

# 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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## BACKGROUND

### SELECTIVE CYTOTOXICITY OF MELFLUFEN

- Melflufen is a lipophilic peptide-conjugated alkylator that rapidly delivers a highly cytotoxic payload into myeloma cells through peptidase-enhanced activity (Figure 1)<sup>1-8</sup>
- In vivo human xenograft mouse models treated with melflufen showed higher inhibition of tumor growth and prolonged survival versus those treated with alkylators such as melphalan alone (Figure 2)<sup>9</sup>
- Melflufen showed pronounced anti-angiogenic activity (up to >100-fold) at lower doses than the alkylator melphalan alone (Figure 2)<sup>9</sup>
- Osteoclasts have a short half-life, but activity against CD14+ osteoclast precursors should lower osteoclast activity and potentially improve bone pain in patients with multiple myeloma (MM)
- Melflufen shows pronounced activity against CD14+ osteoclast precursors at clinically relevant concentrations compared to melphalan (Figure 3)<sup>10</sup>

Figure 1. Melflufen Mechanism of Action

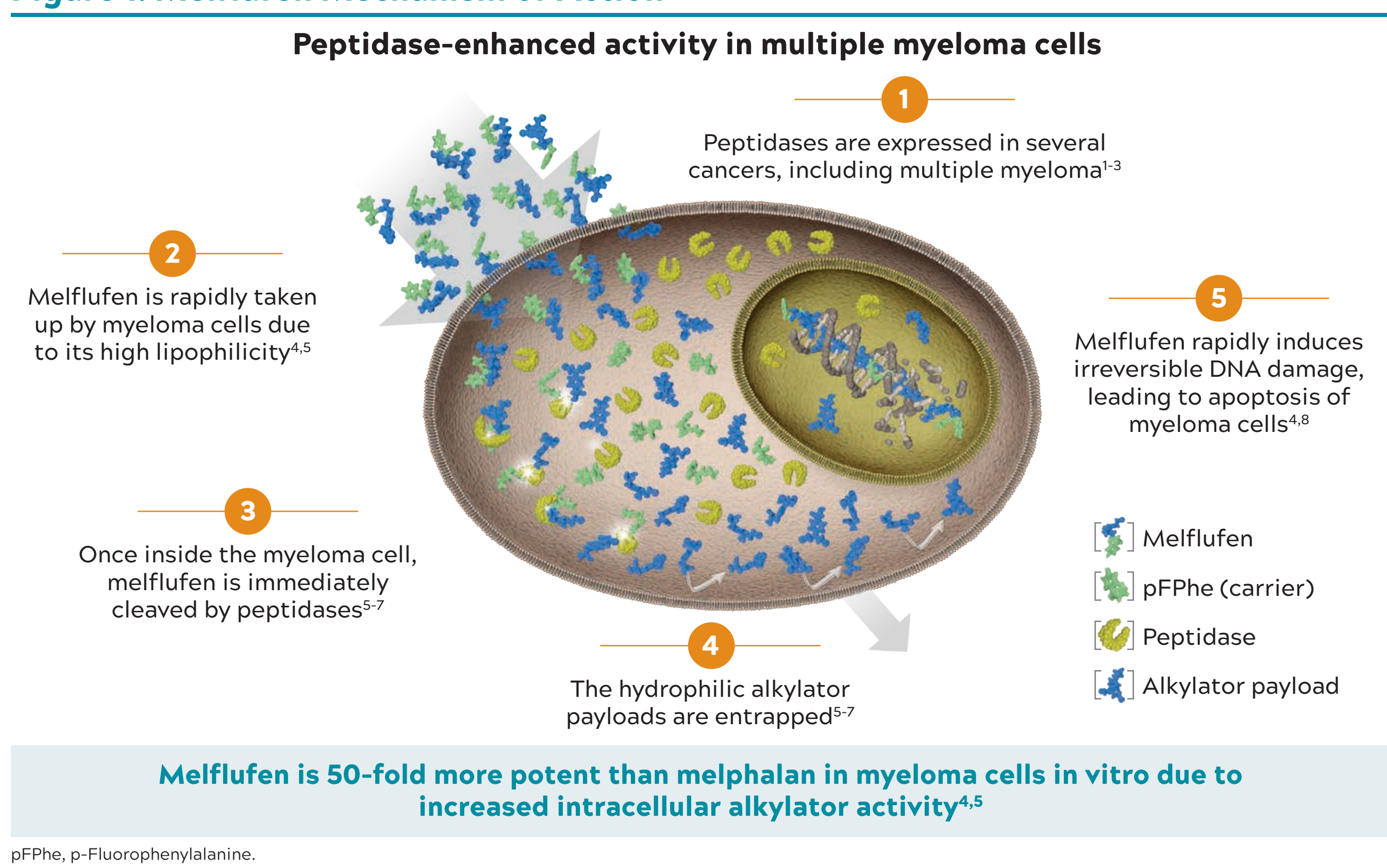
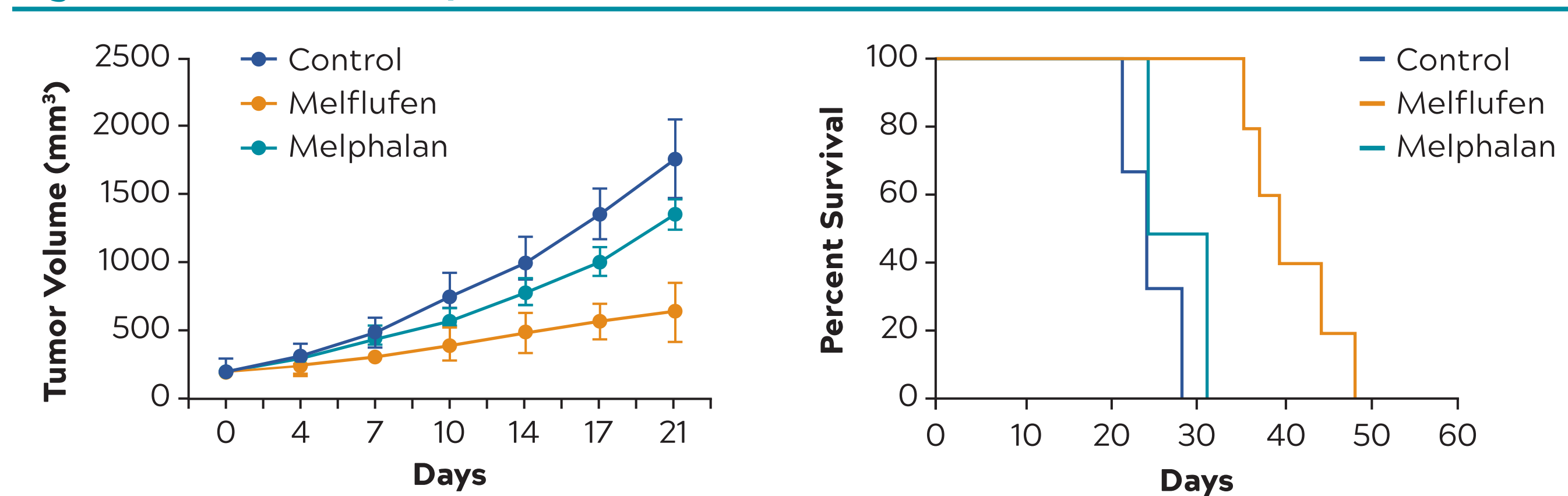
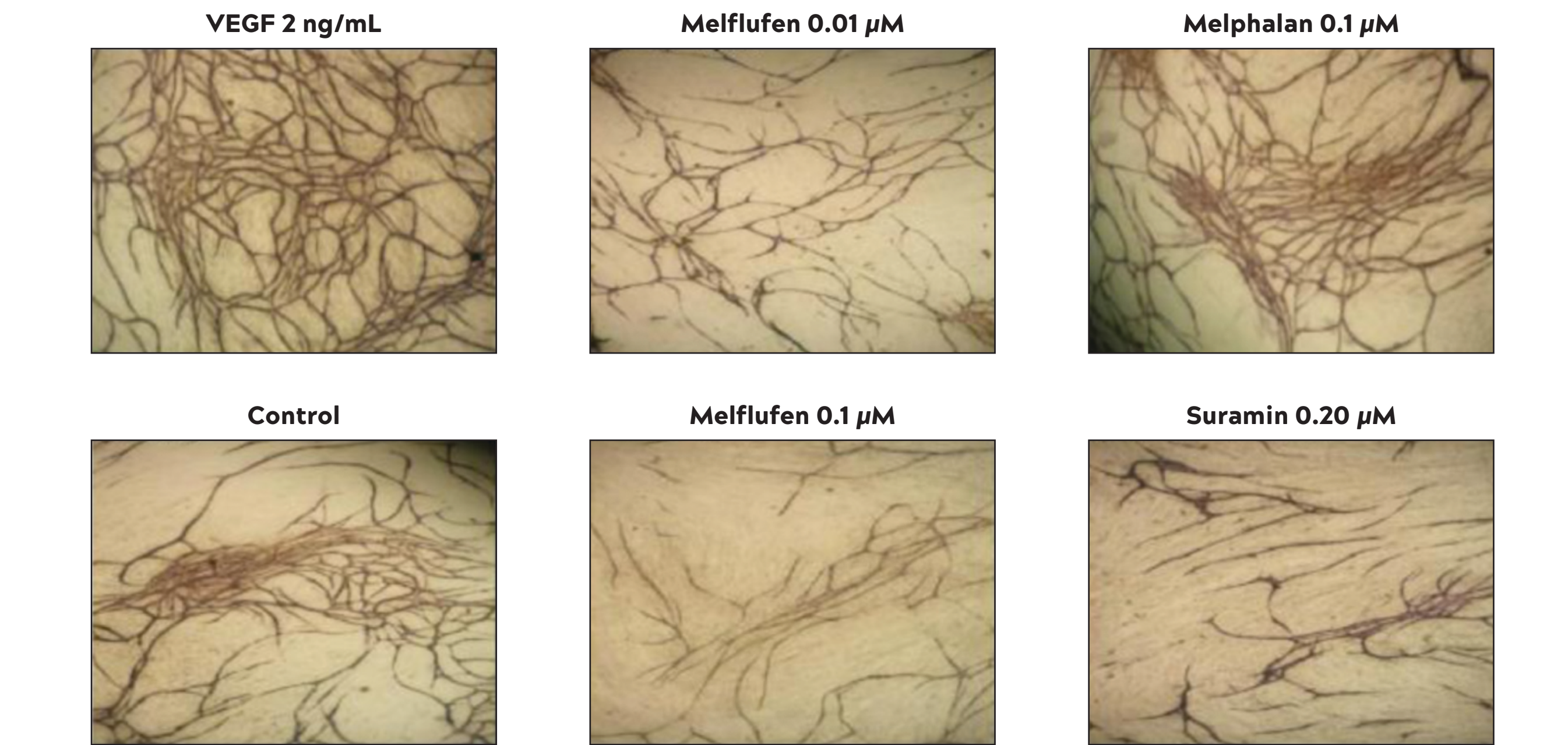


