

# **HORIZON (OP-106) Study of Melflufen in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Daratumumab and/or Pomalidomide: Updated Efficacy and Safety**

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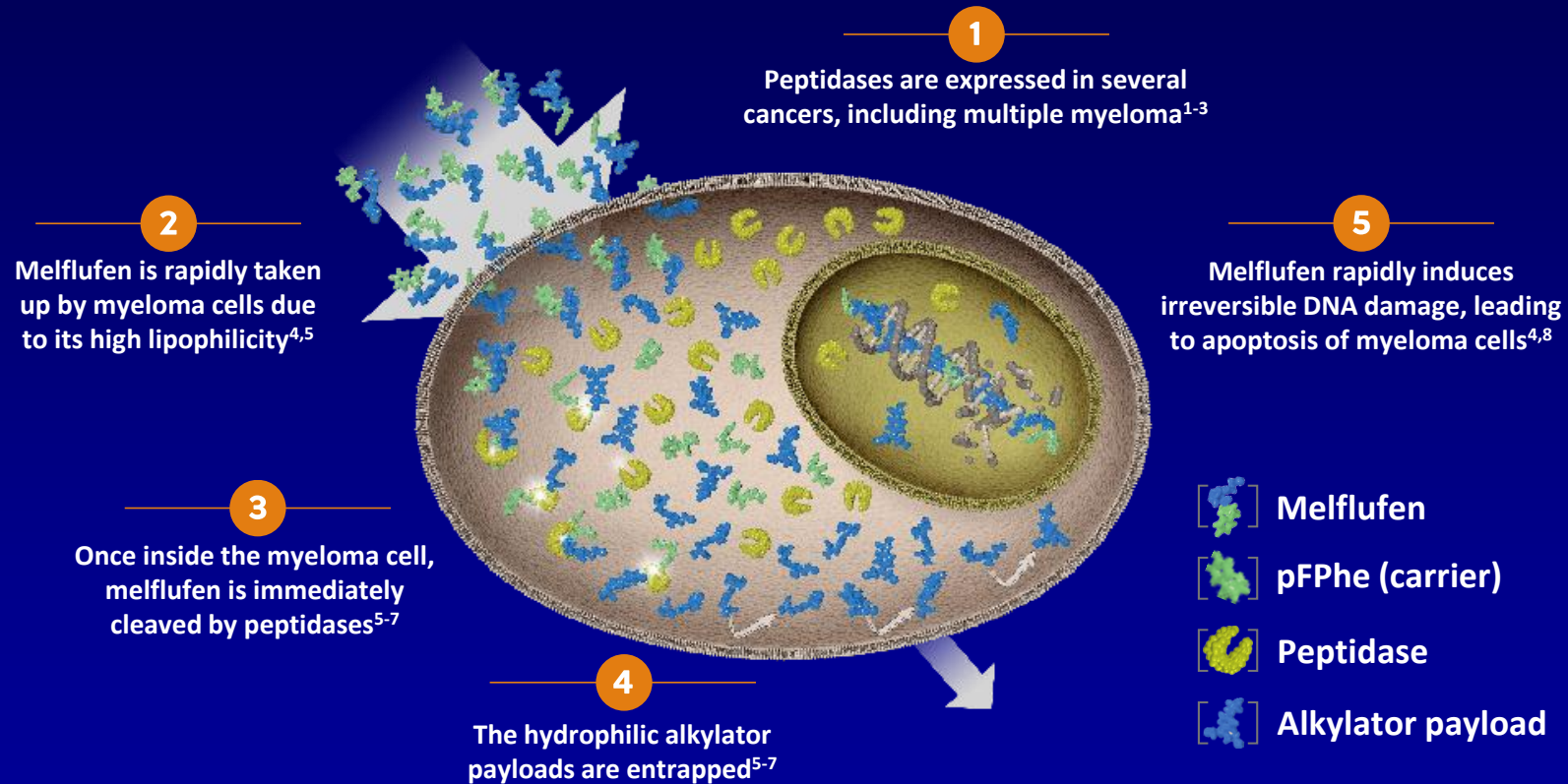
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## **Disclosures:**

**Christopher Maisel: Honoraria from Amgen, Celgene, Gilead, Janssen, Incyte, Takeda, and Verastem.**

# Melflufen Is a Lipophilic Peptide-Conjugated Alkylator That Rapidly Delivers a Highly Cytotoxic Payload Into Myeloma Cells

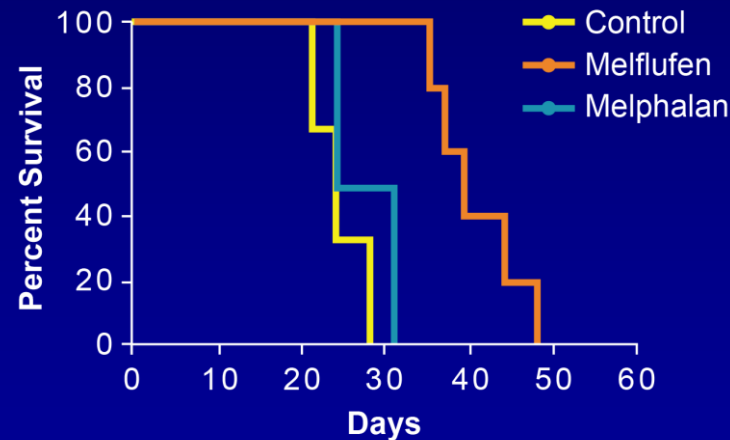
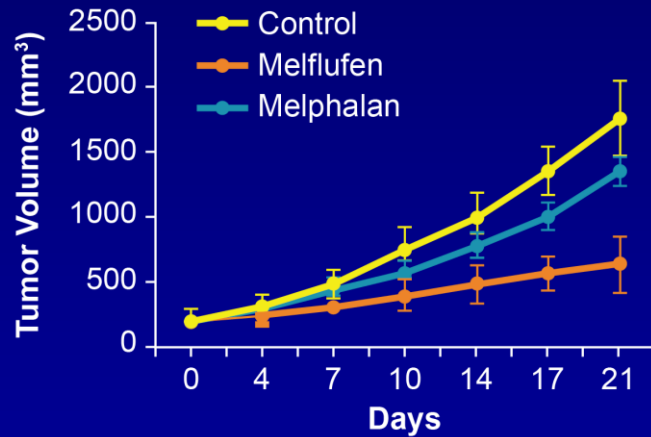
## Peptidase-enhanced activity in multiple myeloma cells



