HORIZON (OP-106): Updated Efficacy and Safety of Melflufen in Relapsed/Refractory Multiple Myeloma Refractory to Daratumumab and/or Pomalidomide

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

[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]Policlinico S. Orsola Malpighi, Bologna, Italy; [8]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]CHU de Poitiers, Poitiers, France; [10]Hospital Universitario La Princesa, Madrid, Spain; [11]Baylor Scott & White Charles A. Sammons Cancer Center, Dallas, TX, USA; [12]Rush University Medical Center, Chicago, IL, USA; [13] The Oncology Institute of Hope and Innovation, Glendale, CA, USA; [14]Karmanos Cancer Institute, Detroit, MI, USA; [15]Hospital Clinico Universitario de Salamanca, Salamanca, Spain; and [16]Oncopeptides AB, Stockholm, Sweden

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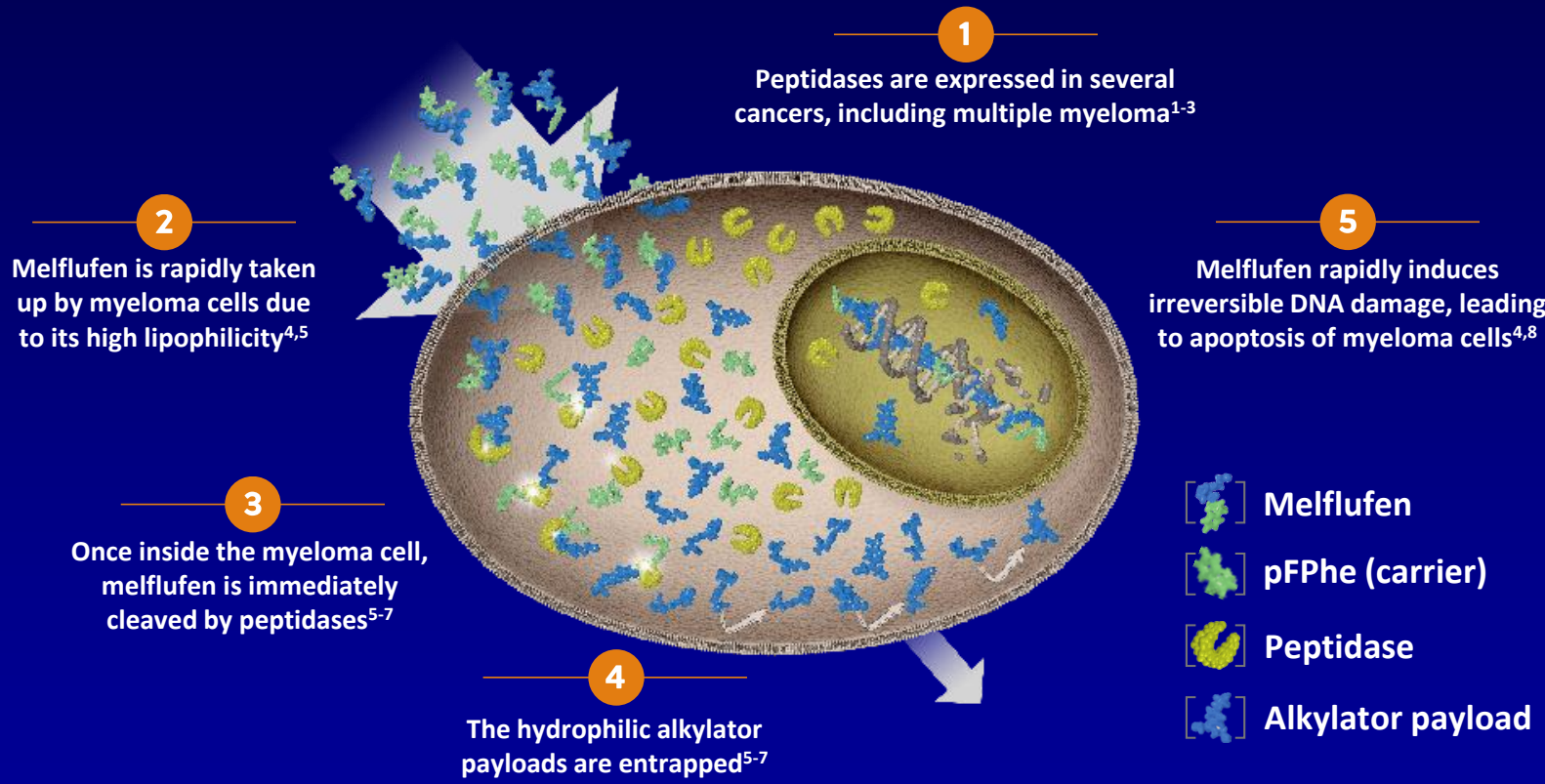
Melflufen Is a Lipophilic Peptide-Conjugated Alkylator That Rapidly Delivers a Highly Cytotoxic Payload Into Myeloma Cells