Figure 2. In Vivo Efficacy of Melflufen

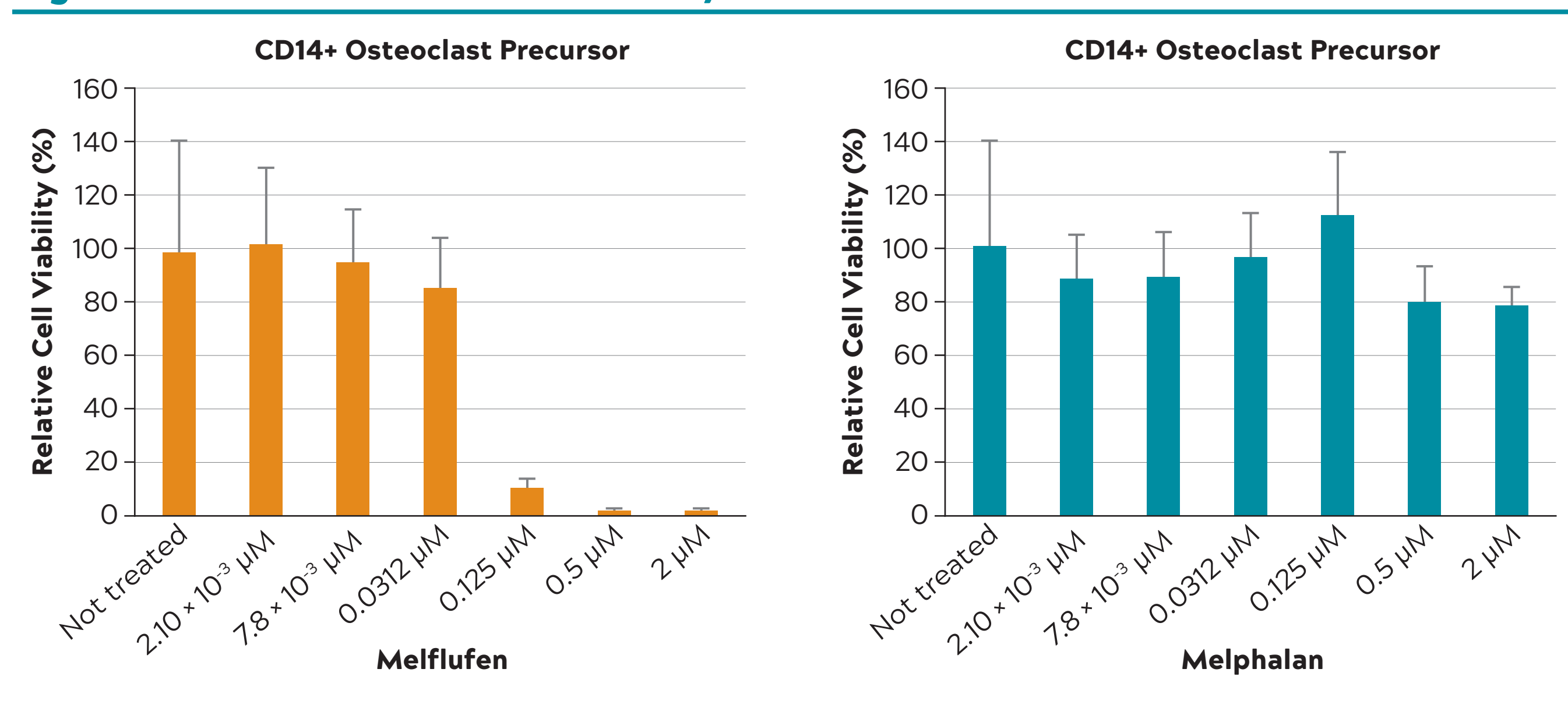


In vivo efficacy of melflufen shown using a human plasmacytoma MM.1S xenograft mouse model. Treatment of tumor-bearing mice with melflufen intravenously significantly inhibited MM.1S tumor growth (P < 0.0001) and prolonged survival (P < 0.0001) of these mice.\*



Decrease in tubule length and vessel junctions shown for melflufen, with dose response seen, compared with the positive control vascular endothelial growth factor receptor (VEGF; 2 ng/mL).\*

Figure 3. Osteoclast Precursor Activity of Melflufen<sup>10</sup>



CD14, cluster of differentiation 14.

### UNMET MEDICAL NEED IN RELAPSED AND REFRACTORY MM (RRMM)

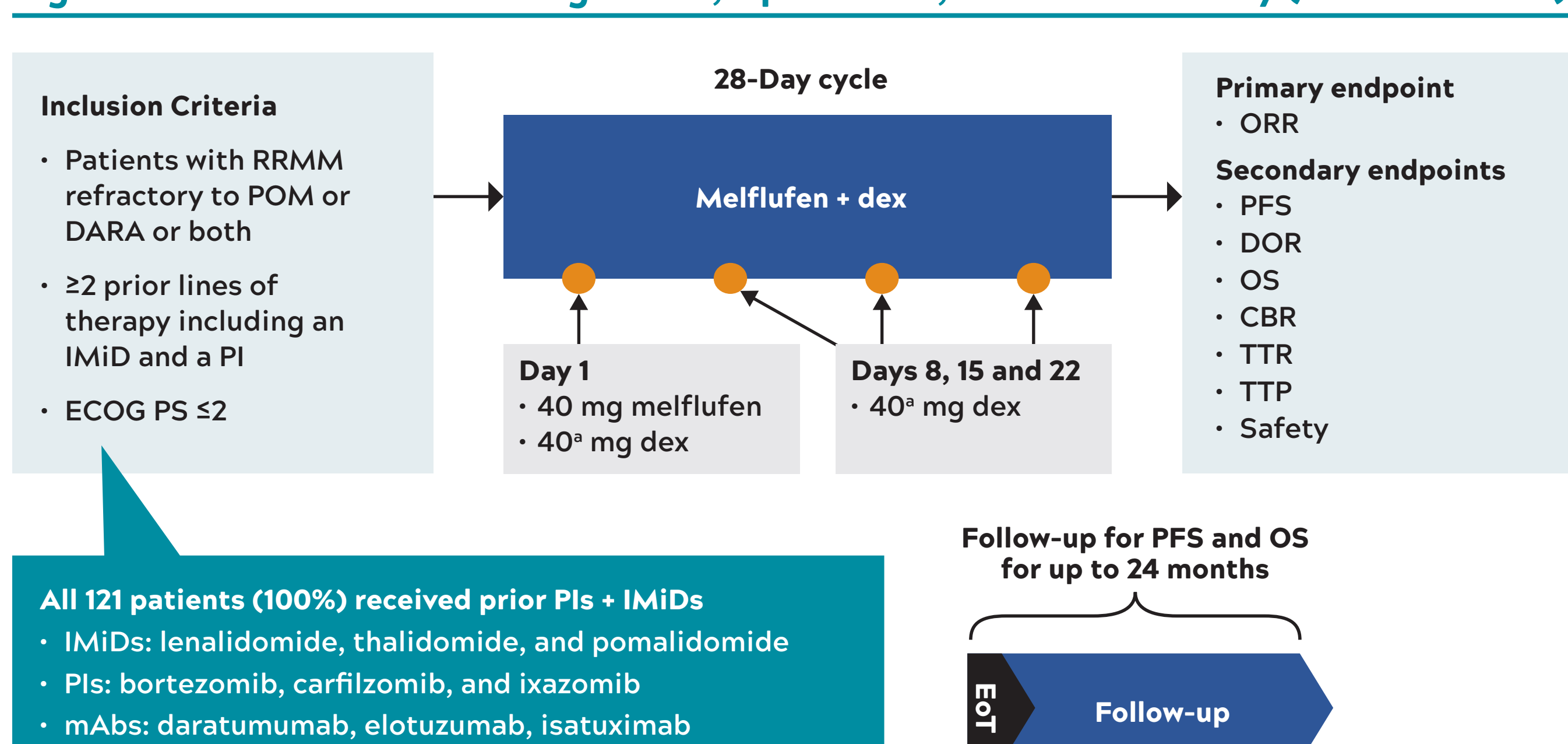
- Lenalidomide and proteasome inhibitor (PI)-based failure in patients who subsequently become refractory to salvage therapy with daratumumab (anti-CD38 monoclonal antibody [mAb]) and/or pomalidomide have limited effective treatment options<sup>11</sup>
- Introducing a treatment class switch with a novel compound may represent an important therapeutic strategy
- Of particular importance is to develop new treatment strategies for patients who are triple-class refractory (IMiD + PI + anti-CD38 mAb), and especially those patients with extramedullary disease (EMD), who have very poor prognosis<sup>12</sup>

