	5.7 months (11.7 in ≥ PR)	3.7 months	4.2 months	3.7 months	3.3 months
Median OS	20.7 months	17.5 months	16.5 months	15.6 months	10.0 months

Richardson PG, Bringhen S, Voorhees P et al., First report on OS and improved PFS in a completed phase 2 study (O-12-M1) of melflufen in advanced RRMM. Presented at the 2017 American Society of Hematology Annual Meeting, Atlanta, December 9-12, 2017; Lonial S, Weiss BM, Usmani SZ et al., Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. The Lancet 2016;387:1551-60; Richardson PG, Siegel DS, Vij R et al., Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood 2014;123(12):1826-32; Siegel DS, Martin T, Wang M et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012;120:2817-25. Hájek R, Masszi T, Petrucci MT et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia 2017;31(1):107-114.

OP-106 HORIZON: Phase 2 of Safety and Efficacy of Melflufen in Pomalidomide- and/or Daratumumab-refractory RRMM Patients

HORIZON

Background	HORIZON Design	Potential Outcomes
• Patients who are daratumumab (dara) and/or pomalidomide (pom) refractory have limited options • Introducing a class change with an effective compound may represent a new best treatment strategy • Data suggests patients could derive clinical benefit if administered Melflufen in this setting	• Single arm, open-label, phase II multicenter study • ≥2 lines of prior therapy and pts are refractory to pomalidomide and/or daratumumab • Primary endpoint: ORR • Secondary endpoints: PFS, DOR, OS, CBR, TTR, TTP, safety and tolerability	• Supports OCEAN to receive regulatory approval



**Patients over the age of 75 receive 20 mg dex*

ClinicalTrials.gov Identifier: NCT02963493

Study Design and Disposition

Primary endpoint ORR (n=83)

HORIZON

Key Inclusion Criteria

- Refractory to pom and/or dara
  - Relapsed on therapy or within 60 days of last dose of pom or dara in any line
  - ≥2 prior therapies including an IMiD and a PI
- Measurable disease (at least one of the following)
  - Serum M protein >0.5 g/dL
  - Urine M protein >200 mg/24hrs
  - SFLC: Involved FLC >10mg/dL and abnormal FLC ratio (<0.26 or >1.65)
- ANC ≥ 1000 cells/mm^3 (1.0x10^9/L)
- Platelets ≥75,000 cells/mm^3 (75x10^9/L)

Study treatment:

Melflufen 40 mg i.v. Day 1 +

Dex 40 mg (20 mg for patients ≥75 yrs) Day 1, 8, 15, 22

Treatment up to PD, withdrawal of consent or unacceptable AE

PFS follow-up monthly until progression/ start of new therapy

OS follow-up every 3 months for up to 24 months*

*In the event that we would like to determine the OS status of patients following 24 months, future inquiries about their health status may be conducted.

- At data cut-off (22 Oct 2018):
  - 83 patients (pts) treated; 82 evaluable for response (80 with M-protein data)
  - 19 pts (23%) ongoing on treatment and
  - 64 pts (77%) discontinued treatment;
    57% due to PD, 13% due to AEs and 7% due to other reasons
- Study is ongoing and will recruit up to approximately 150 pts (including Quality of Life data for 50 pts)

Patient Characteristics at Study Entry (n=83)

HORIZON

		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 β_2 microglobulin $\geq$ 3.5 mg/l	50 %	

*ISS at study entry unknown for 3 pts

**HR status data pending/missing in 23 pts

Prior Treatment and Refractory Characteristics (n=83)