Peptidase-enhanced activity in multiple myeloma cells

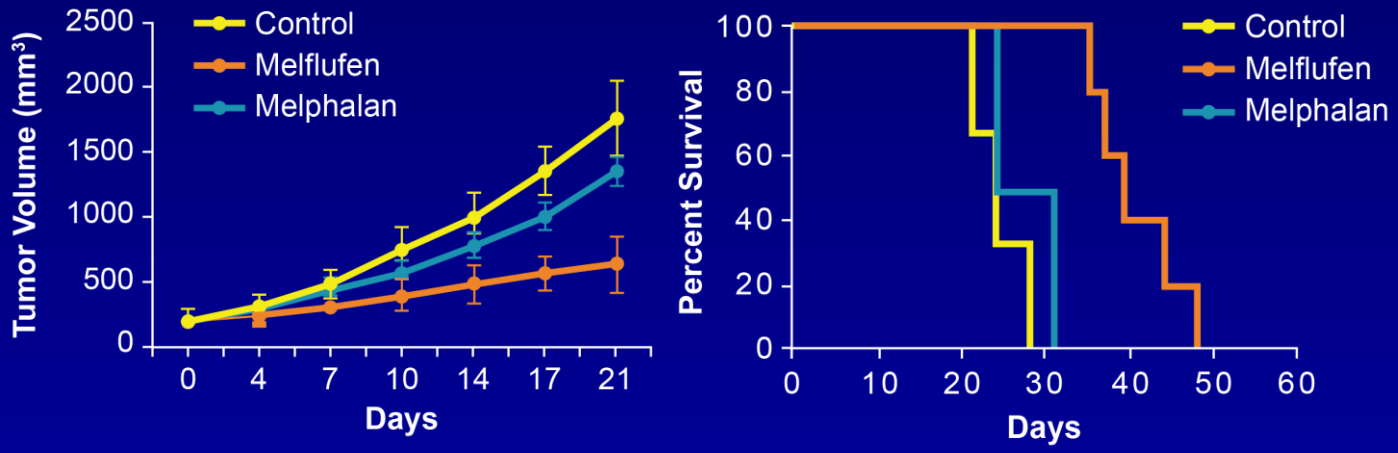


Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to increased intracellular alkylator activity[4,5]

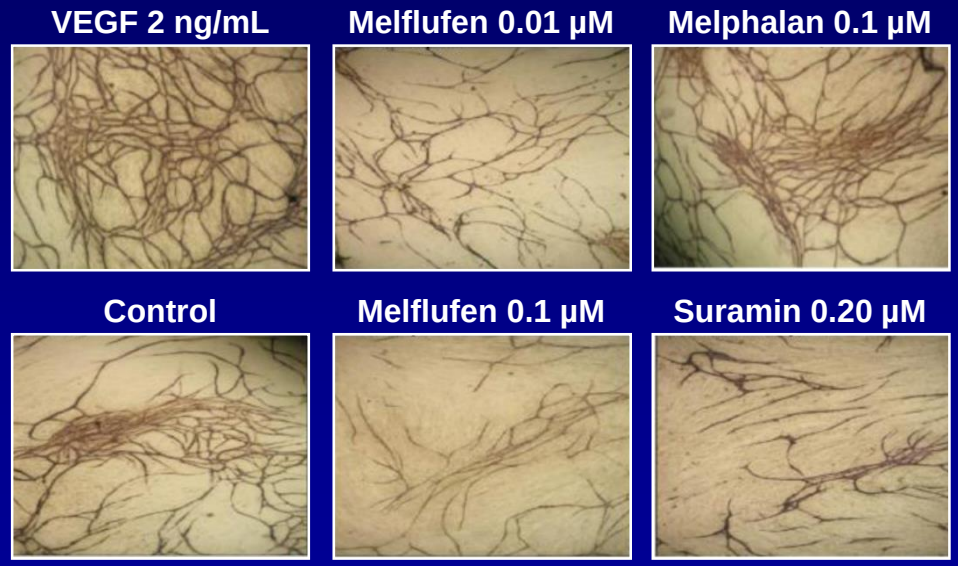
1. Hitzerd SM, et al. *Amino Acids.* 2014;46:793-808. 2. Moore HE, et al. *Mol Cancer Ther.* 2009;8:762-770. 3. Wickström M, et al. *Cancer Sci.* 2011;102:501-508. 4. Chauhan D, et al. *Clin Cancer Res.* 2013;19:3019-3031. 5. Wickström M, et al. *Oncotarget.* 2017;8:66641-66655. 6. Wickström M, et al. *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[1]**
- **Melflufen showed pronounced anti-angiogenic activity (up to >100-fold) at lower doses than the alkylator melphalan alone[2]**



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.[1]**



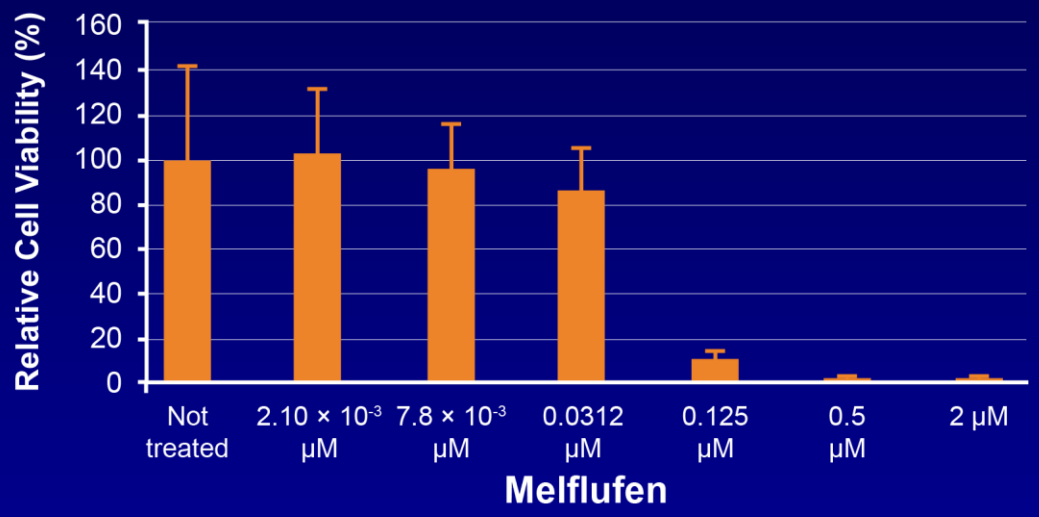
Decrease in tubule length and vessel junctions shown for melflufen, with dose response seen, compared with the positive control VEGF (2 ng/mL).[2]