### MELFLUFEN IN RRMM: O-12-M1 AND ANCHOR

- O-12-M1 (N=45): melflufen plus dexamethasone (dex) demonstrated promising and durable response in heavily pretreated RRMM<sup>13,14</sup>
- Patients were refractory to both immunomodulators (IMiDs) and PIs and had progressed on their last line of therapy
- Overall response rate (ORR) was 31% and clinical benefit rate (CBR) was 49% (with similar results regardless of disease status)
- ORR was 33% in patients (8 of 24) refractory to prior alkylator therapy
- ORR was 42% in patients (5 of 12) who progressed on prior alkylator therapy within ≤12 months
- Median duration of response (DOR) was 8.4 months, progression-free survival (PFS) 5.7 months, and overall survival (OS) was 20.7 months
- Favorable tolerability - hematologic toxicity common but clinically manageable; nonhematologic adverse events (AEs) infrequent
- Phase 1/2 study ANCHOR, melflufen plus dex demonstrated high response rate when combined with bortezomib or daratumumab in RRMM patients<sup>15</sup>
- 100% ORR with bortezomib
- 82% ORR with daratumumab (in patients with ≥2 completed cycles of therapy)

## METHODS

Figure 4. HORIZON: Phase 2 Single-Arm, Open-Label, Multicenter Study (NCT02963493)



All 121 patients (100%) received prior PIs + IMiDs  
IMiDs: lenalidomide, thalidomide, and pomalidomide  
Pis: bortezomib, carfilzomib, and ixazomib  
mAbs: daratumumab, elotuzumab, isatuximab

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; CBR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.  
\*Patients aged >75 years received dex 20 mg.