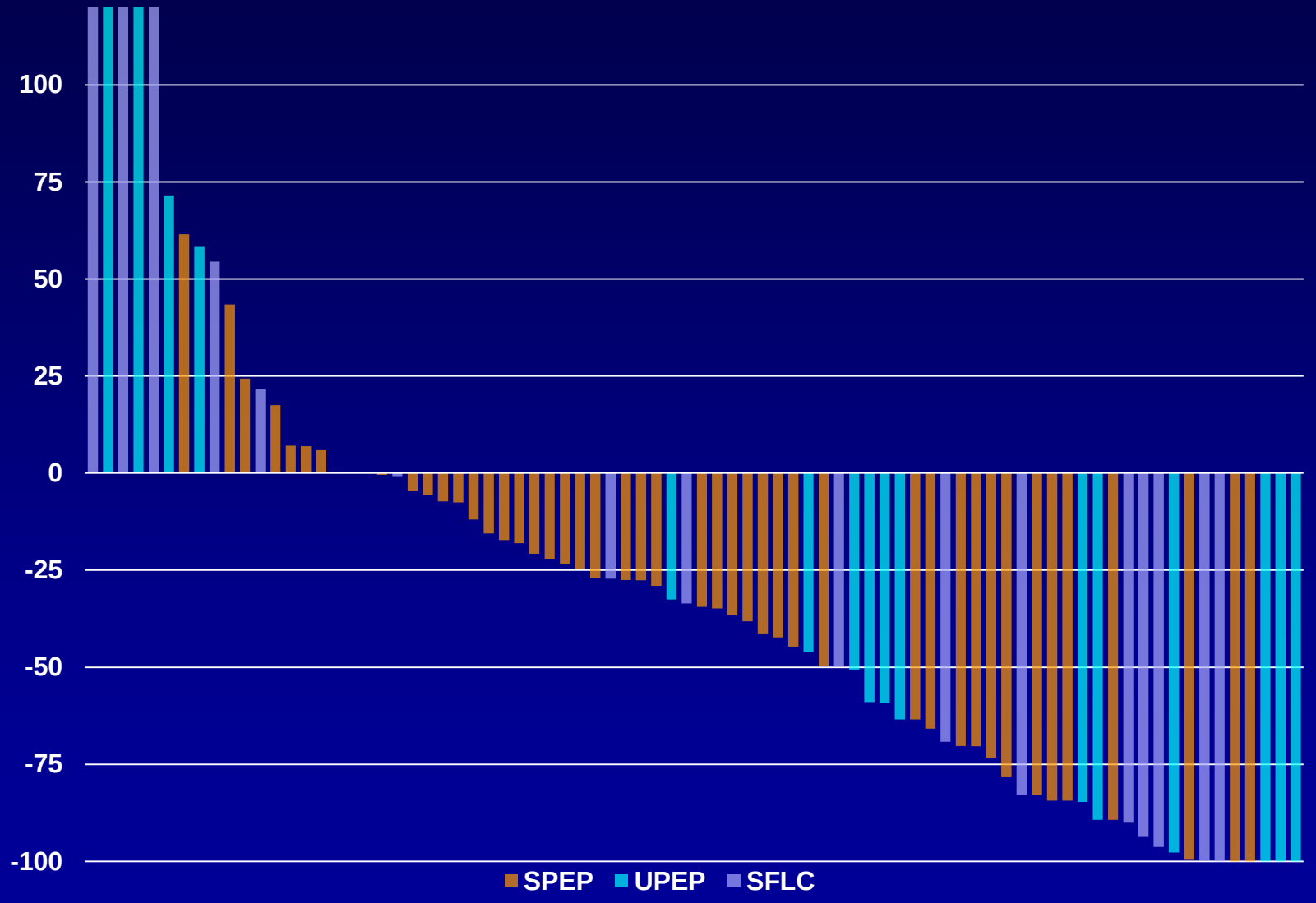
HORIZON

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

- All 83 (100%) pts 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
- MoAbs include daratumumab, elotuzumab, isatuximab

Best M-Protein Response: Majority of Patients show Disease Stabilization and/or Reduction of Tumor Burden (n=80)