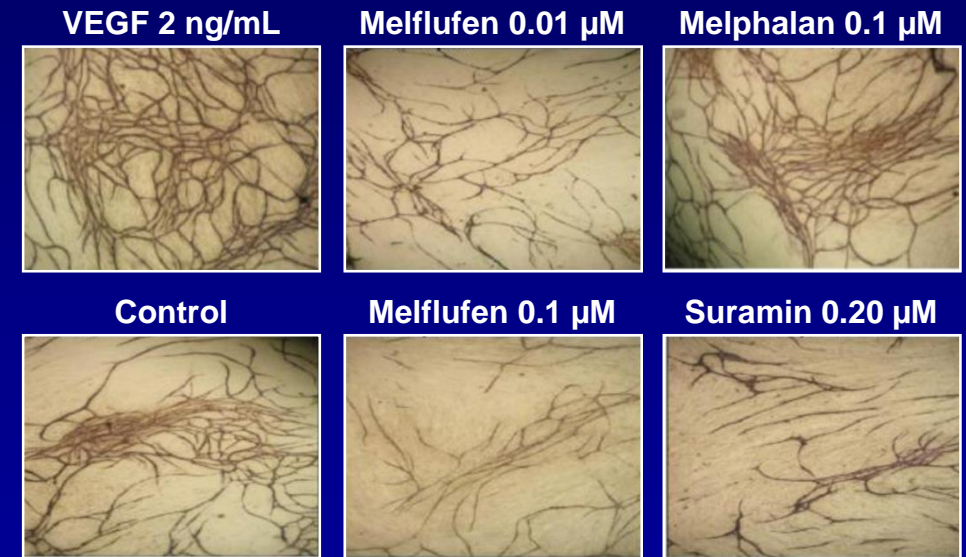
1. Hitzerd SM, et al. *Amino Acids*. 2014;46:793-808. 2. Moore HE, et al. *Mol Cancer Ther*. 2009;8:762-770. 3. Wickström M, et al. *Cancer Sci*. 2011;102:501-508. 4. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019-3031. 5. Wickström M, et al. *Oncotarget*. 2017;8:66641-66655. 6. Wickström M, et al. *Biochem Pharmacol*. 2010;79:1281-1290. 7. Gullbo J, et al. *J Drug Target*. 2003;11:355-363. 8. Ray A, et al. *Br J Haematol*. 2016;174:397-409.

# Selective Cytotoxicity of Melflufen: In Vivo Efficacy

- *In vivo* human xenograft mouse models treated with melflufen showed higher inhibition of tumor growth and prolonged survival vs those treated with alkylators such as melphalan alone<sup>1</sup>
- Melflufen showed pronounced anti-angiogenic activity (up to >100-fold) at lower doses than the alkylator melphalan alone<sup>2</sup>



*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 MM tumor growth ( $P = 0.001$ ) and prolonged survival ( $P < 0.001$ ) of these mice.<sup>1</sup>

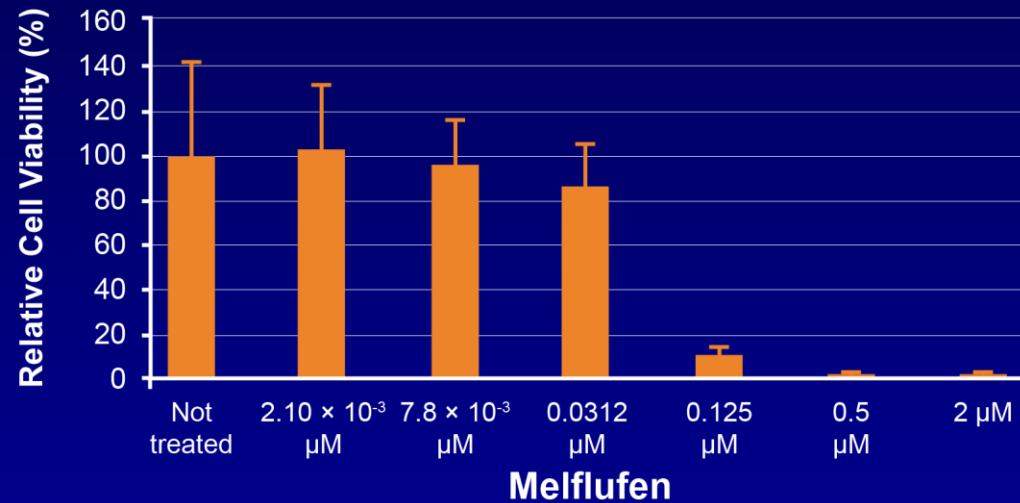


Decrease in tubule length and vessel junctions shown for melflufen, with dose response seen, compared with the positive control VEGF (2 ng/mL).<sup>2</sup>