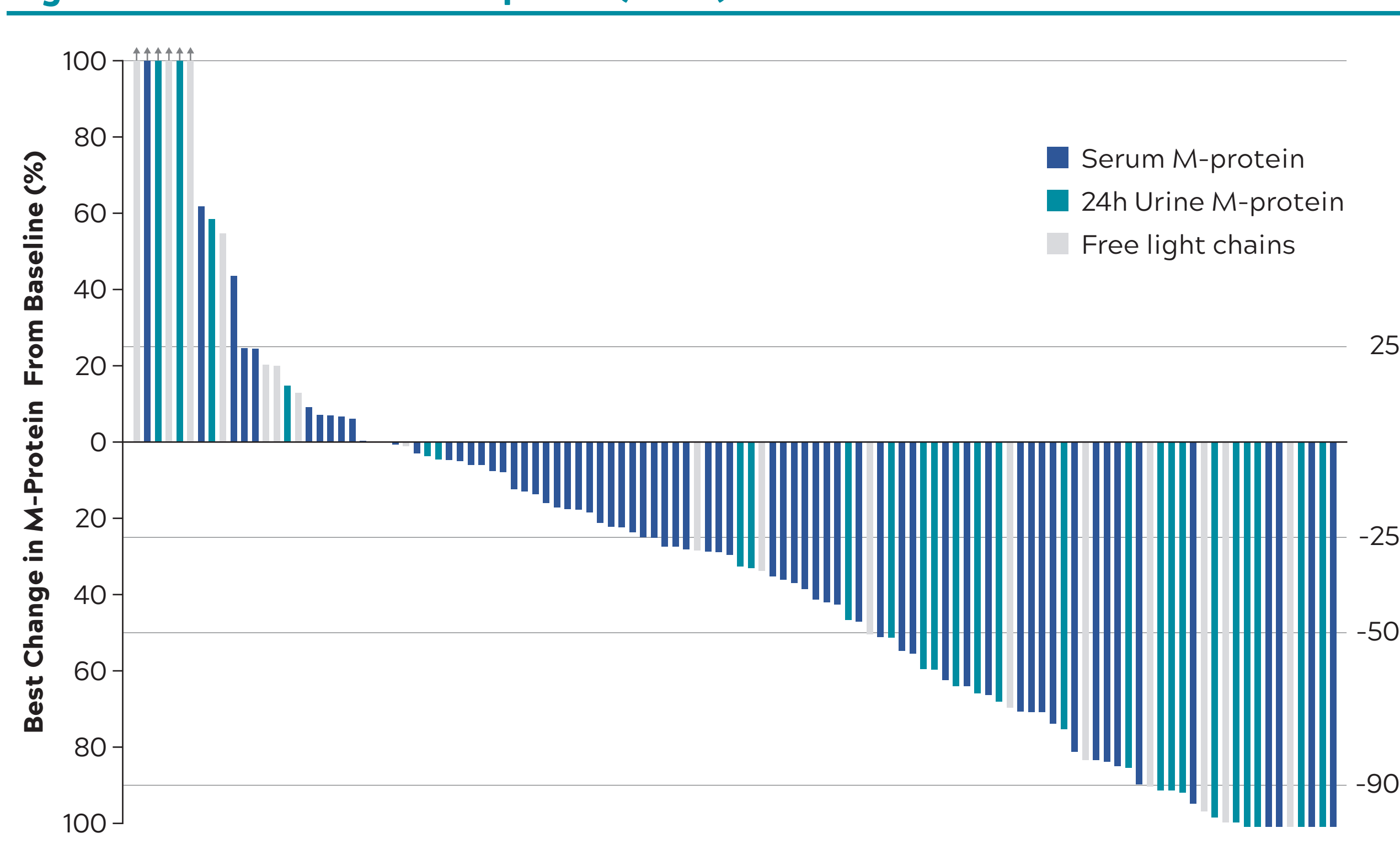
## RESULTS

Table 1. Baseline Patient Characteristics

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,* %	38 / 30 / 29 / 4
ECOG PS 0 / 1 / 2,* %	24 / 61 / 14
High-risk cytogenetics, <sup>†</sup> %	62
≥2 high-risk abnormalities, %	19
Del(17p), %	17
Extramedullary disease, <sup>‡</sup> %	60

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; \*ISS stage and ECOG PS at study entry, with data pending for 16 and 10 patients, respectively; <sup>†</sup>high-risk cytogenetics (t(4;14), del(17p), t(8;21), t(14;16), t(12;21), nonhyperdiploidy, gain(1q) or loss(13) at study entry; data pending for 40 patients; 5 patients with unknown status at study entry had high-risk cytogenetics at diagnosis and were included in the high-risk group; <sup>‡</sup>data pending for 54 patients; Data cutoff 06 May 2019.

Figure 5. Best M-Protein Response (n=113)<sup>\*</sup>



\*M-protein data for 8 patients pending at time of data cutoff. Data cutoff 06 May 2019.

- Disease stabilization rate (≥stable disease [SD]) 86% (Figure 5)

Table 4. Best Response for EMD and Non-EMD Patients (n=67)

	ORR, %
EMD-relapsed/refractory patients* (n=40)	29
Non-EMD-relapsed/refractory patients* (n=27)	38
EMD triple-class refractory* (n=37)	23
Non-EMD triple-class refractory* (n=20)	26

EMD, extramedullary disease; EoL, end of treatment; ORR, overall response rate; \*Not anti-CD38 refractory; <sup>†</sup>Not anti-CD38 refractory; <sup>‡</sup>Not anti-CD38 refractory; <sup>§</sup>Not anti-CD38 refractory; <sup>||</sup>Not anti-CD38 refractory; Data cutoff 06 May 2019.

Table 2. Prior Treatment and Refractory Status

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; Data cutoff 06 May 2019.

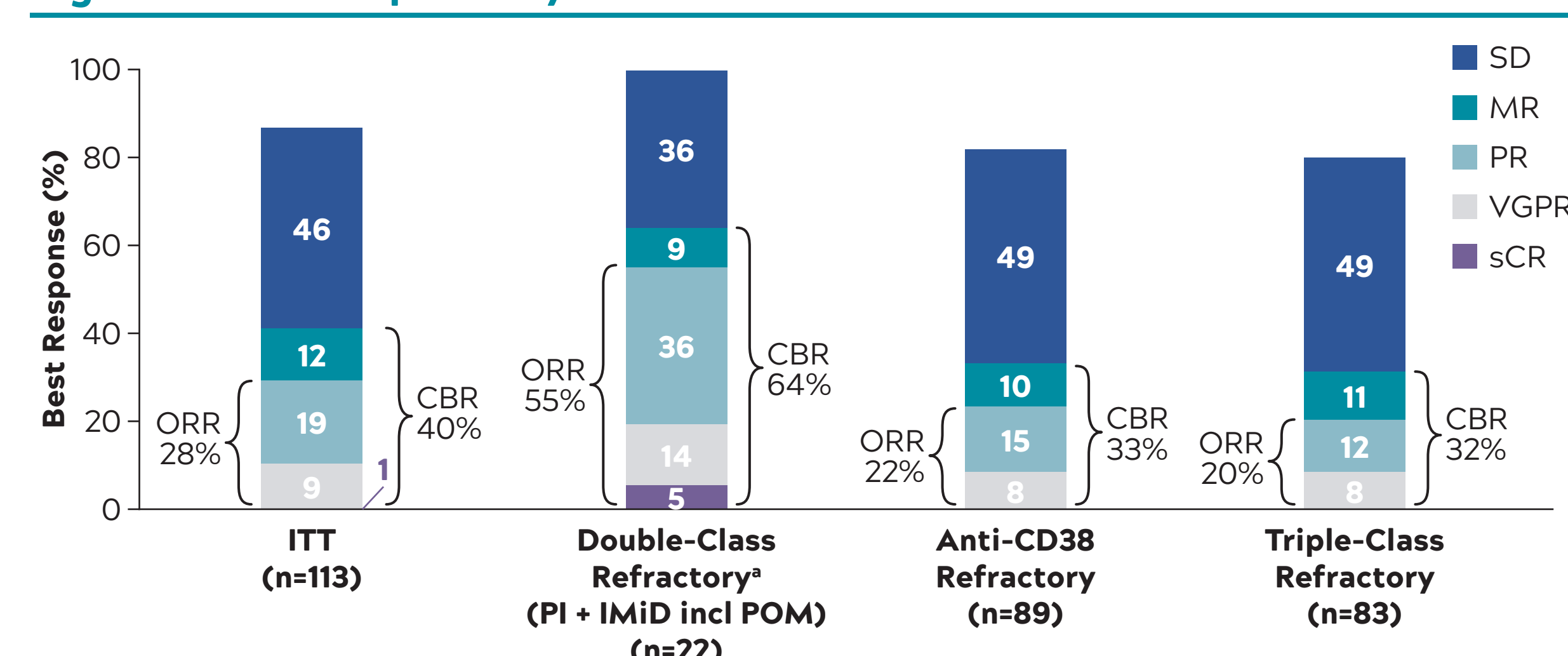
- 36% used ≥3 treatment regimens in last 12 months prior to enrollment

Table 3. Patient Disposition

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

<sup>†</sup>Percentages for discontinuation cause have been calculated as fraction of patients who discontinued (n=88). Data cutoff 06 May 2019.