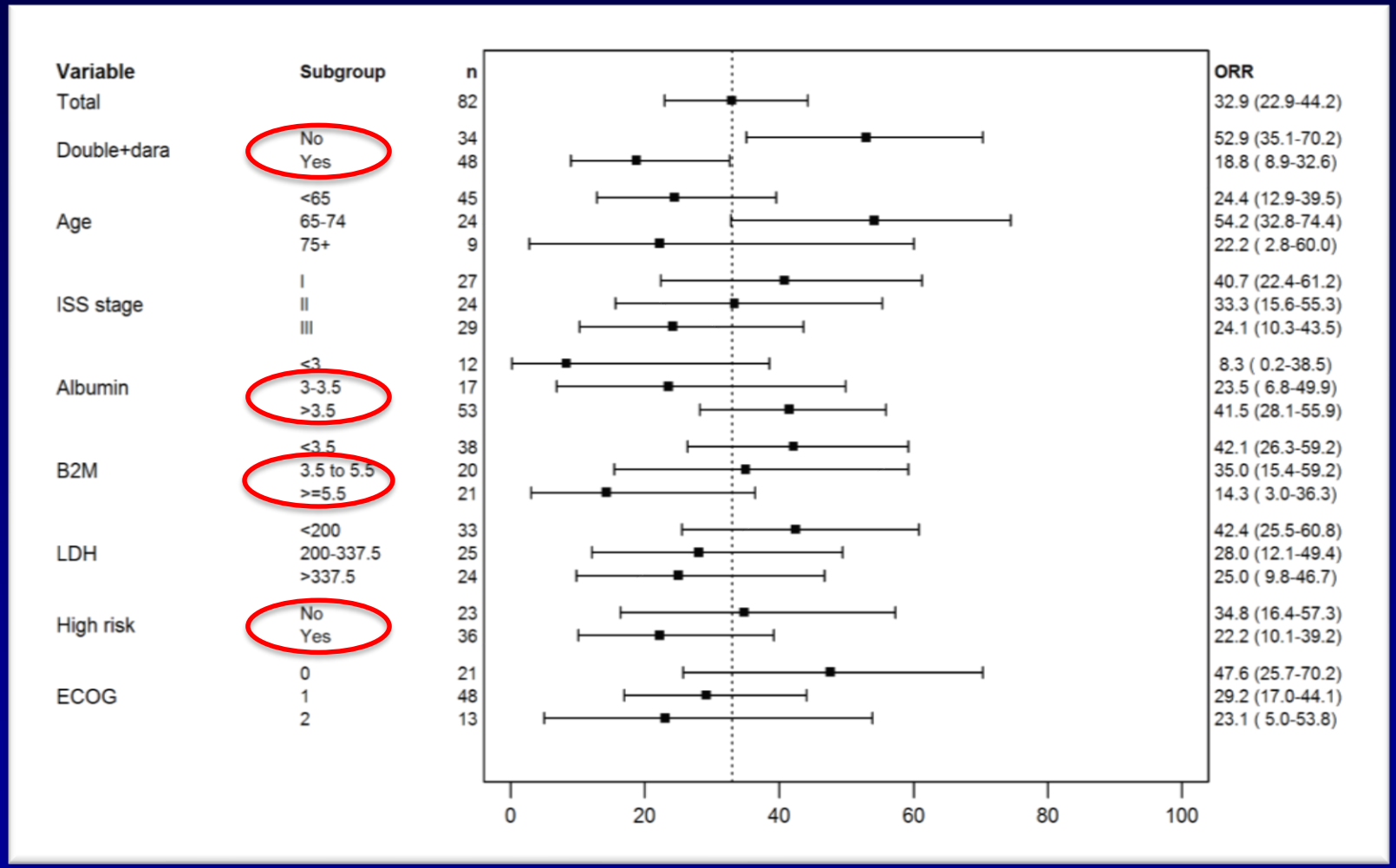
ORR in Multi-Refractory RRMM patients (n=83)

HORIZON

	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

- Overall response rate (≥PR) 33%
- Clinical Benefit Rate (≥MR) 39%
- Disease stabilization (≥SD) 84%

Overall Response Rate in Patient Subgroups (n=82)



Areas of further investigation:

- **Good signal in extramedullary disease**
- **Alkylator exposed/ refractory/ disease stage**
- **Detailed refractory status breakdown**

Prognostic Factors Associated with Response
Albumin and β_2 microglobulin in Response Evaluable Pts

	n	Overall Response Rate	Albumin ≥3.5 g/dL	Albumin ≥3.5 g/dL and β_2 microglobulin <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%

Important to know underlying biological performance status to evaluate response data in late-stage RRMM pts

Serum Albumin: Strongest Predictor of ORR (β_2M and LDH lose significance once adjusted for albumin)

	n	Odds ratio	95% CI	P-value
Albumin	79	2.62	(0.91-7.56)	0.075
β_2M	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

- In an exploratory multivariable logistic regression model, only baseline albumin emerged as a prognostic factor for ORR.