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

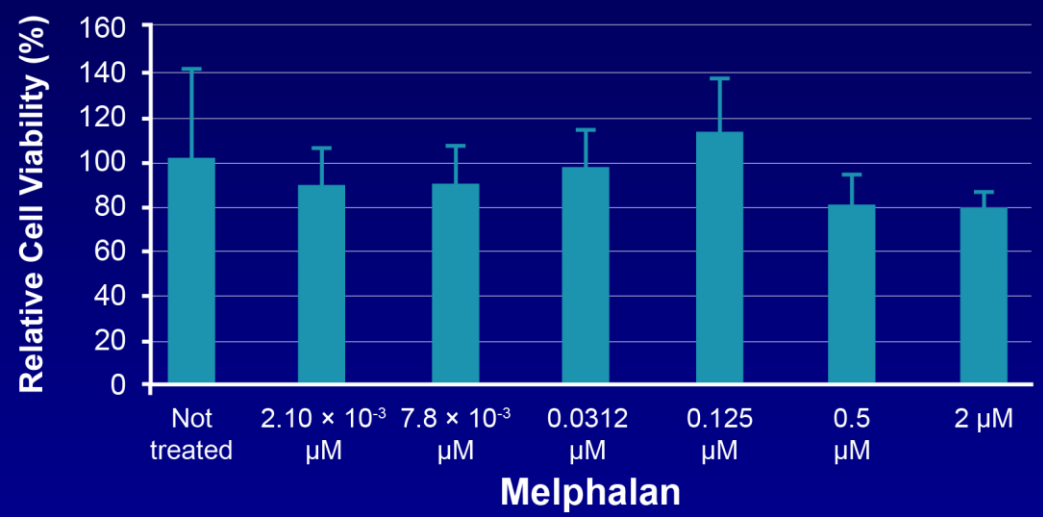
Selective Cytotoxicity of Melflufen:
Osteoclast Precursor Activity

HORIZON

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

Oncopeptides: Unpublished data (data on file).

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[1]
- 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[2]

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

HORIZON

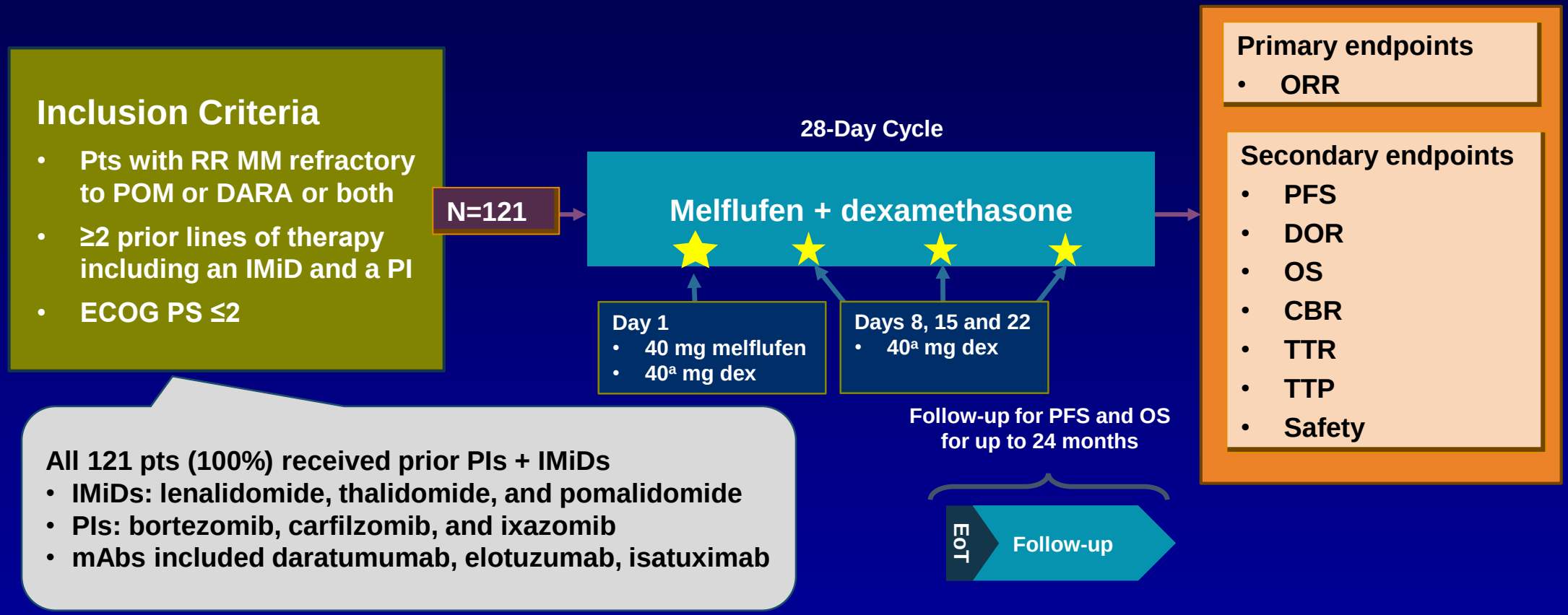
- O-12-M1 (N=45): melflufen + dex demonstrated promising and durable response in heavily pretreated RR MM[1,2]
  - Pts refractory to both IMiDs/PIs and progressed on last line of therapy
  - ORR 31% and CBR 49% (with similar results regardless of disease status)
    - ORR 33% in pts (8 of 24) refractory to prior alkylator therapy
    - ORR 42% in pts (5 of 12) who progressed on prior alkylator therapy within ≤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[3]
  - 100% ORR with bortezomib
  - 82% ORR with daratumumab (in pts with ≥2 completed cycles of therapy)