Figure 6. Best Response by IMWG<sup>16</sup>



CBR, clinical benefit rate; IMiD, immunomodulatory; IMWG, International Myeloma Working Group; ITT, intention-to-treat; MR, minimal response; ORR, overall response rate; PI, proteasome inhibitor; POM, pomalidomide; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response; <sup>†</sup>Not anti-CD38 refractory; Data cutoff 06 May 2019.

- Eight patients did not have available response information at data cutoff; 2 patients response evaluable, PI exposed, but refractoriness to PI subject to confirmation, thus excluded from subgroup analysis (Figure 6)
- One patient with stringent complete response (sCR) also confirmed as minimal residual disease negative (10<sup>-5</sup> sensitivity), with ongoing progression-free period of 13.6 months
- Median time to response 1.2 months

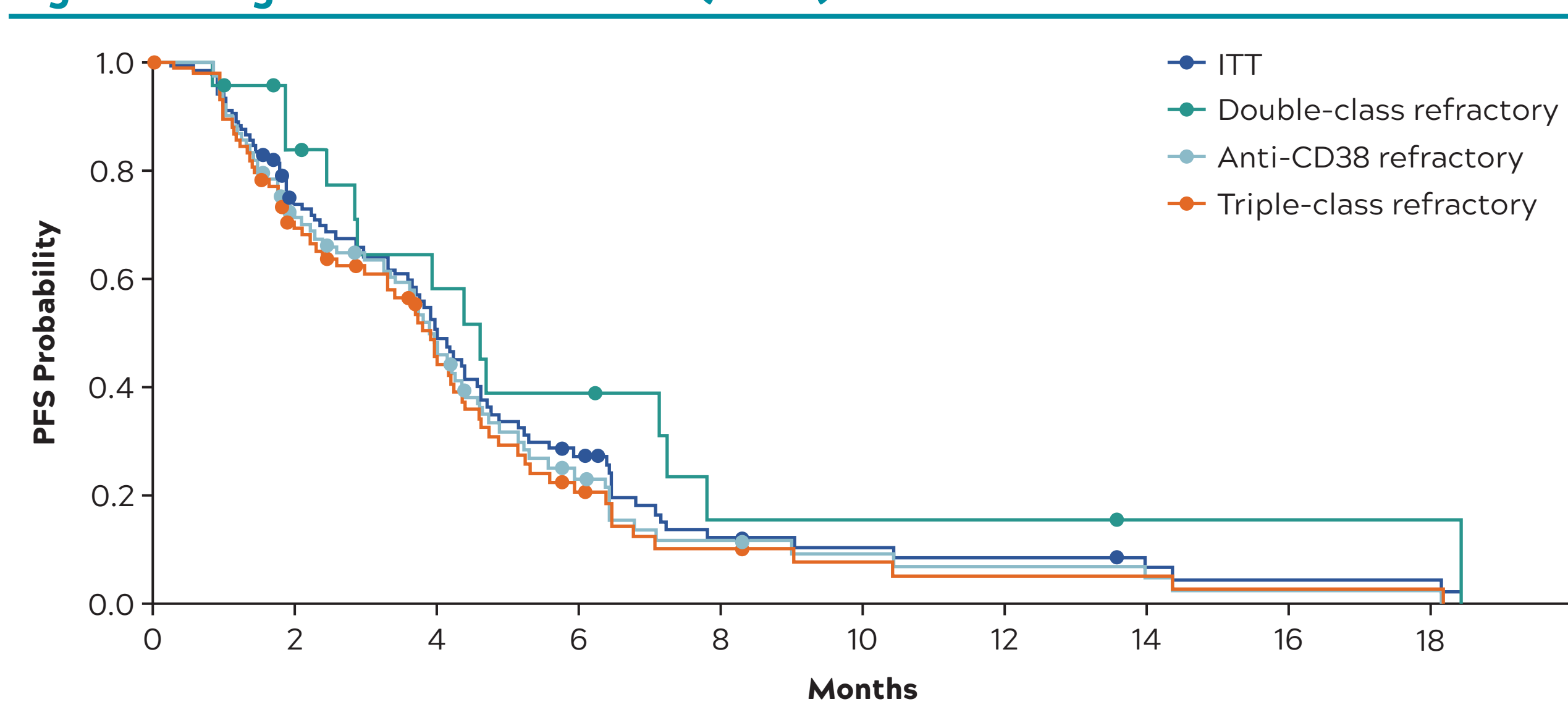
Table 5. Duration of Response in Patient Subgroups

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

DOR, duration of response; EMD, extramedullary disease; <sup>†</sup>1 and 4 responding patients respectively had missing EMD data; Data cutoff 06 May 2019.

- Poor outcomes observed across the limited clinical trial datasets available<sup>17,21</sup>
- Studies have failed to demonstrate any significant and/or durable response in patients with relapsed EMD: only daratumumab and pomalidomide have shown response with ORRs of 17% and 9%, respectively (≥3 prior lines of therapy; daratumumab and pomalidomide naive)<sup>17,21</sup>
- HORIZON is one of the largest clinical trial cohorts of EMD-relapsed/refractory patients to date
- EMD data pending for 54 patients (across 3 major participating centers with recently enrolled patients, limited data entry to date)