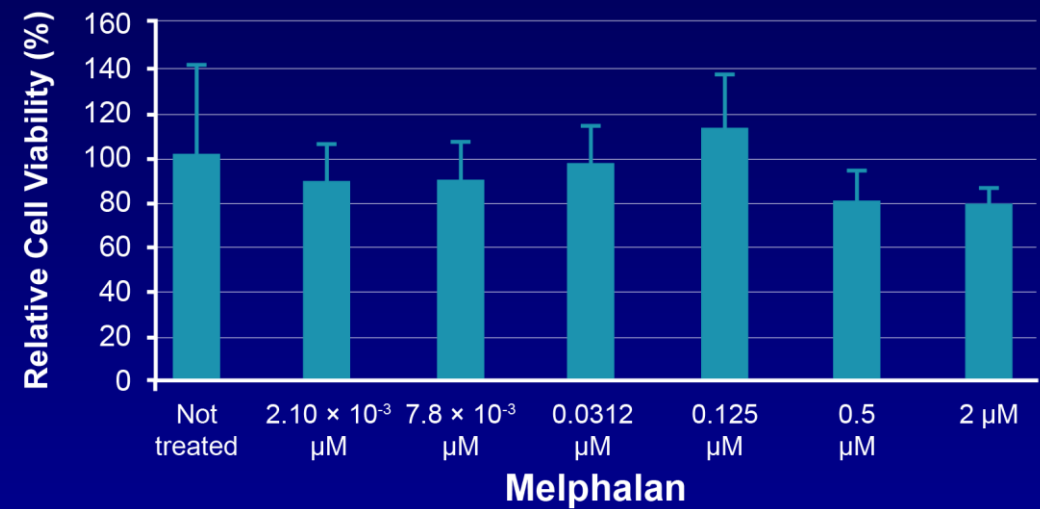
1. Chauhan D, et al. *Clin Cancer Res.* 2013;19:3019-3031. 2. Strese S, et al. *Biochem Pharmacol.* 2013;86:888-895.

# Selective Cytotoxicity of Melflufen: Osteoclast Precursor Activity

**CD14+ Osteoclast Precursor**



**CD14+ Osteoclast Precursor**



- Osteoclasts have short half-life, but activity against CD14+ osteoclast precursors should lower osteoclast activity and potentially improve bone pain in patients (pts) with multiple myeloma (MM)
- Melflufen shows pronounced activity against CD14+ osteoclast precursors at clinically relevant concentrations compared to melphalan

# Unmet Medical Need in Relapsed and Refractory Multiple Myeloma (RR MM)

- Lenalidomide and PI-based failure in pts who subsequently become refractory to salvage therapy with daratumumab (anti-CD38 mAb) and/or pomalidomide have limited effective treatment options<sup>1</sup>
- Introducing a treatment class switch with a novel compound may represent an important therapeutic strategy
- Of particular importance is to develop new treatment strategies for pts who are triple-class refractory (IMiD + PI + anti-CD38 mAb), and especially those pts with extramedullary disease (EMD), who have very poor prognosis<sup>2</sup>

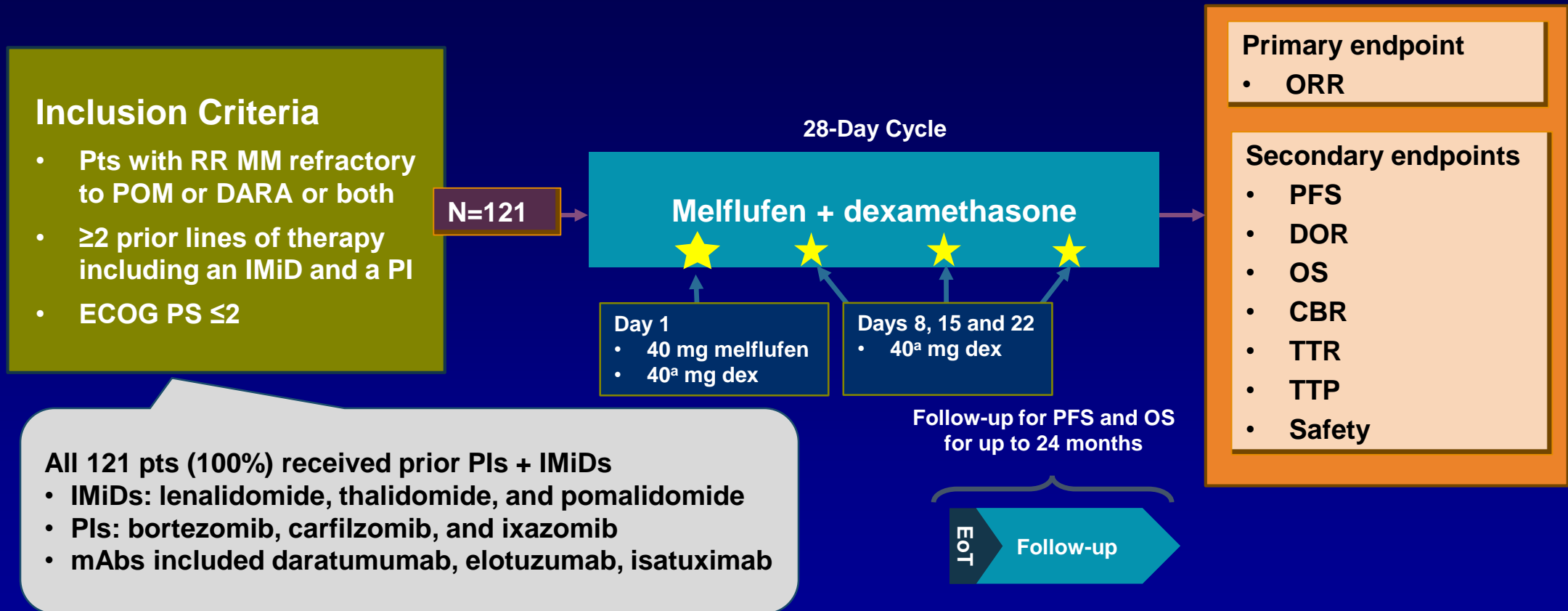
1. Ghandi UH, et al. *Leukemia*. 2019. [epub ahead of print]. 2. Usmani SZ, et al. *Haematologica*. 2012;97:1761-1777.