1. Richardson PG, et al. *Blood.* 2018;132(suppl, abstr):600. 2. Richardson PG, et al. [manuscript submitted]. 3. Pour L, et al. EHA 2019. Abstr PF608.

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.
[a]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,[a] %	38 / 30 / 29 / 4
ECOG PS 0 / 1 / 2,[a] %	24 / 61 / 14
High-risk cytogenetics,[b] % ≥2 high-risk abnormalities, % Del(17p), %	62 19 17
Extramedullary disease,[c] %	60

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.
[a]ISS stage and ECOG PS at study entry, with data pending for 16 and 10 pts, respectively.
[b]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.
[c]Data pending for 54 pts.

Data cutoff 06 May 2019.

Prior Treatment and Refractory Status (N=121)

HORIZON

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 ≥2 Prior ASCTs Relapsed ≤1 year after ASCT	69% 11% 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

Data cutoff 06 May 2019.

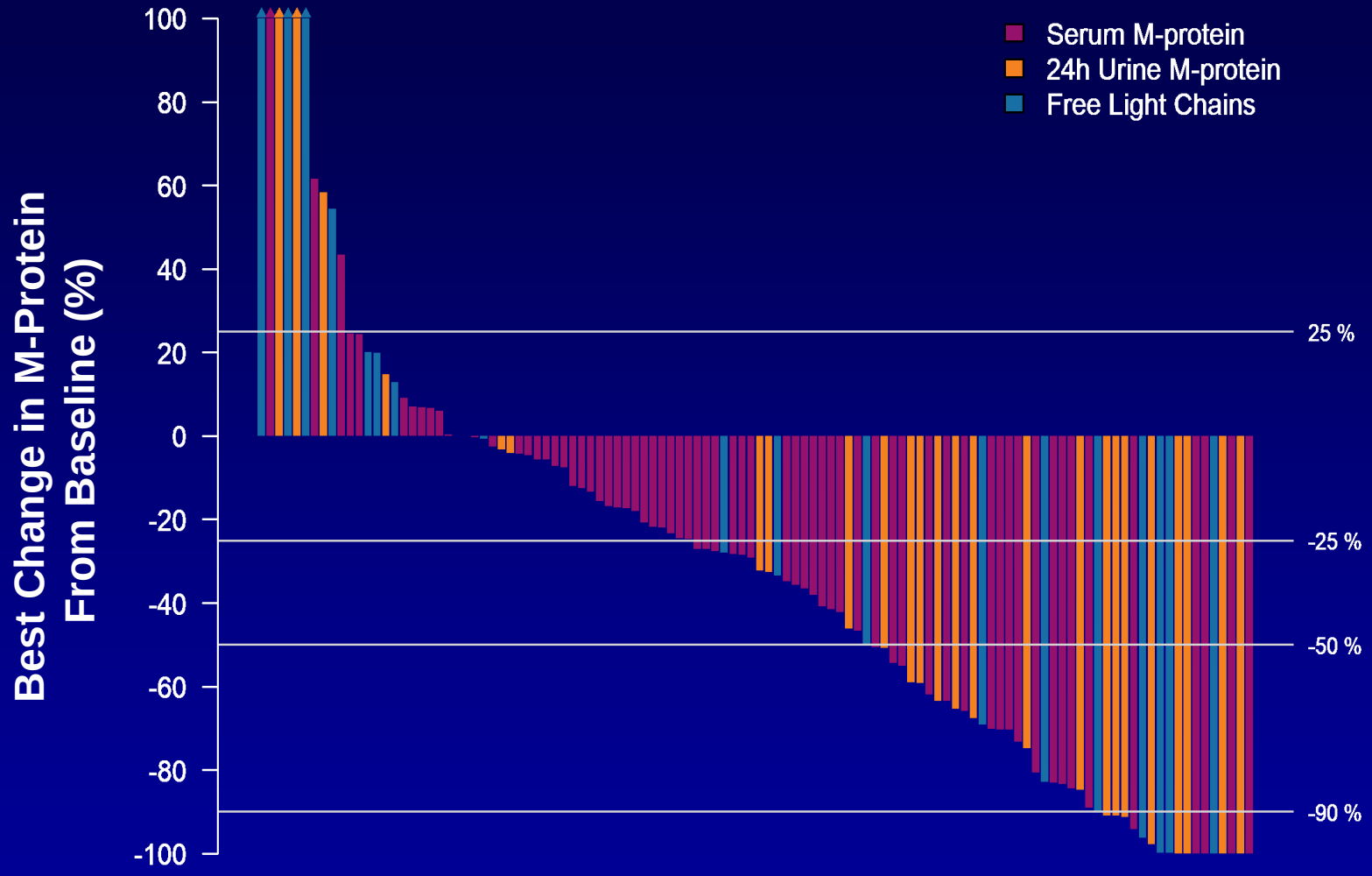
Patient Disposition (N=121)