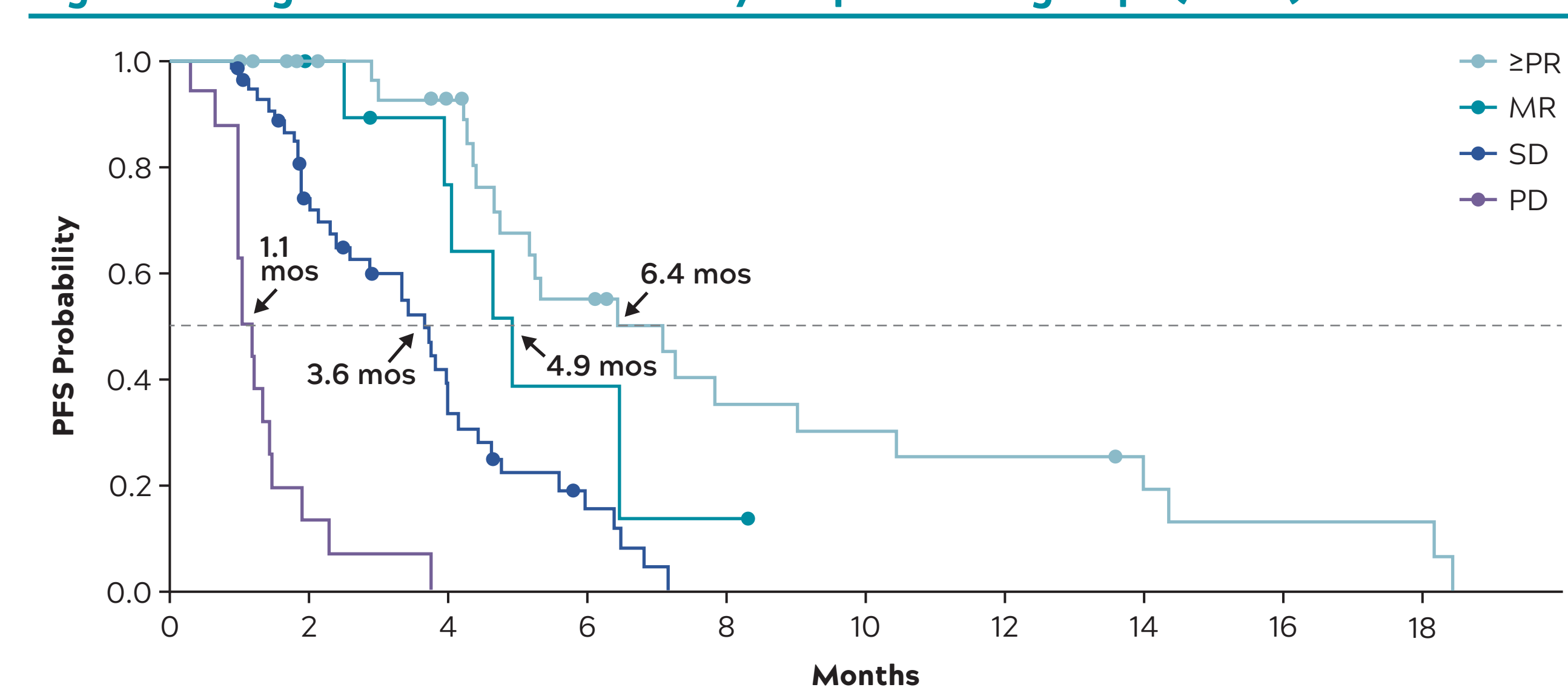
Figure 7. Progression-Free Survival (N=121)



IMiD, immunomodulatory; ITT, intention-to-treat; PFS, progression-free survival; PI, proteasome inhibitor; <sup>†</sup>Not anti-CD38 refractory; <sup>‡</sup>Not anti-CD38 refractory; Data cutoff 06 May 2019.

- Median PFS 4.0 months (95% CI, 3.7-4.6; Figure 7)
- Similar PFS seen across different refractory subgroups (Figure 7)

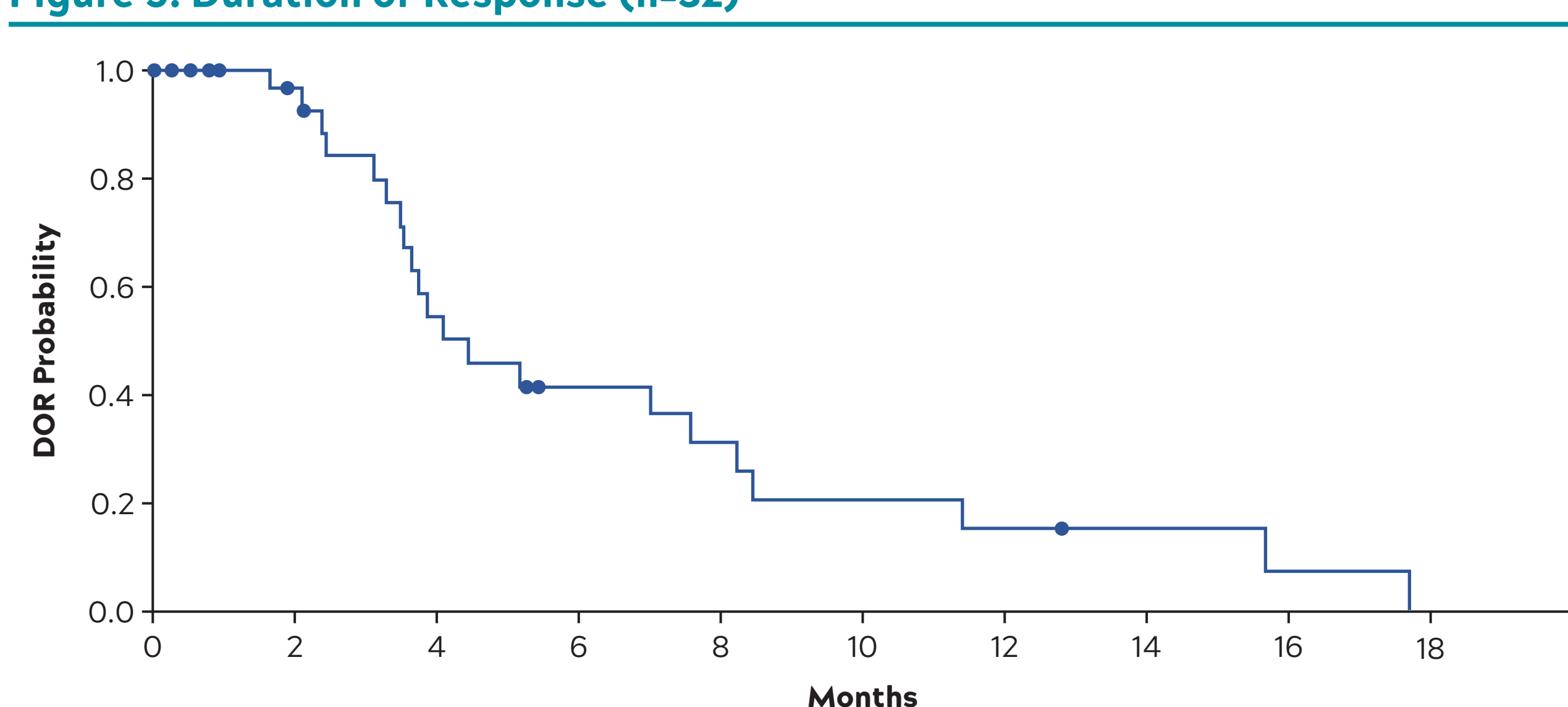
Figure 8. Progression-Free Survival by Response Subgroups (N=121)



MR, minimal response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; Data cutoff 06 May 2019.