# Melflufen in RR MM: O-12-M1 and ANCHOR

- **O-12-M1 (N=45): melflufen + dex demonstrated promising and durable response in heavily pretreated RR MM<sup>1,2</sup>**
  - Pts refractory to both IMiDs/Pis and progressed on last line of therapy
  - **ORR 31% and CBR 49% (with similar results regardless of disease status)**
    - ORR 33% in pts (8 of 24) refractory to prior alkylator therapy
    - ORR 42% in pts (5 of 12) who progressed on prior alkylator therapy within  $\leq 12$  months
  - Median DOR 8.4 months; PFS 5.7 months and OS 20.7 months
  - Favorable tolerability - hematologic toxicity common but clinically manageable; nonhematologic AEs infrequent
- **Phase 1/2 study ANCHOR: melflufen plus dexamethasone demonstrated high response rate when combined with bortezomib or daratumumab in RR MM pts<sup>3</sup>**
  - 100% ORR with bortezomib
  - 82% ORR with daratumumab (in pts with  $\geq 2$  completed cycles of therapy)

# HORIZON: Study Design

## Phase 2, Single-Arm, Open-Label, Multicenter Study



- **With median follow-up of 10.8 months, 29% of pts on ongoing treatment** (data cutoff 06 May 2019)

ClinicalTrials.gov Identified: NCT02963493.

CBR, clinical benefit rate; DARA, daratumumab; dex, dexamethasone; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IMiD, immunomodulatory agent; mAbs, monoclonal antibodies; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; RR MM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

<sup>a</sup>Pts aged >75 years received dex 20 mg.

# Baseline Patient Characteristics (N=121)

Characteristic	N=121
Age, median (range), years	64 (35-86)
Gender (male / female), %	55 / 45
Time since diagnosis, median, years	6.2 (0.7-25)
No. of prior lines of therapy, median (range)	5 (2-12)
ISS stage I / II / III / unknown, <sup>a</sup> %	38 / 30 / 29 / 4
ECOG PS 0 / 1 / 2, <sup>a</sup> %	24 / 61 / 14
High-risk cytogenetics, <sup>b</sup> %	62
≥2 high-risk abnormalities, %	19
Del(17p), %	17
Extramedullary disease, <sup>c</sup> %	60

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

<sup>a</sup>ISS stage and ECOG PS at study entry, with data pending for 16 and 10 pts, respectively.

<sup>b</sup>High-risk cytogenetics [t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, gain(1q) or karyotype del(13)] at study entry; data pending for 40 pts; 5 pts with unknown status at study entry had high-risk cytogenetics at diagnosis and were included in the high-risk group.

<sup>c</sup>Data pending for 54 pts.

# Prior Treatment and Refractory Status (N=121)

Prior Therapy Status	N=121
Double-class (IMiD + PI) exposed / refractory	100% / 91%
Anti-CD38 mAb exposed / refractory	79% / 79%
Triple-class (IMiD + PI + anti-CD38 mAb) exposed / refractory	79% / 74%
Alkylator exposed / refractory	86% / 59%
≥1 Prior ASCT	69%
≥2 Prior ASCTs	11%
Relapsed ≤1 year after ASCT	20%
Refractory in last line of therapy	98%

ASCT, autologous stem cell transplantation; IMiD, immunomodulatory agent; PI, proteasome inhibitor; mAb, monoclonal antibody.

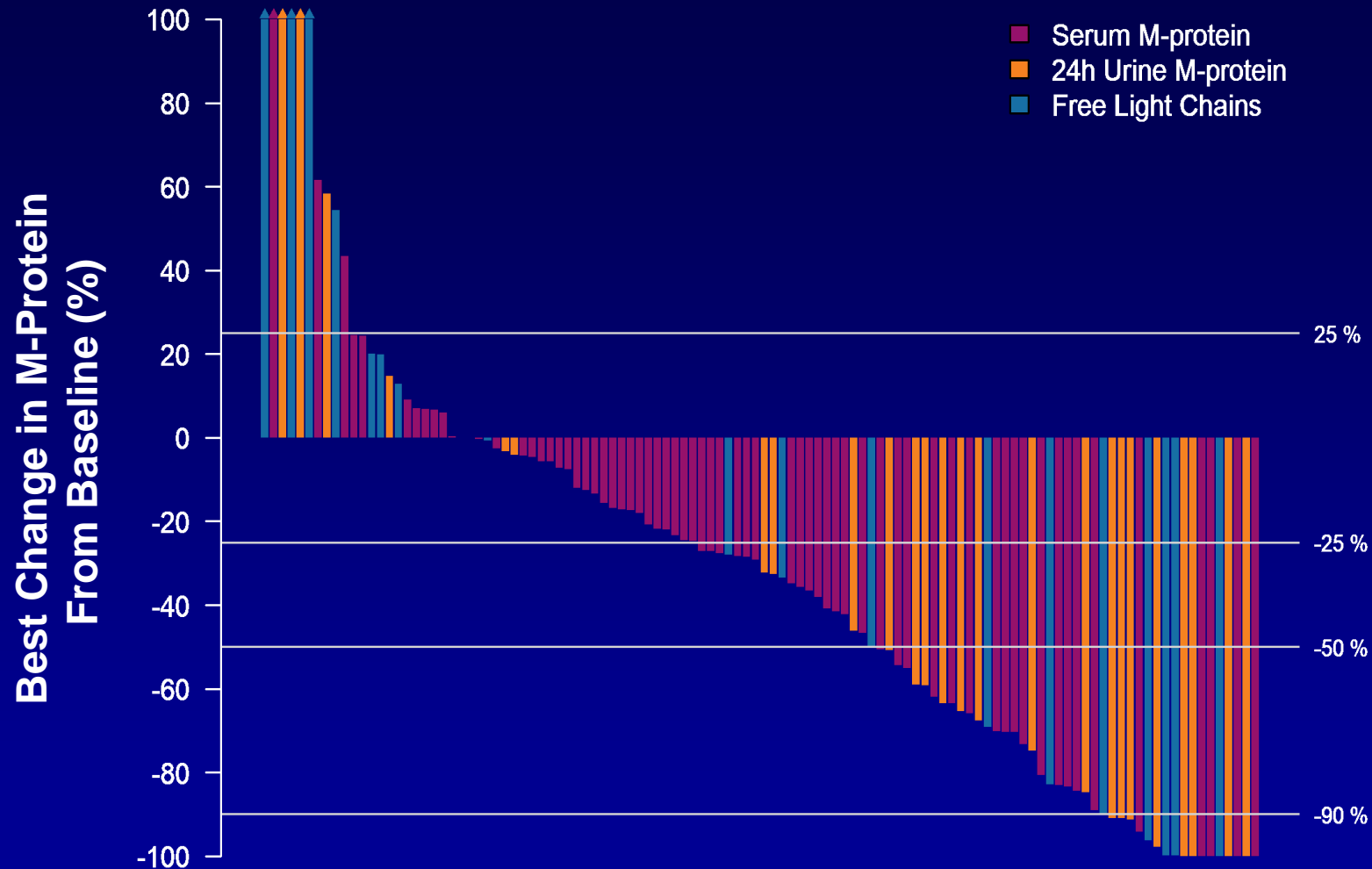
- 36% used ≥ 3 treatment regimens in last 12 months prior to enrolment