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

[a]Percentages for discontinuation cause have been calculated as fraction of pts who discontinued (n=86).

Data cutoff 06 May 2019.

Best M-Protein Response (n=113)[a]

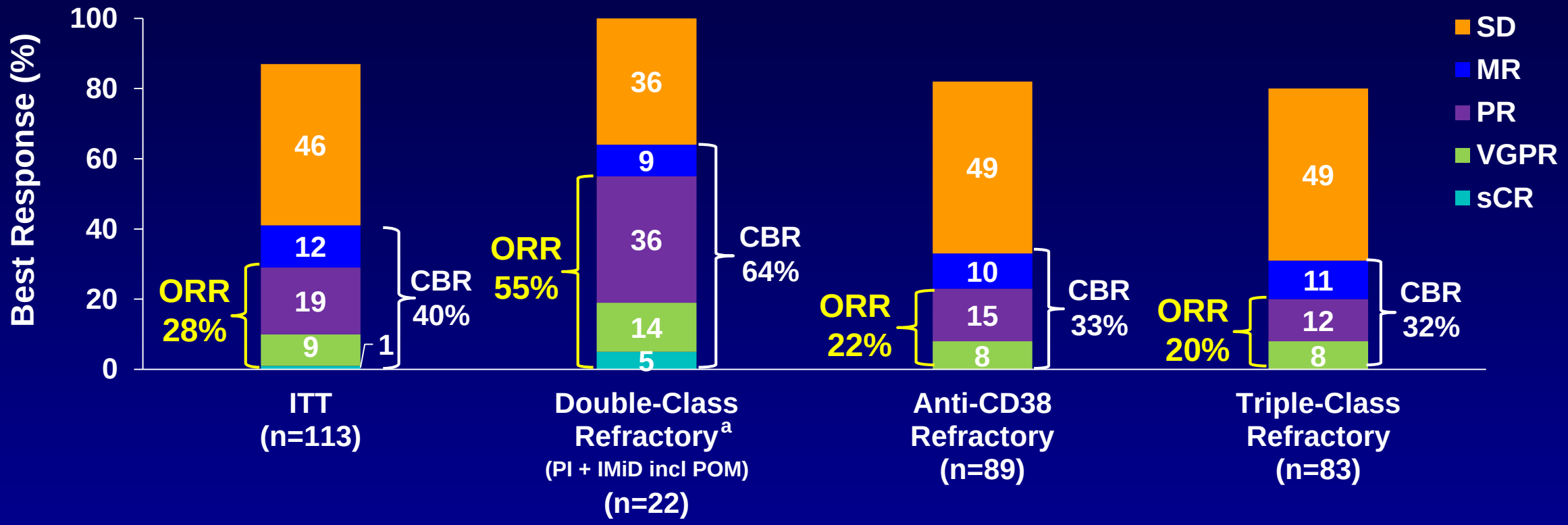


[a]M-protein data for 8 pts pending at time of data cut-off.

Disease stabilization rate (≥SD) 86%

Data cutoff 06 May 2019.

Best Response (IMWG[1])



- 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

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

[a]Not anti-CD38 refractory.

Data cutoff 06 May 2019.

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

	ORR, %
EMD-relapsed/refractory pts[a] (n=40)	29
Non–EMD-relapsed/refractory pts[a] (n=27)	38
EMD triple-class refractory[a] (n=37)	23
Non-EMD triple-class refractory[a] (n=20)	26