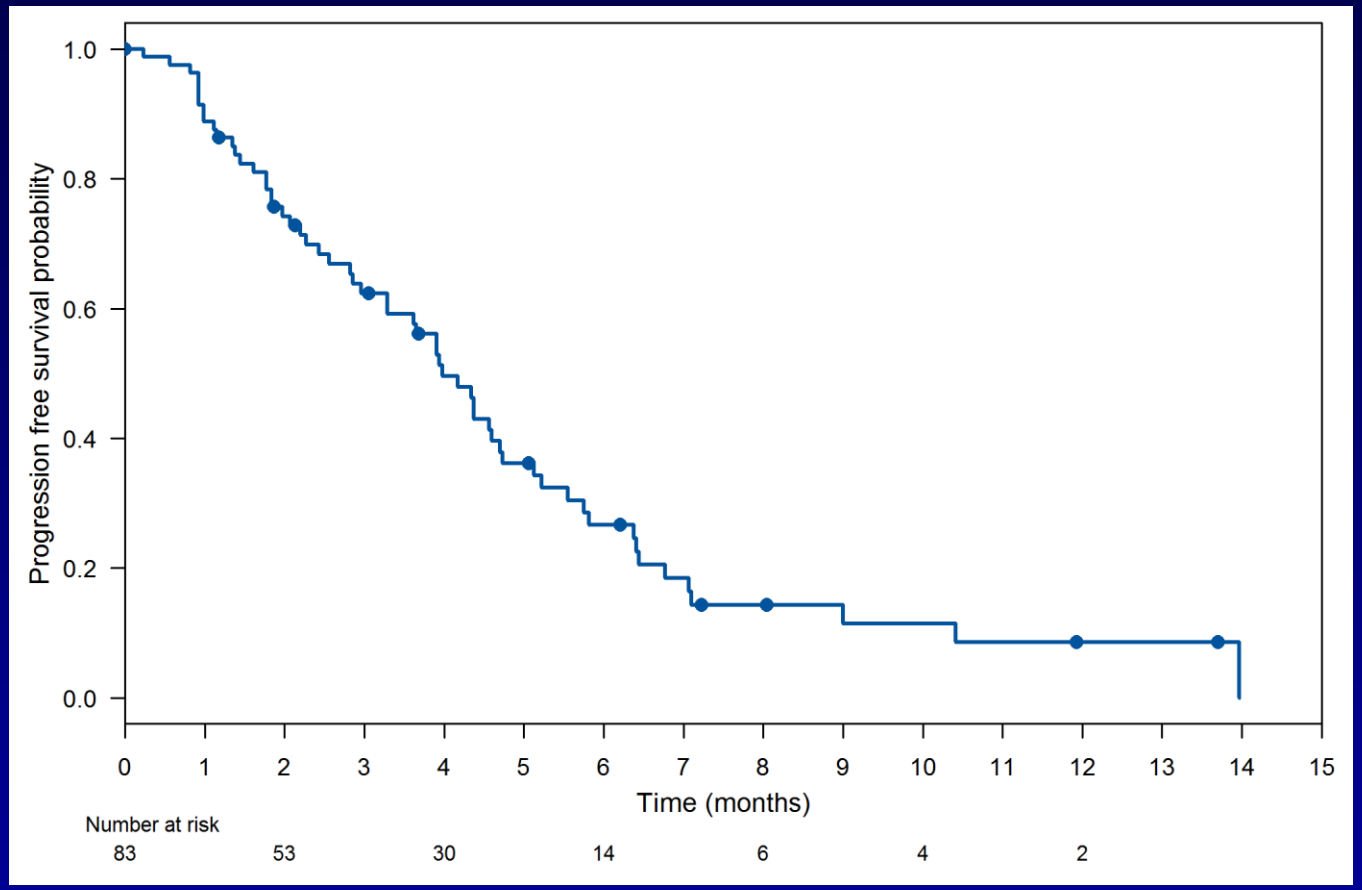
  Baseline LDH, β_2M and ISS at study entry did not add additional information.

- Further verified after a stepwise selection process where albumin remained only independent factor.