# Patient Disposition (N=121)

<b>Disposition</b>	<b>N=121</b>
<b>On treatment at data cutoff</b>	<b>35 (29%)</b>
<b>Discontinued treatment at data cutoff<sup>a</sup></b>	<b>86 (71%)</b>
<b>Disease progression</b>	<b>59 (69%)</b>
<b>Adverse event(s)</b>	<b>17 (20%)</b>
<b>Physician decision</b>	<b>4 (5%)</b>
<b>Lack of response</b>	<b>3 (3%)</b>
<b>Pt request</b>	<b>3 (3%)</b>

<sup>a</sup>Percentages for discontinuation cause have been calculated as fraction of pts who discontinued (n=86).

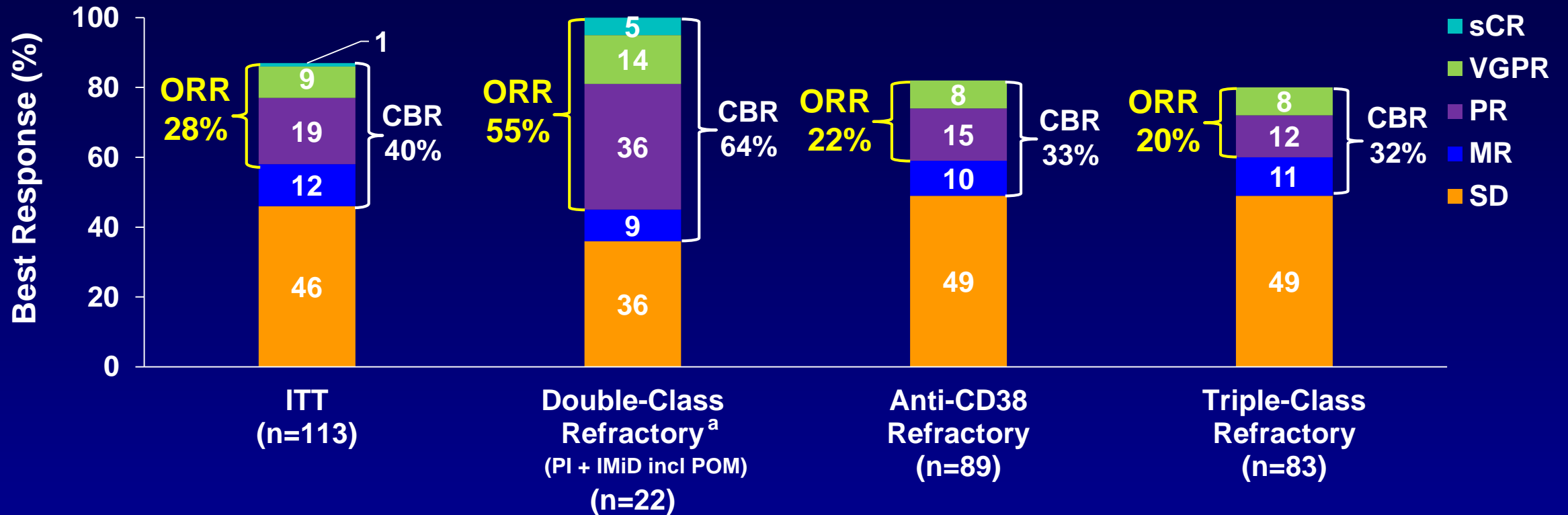
# Best M-Protein Response (n=113)<sup>a</sup>



<sup>a</sup>M-protein data for 8 pts pending at time of data cut-off.

**Disease stabilization rate ( $\geq$ SD) 86%**

# Best Response (IMWG<sup>1</sup>)



- 8 pts did not have available response information at data cutoff; 2 pts response evaluable, PI exposed, but refractoriness to PI subject to confirmation, so excluded from subgroup analysis
- One pt with sCR also confirmed as MRD negative ( $10^{-6}$  sensitivity), with ongoing progression-free period of 13.6 mos
- Median time to response 1.2 mos

<sup>a</sup>Not anti-CD38 refractory.