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

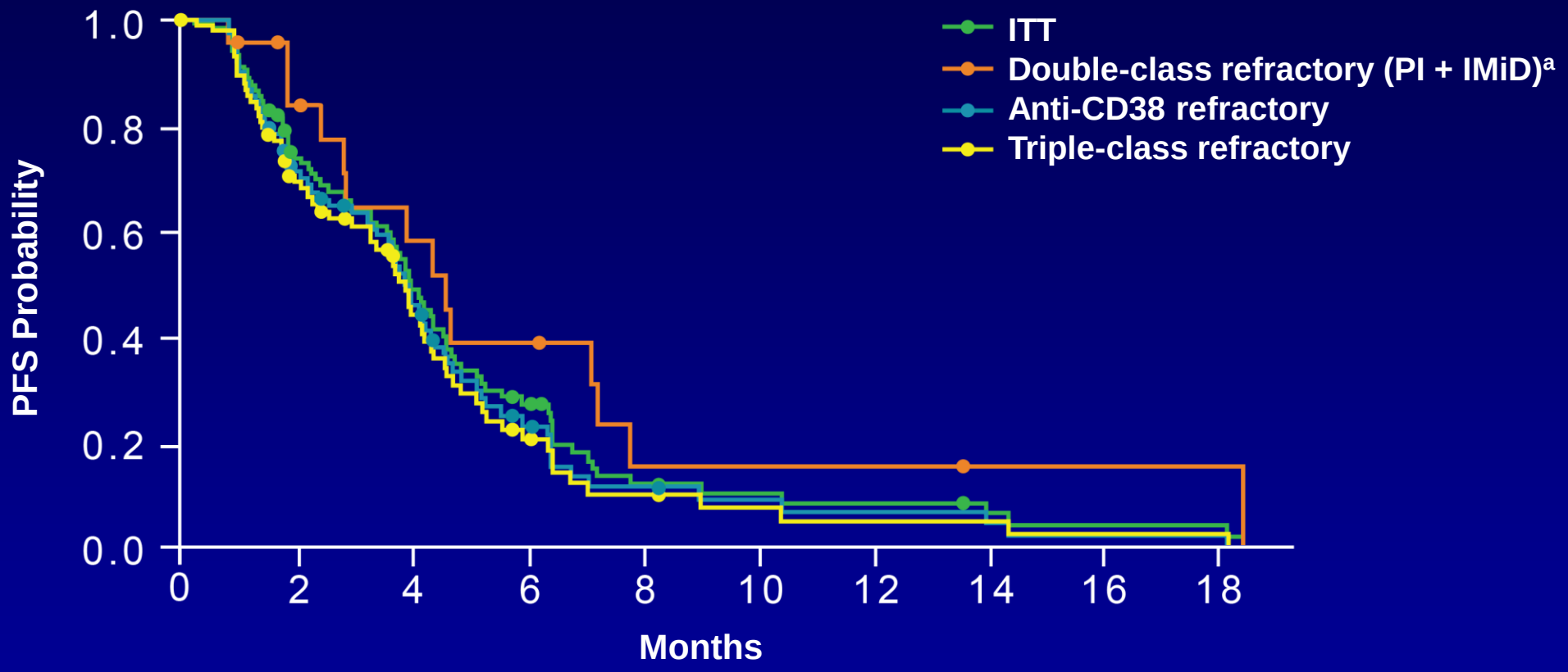
[a]2, 1, 2, 1 ps, respectively, did not have any available response data or EoT data at the time of data cutoff.

- Poor outcomes observed across the limited clinical trial datasets available[1-5]
- 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 (≥3 prior lines of therapy; dara and pom naïve)[1-5]
- 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 Survival (N=121)