	n	Odds ratio	95% CI	P-value
Albumin	79	3.21	(1.19-8.69)	0.021

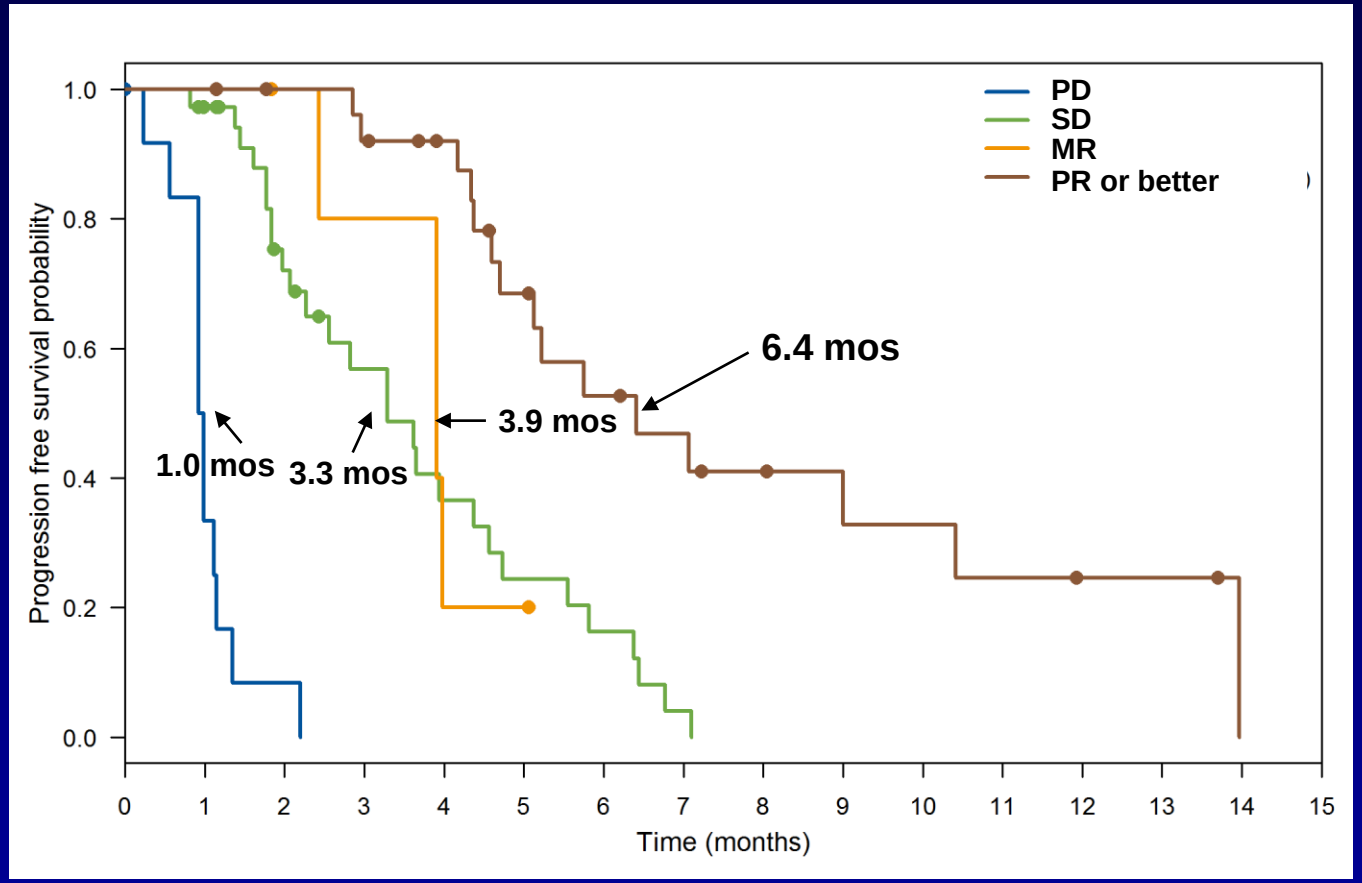
- Further evaluation ongoing, but caution warranted given relatively low number of events, non pre-specified analysis

Progression-Free Survival (n=83)



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

PFS by Response Category (n=83)



Overview of Safety and Tolerability (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)
Treatment-related SAEs	14 (16)*	5 (6)

- No treatment-related deaths.
- G4 lab thrombocytopenia at Day 29 in 4% of cyles.
- 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%
- Discontinuation rate due to AEs 13% (8 of 11 due to thrombocytopenia).

*Most frequent: febrile neutropenia (5 of 14), neutropenia (3 of 14) and thrombocytopenia (2 of 14).