1. Rajkumar SV, et al. *Blood*. 2011;117:4691-4695.

# Best Response for EMD and Non-EMD Patients (n=67)

	ORR, %
<b>EMD-relapsed/refractory pts<sup>a</sup></b> (n=40)	<b>29</b>
<b>Non-EMD-relapsed/refractory pts<sup>a</sup></b> (n=27)	<b>38</b>
<b>EMD triple-class refractory<sup>a</sup></b> (n=37)	<b>23</b>
<b>Non-EMD triple-class refractory<sup>a</sup></b> (n=20)	<b>26</b>

EMD, extramedullary disease; EoT, end of treatment; ORR, overall response rate.

<sup>a</sup>2, 1, 2, 1 ps, respectively, did not have any available response data or EoT data at the time of data cutoff.

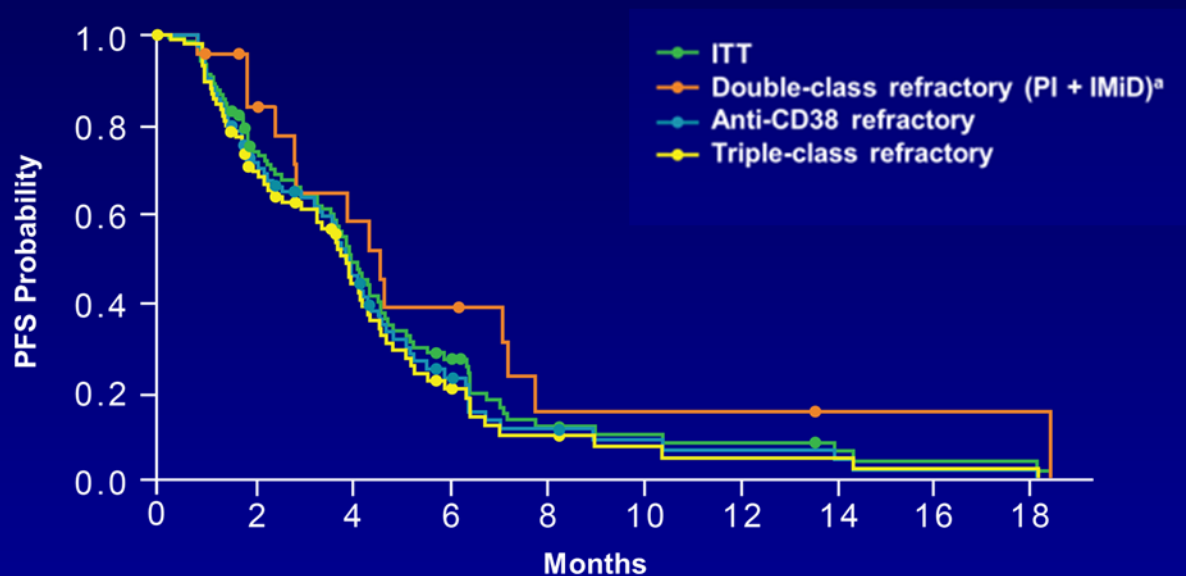
- Poor outcomes observed across the limited clinical trial datasets available<sup>1-5</sup>
- Studies have failed to demonstrate any significant and/or durable response in pts with relapsed EMD: only dara and pom have shown response with ORRs of 17% and 9%, respectively ( $\geq 3$  prior lines of therapy; dara and pom naïve)<sup>1-5</sup>
- HORIZON is one of the largest clinical trial cohorts of EMD-relapsed/refractory pts to date
  - EMD data pending for 54 pts (across 3 major participating centers with recently enrolled pts, limited data entry to date)

1. Jiménez-Segura R, et al. *Blood*. 2016;128:Abstract 5709. 2. Rosiñol L, et al. *Haematologica*. 2004;89:832-836. 3. Jiménez-Segura R, et al. *Eur J Haematol*. 2019;102:389-394. 4. Usmani SZ, et al. *Blood*. 2016;128:37-44. 5. Ichinohe T, et al. *Exp Hematol Oncol*. 2016;5:11.

Data cutoff 06 May 2019.

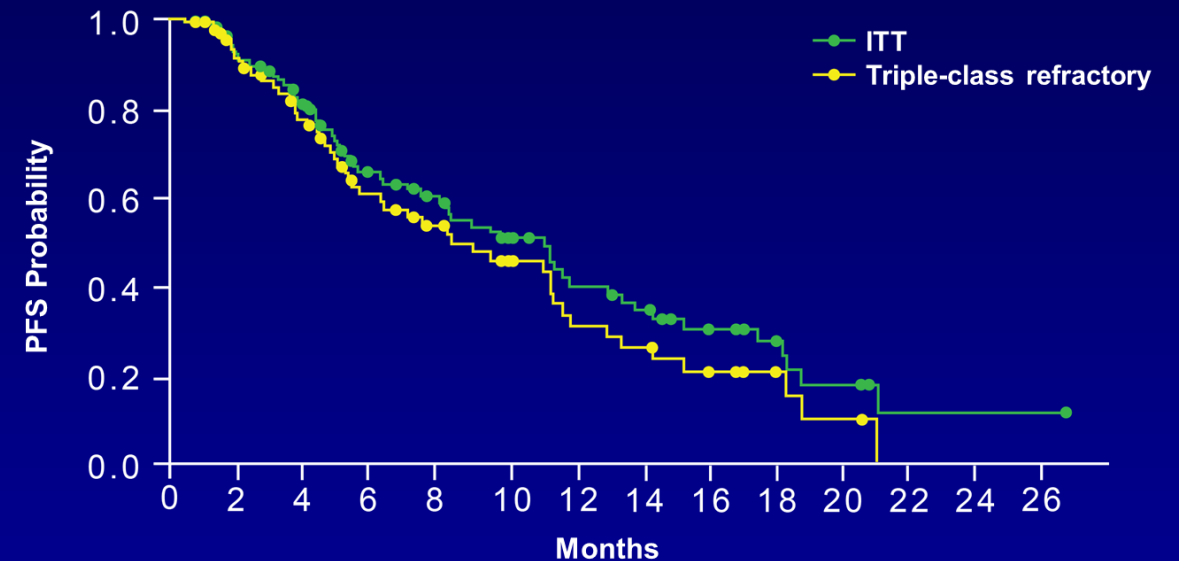
# Progression-Free and Overall Survival (N=121)