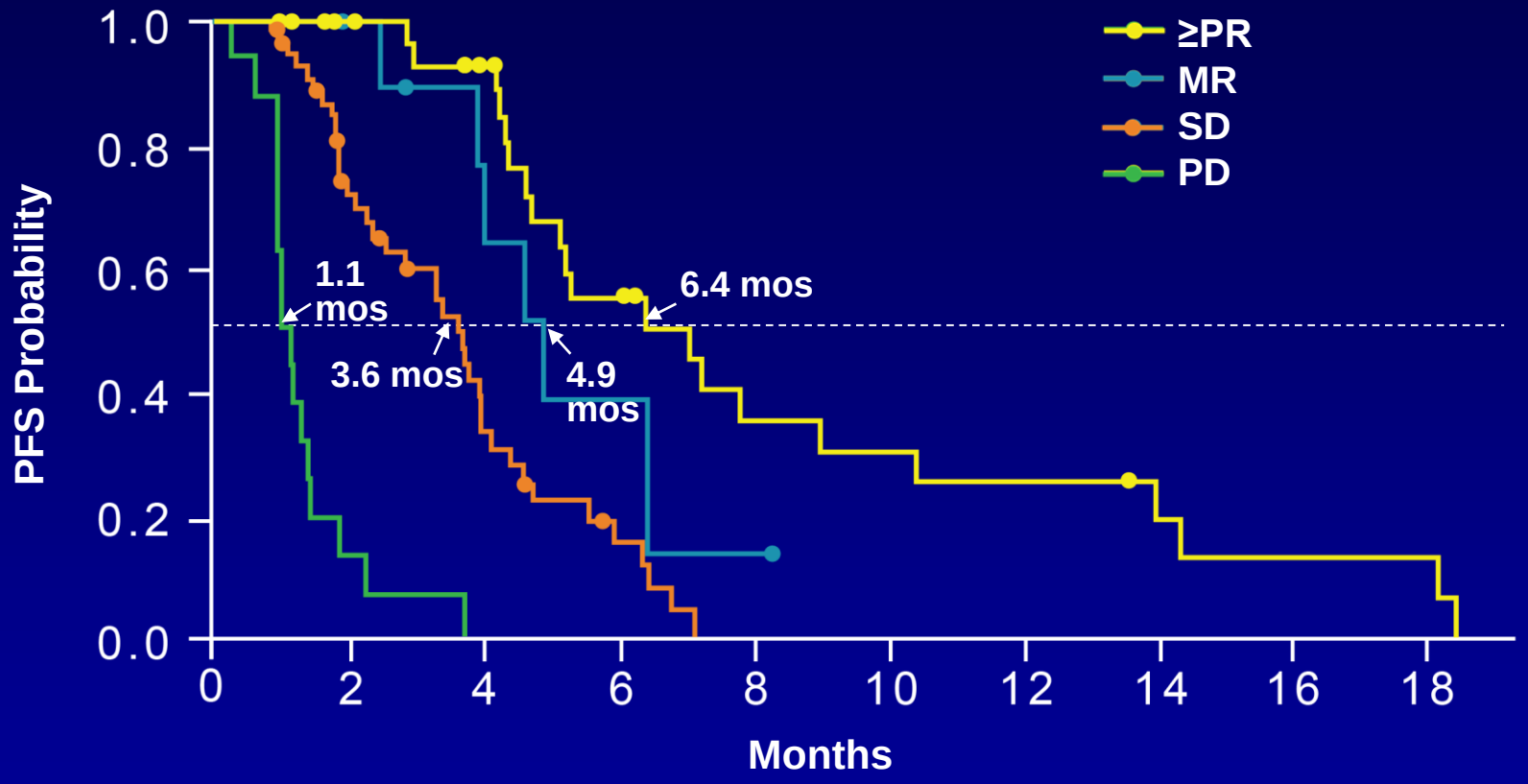


- Median PFS 4.0 months (95% CI, 3.7-4.6)
- Similar PFS seen across different refractory subgroups

[a]Not anti-CD38 refractory.

Data cutoff 06 May 2019.

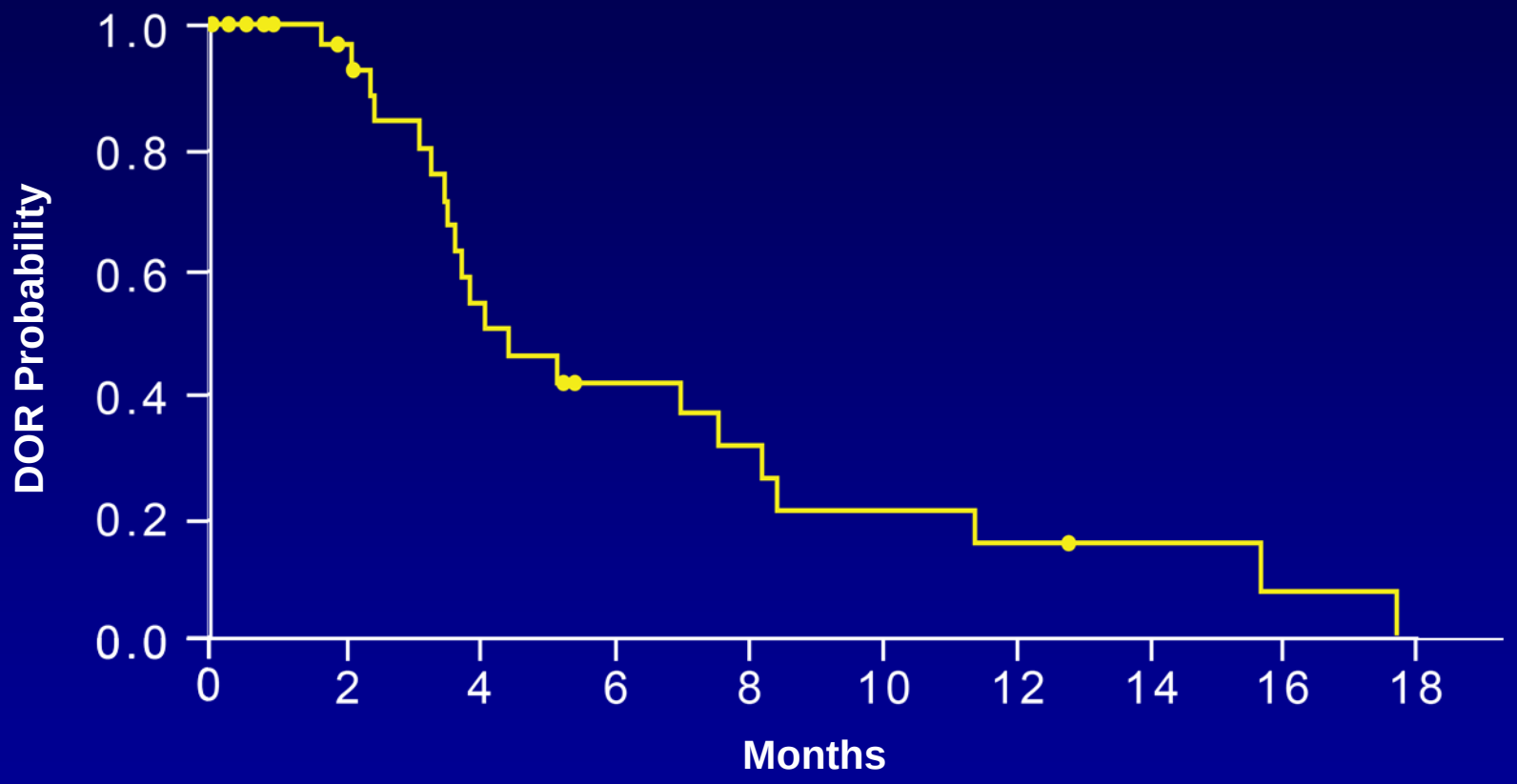
PFS by Response Subgroups (N=121)



- Median PFS 6.4 months in pts with ≥ PR; 4.9 months in those with MR

Data cutoff 06 May 2019.

Duration of Response (n=32)



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

Data cutoff 06 May 2019.