HORIZON: Patient Case

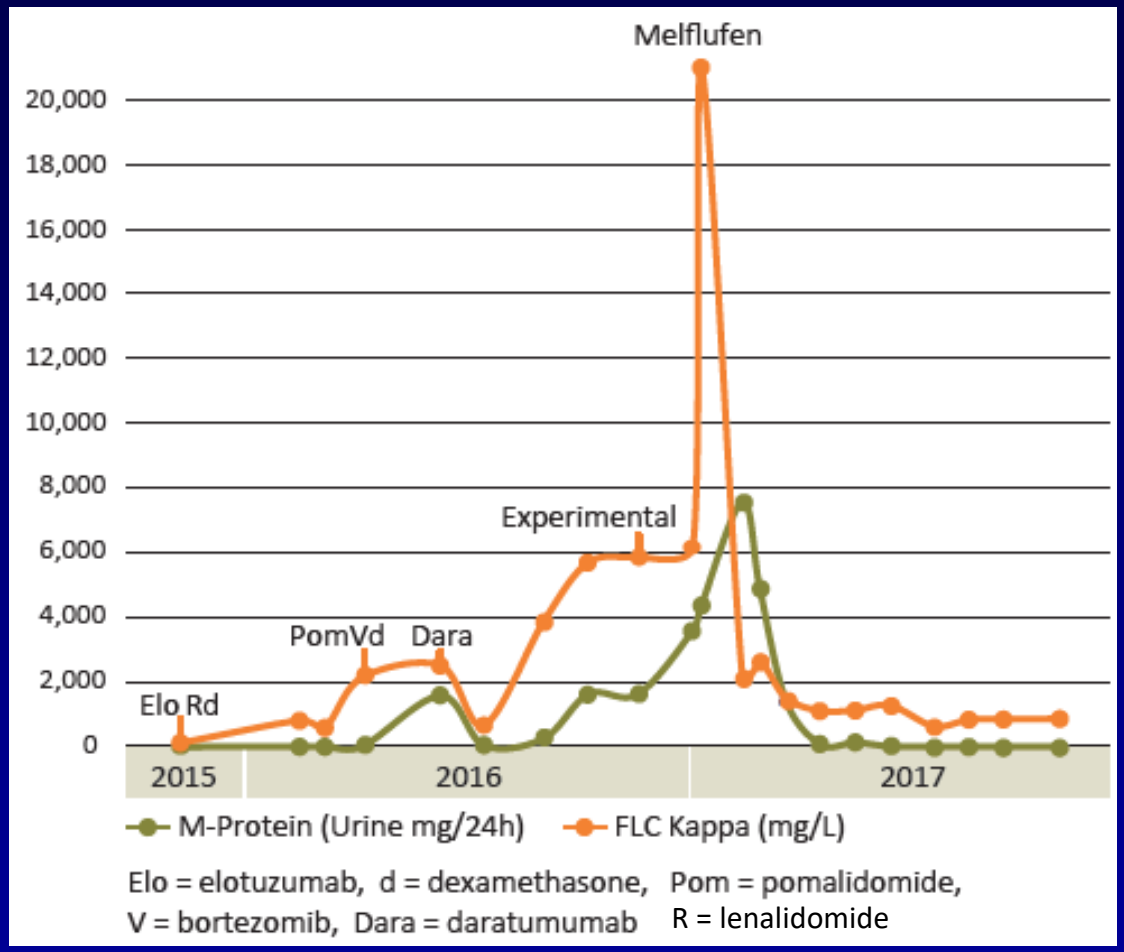
Treatment History
(Initial Treatment and Salvage from 2007-2015)

MM BJ Kappa LC MM
42 year gentleman at diagnosis

Prior lines:
1. Thalidomide, Dex + ASCT → CR
2. Bortezomib, Dex + 2nd ASCT → CR
3. Lenalidomide, Dex → VGPR
4. VTD x2, DCEP x2, PomDex → PR
5. VBCMP/VBAD + Allo-SCT → PR

6. Elo Rd → PD
7. Pom Dex, Bortezomib (PVD) → PD
8. Dara → PD
9. Experimental drug (ADC targeting CS1) → PD

PD with RR MM (2015-2016)
Refractory to last 4 lines, with 9 lines of treatment overall



- Started 40 mg melflufen/dex (2017)
- Received 9 cycles per protocol VGPR as best response in cycle 3
- Experienced treatment-related G4 thrombocytopenia, G3 anemia, G3 neutropenia, otherwise well tolerated
- EOT due to PD after 9 cycles completed
- PFS: 10.4 months

Mateos MV, Rocafiguera AO, Otero PR, et al. The HORIZON study: a preliminary report on efficacy and safety of melflufen in late stage relapsed-refractory myeloma (RRMM) patients refractory to pomalidomide and/or daratumumab. Presented at the 2018 European Hematology Association Annual Meeting, Stockholm, June 14-17, 2018.

Conclusions and Future Directions

HORIZON

- Melflufen/dex 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 is a strong 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/dexamethasone and pomalidomide/dexamethasone in RRMM ongoing (OCEAN)
- Phase 1/2 combination study (NCT03481556) in RRMM of Melflufen/dex with daratumumab and bortezomib ongoing (ANCHOR) (ASH 2018; abs. 1967)

Acknowledgements and Thank You

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