## Progression-Free Survival



- Median PFS 4.0 months (95% CI, 3.7-4.6)
- Similar PFS seen across different refractory subgroups

## Overall Survival

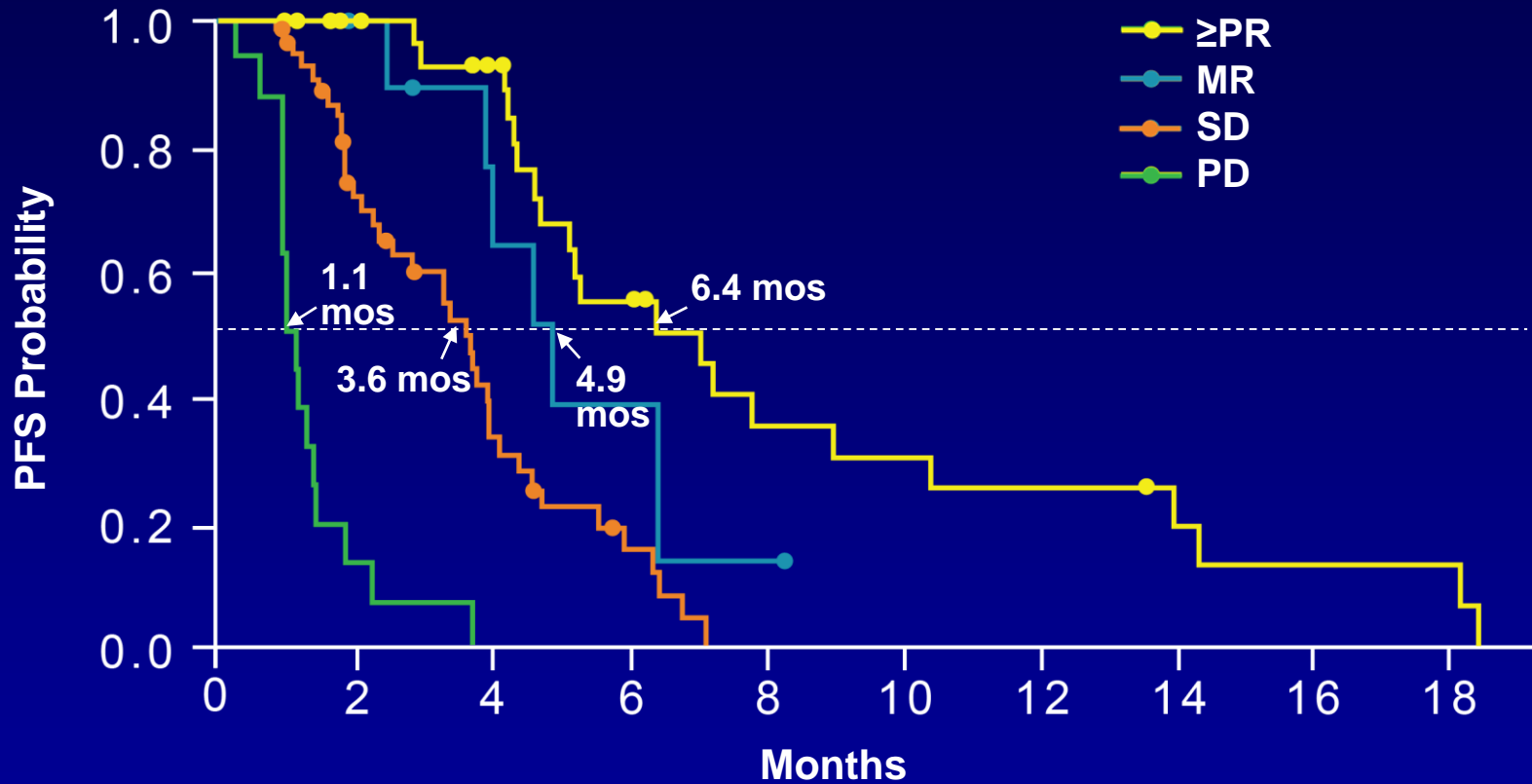


- Median OS 11.2 months (95%CI, 8.1-13.9) for the ITT population (N=121), and 8.5 months (95%CI, 6.4-11.8) for triple-class refractory population (n=89)

<sup>a</sup>Not anti-CD38 refractory.