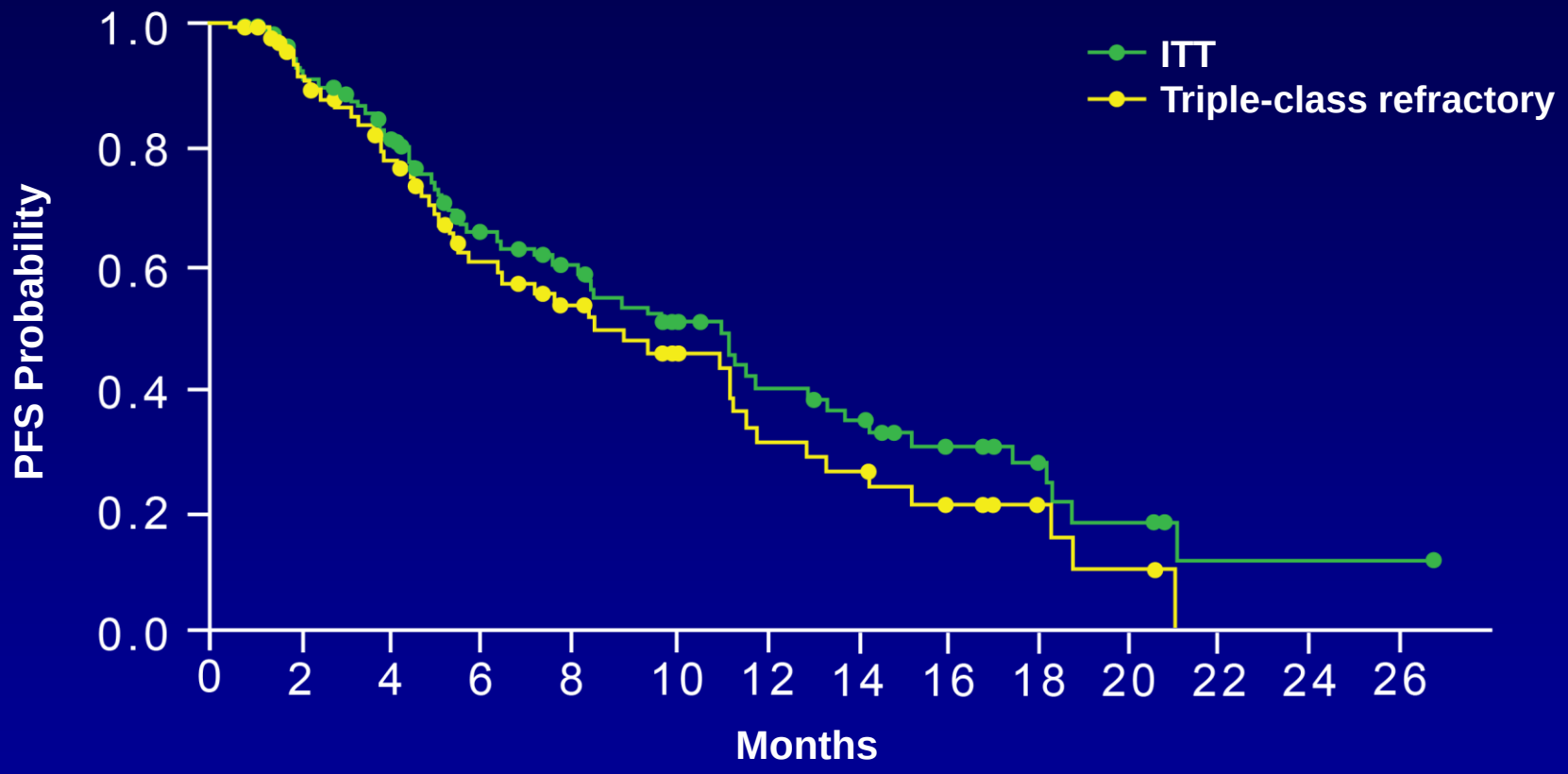
Duration of Response – Subgroup Analysis

	Median DOR, mos	Events, n (%)
All responders[a] (n=32)	4.4	21 (66)
Non-EMD (n=10)	8.1	5 (50)
EMD (n=11)	3.7	7 (64)
Triple-class refractory[a] (n=17)	3.6	12 (71)
Non-EMD (n=5)	7.5	3 (60)
EMD (n=8)	3.7	5 (63)

[a]11 and 4 responding pts respectively had missing EMD data.
DOR, duration of response; EMD, extramedullary disease; ITT, intention-to-treat.

Data cutoff 06 May 2019.

Overall Survival (N=121)



- 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)

Data cutoff 06 May 2019.

Dose Modifications Due to TEAEs

Action Taken With Melflufen (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 melflufen and may be included in more than 1 category.

Data cutoff 06 May 2019.

Safety and Tolerability

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

- 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.
[a]Grade 3 AEs occurring in ≥5% of pts.

Data cutoff 06 May 2019.

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% (≥PR), CBR 40% (≥MR), disease stabilization (≥SD) 86%
    - ORR 55% double-class refractory (incl POM), 22% anti-CD38 refractory, 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)

AE, adverse event; CBR, clinical benefit rate; EMD, extramedullary disease; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RR MM, relapsed/refractory multiple myeloma; SD, stable disease.

Acknowledgments

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HORIZON

Global Study With 16 Sites in 4 Countries

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Richardson PG, et al EHA 2019 #S1605