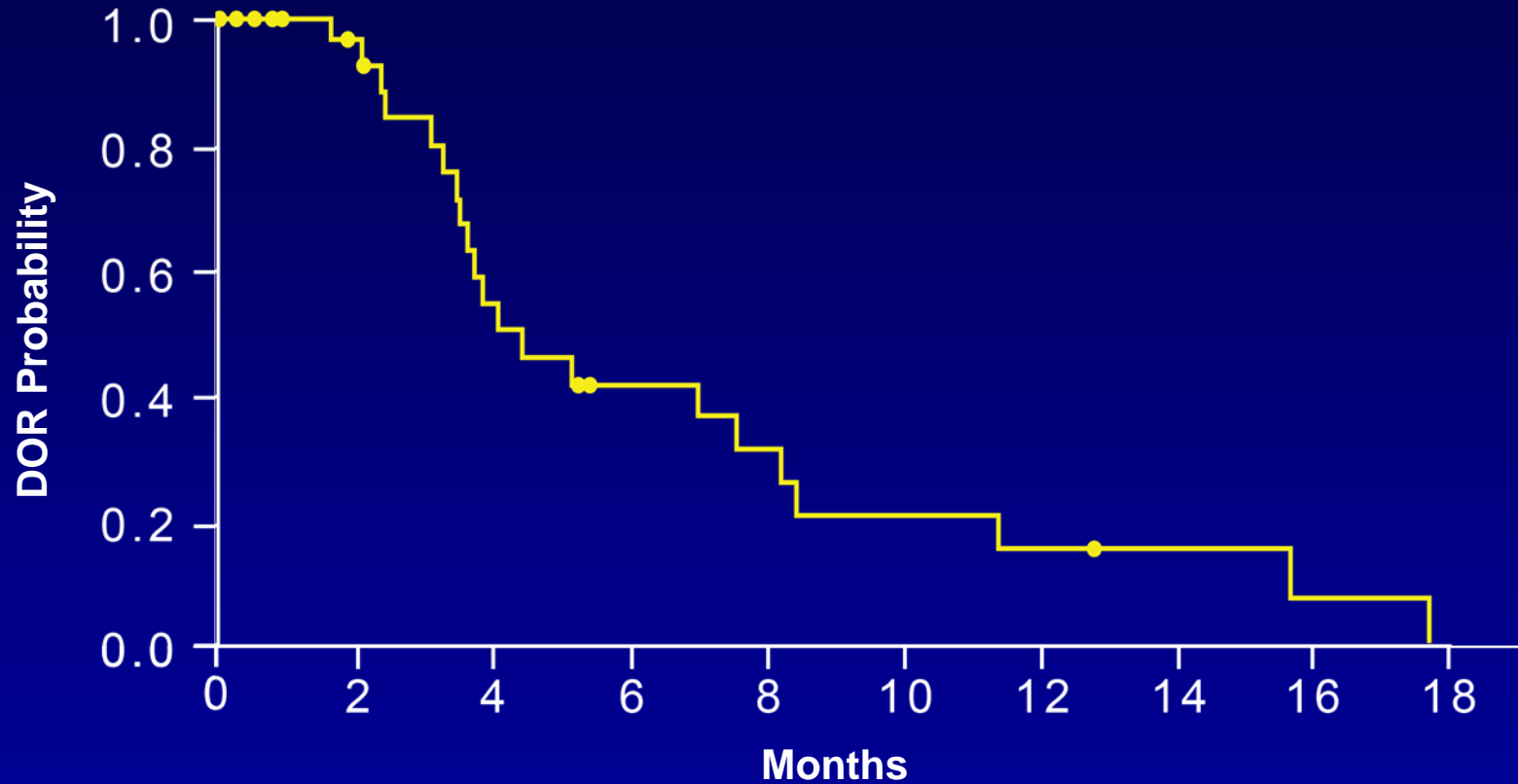
Data cutoff 06 May 2019.

# PFS by Response Subgroups (N=121)



- Median PFS 6.4 months in pts with  $\geq$  PR; 4.9 months in those with MR

# Duration of Response (n=32)



- Median DOR 4.4 months (95% CI, 3.6-8.3)

# Dose Modifications Due to TEAEs

Action Taken With Meflufen (N=121)	n (%)
Dose modification due to TEAE	56 (46)
Dose reduced	27 (22)
Dose delayed	43 (36)
Drug discontinued	29 (24)

Dose modification calculated as the number of pts with a TEAE requiring a dose modification at any time point. Dose delayed calculated as number of pts with a TEAE leading to a dose delay. Pts may have had more than 1 action taken with meflufen and may be included in more than 1 category.

# Safety and Tolerability

<b>Treatment-Related AEs, n (%)</b>	<b>Grade 3<sup>a</sup> (N=121)</b>	<b>Grade 4 (N=121)</b>
<b>Any AE</b>	<b>29 (24)</b>	<b>59 (49)</b>
<b>Thrombocytopenia</b>	<b>26 (21)</b>	<b>44 (36)</b>
<b>Neutropenia</b>	<b>31 (26)</b>	<b>37 (31)</b>
<b>Anemia</b>	<b>31 (26)</b>	<b>1 (1)</b>

- Treatment-related SAEs in 20% of pts
  - Most commonly, febrile neutropenia (5%) and thrombocytopenia (2%)
- Grade 4 platelet values at day 29 in 4% of cycles
- 6 pts (6%) experienced treatment-related bleeding: grade 1 in 4 pts, grade 3 in 2 pts
- Low overall incidence of nonhematologic AEs
- No treatment-related deaths

AE, adverse event; SAE, serious adverse event.  
<sup>a</sup>Grade 3 AEs occurring in ≥5% of pts.

# Conclusions and Future Directions

- **Melflufen continues to demonstrate promising activity in pts with RR MM (majority with EMD) refractory to lenalidomide- and PI-based regimens and subsequently resistant to daratumumab- and/or pomalidomide-based salvage therapy**
  - **ORR 28% ( $\geq$ PR), CBR 40% ( $\geq$ MR), disease stabilization ( $\geq$ SD) 86%**
    - ORR 55% double-class refractory (incl POM), 22% anti-CD38 refractory
    - ORR 20% triple-class refractory
    - ORR 29% in pts with EMD
  - **PFS 4.0 months; DOR 4.4 months**
- **Treatment generally well tolerated, with manageable toxicity**
  - **Nonhematologic AEs infrequent**
  - **Low rate of discontinuation because of AEs**
- **OCEAN phase 3 study comparing melflufen/dexamethasone and pomalidomide/dexamethasone in RR MM is ongoing (NCT03151811)**

# Acknowledgments

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# HORIZON

## Global Study With 16 Sites in 4 Countries



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