- Median PFS 6.4 months in patients with ≥PR; 4.9 months in those with minimal response (MR; Figure 8)

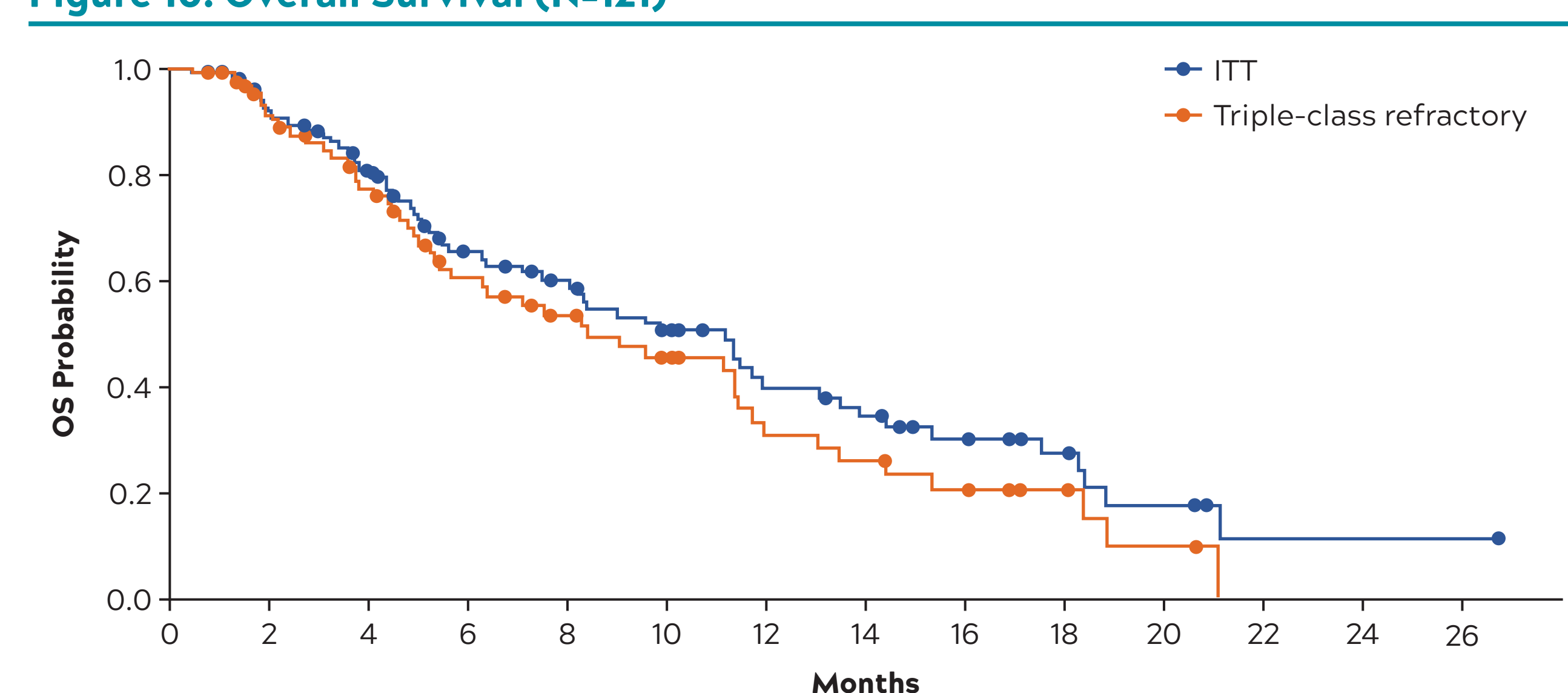
Figure 9. Duration of Response (n=32)



DOR, duration of response; Data cutoff 06 May 2019.

- Median DOR 4.4 months (95% CI, 3.6-8.3; Figure 9)

Figure 10. Overall Survival (N=121)



ITT, intention-to-treat; OS, overall survival; Data cutoff 06 May 2019.

- Median OS 11.2 months (95% CI, 8.1-13.9) for the intention-to-treat population (N=121), and 8.5 months (95% CI, 6.4-11.8) for triple-class refractory population (n=89; Figure 10)

Table 6. Dose Modifications Due to TEAEs

Action Taken With Melflufen (N=121)	n (%)
Dose modification due to TEAE	56 (46)
Dose reduced <sup>a</sup>	27 (22)
Dose delayed <sup>b</sup>	43 (36)
Drug discontinued	29 (24)

TEAE, treatment-emergent adverse event; <sup>a</sup>Dose modification calculated as the number of patients with a TEAE requiring a dose modification at any time point; <sup>b</sup>Dose delayed calculated as number of patients with a TEAE leading to a dose delay. Patients may have had more than 1 action taken with melflufen and may be included in more than 1 category; Data cutoff 06 May 2019.

Table 7. Safety and Tolerability of Melflufen

Treatment-Related AEs, n (%)	Grade 3 <sup>a</sup> (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)

AE, adverse event; SAE, serious adverse event; <sup>a</sup>Grade 3 AEs occurring in 15% of patients; Data cutoff 06 May 2019.

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

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## CONCLUSIONS

- Melflufen continues to demonstrate promising activity in patients with RRMM (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 (including pomalidomide), 22% anti-CD38 refractory, 20% triple-class refractory
- ORR 29% in patients 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 RRMM is ongoing (NCT03151811)

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## DISCLOSURES

PG: consulting/advisory role with Oncopeptides and research funding from Oncopeptides. AC: consulting/advisory role with Amgen, Janssen, Celgene, and Takeda. AL: honoraria from Amgen, Bristol-Myers Squibb, Celgene, and Janssen-Cilag. PRO: honoraria from Celgene and Janssen; consulting/advisory role with Celgene and Janssen; research funding from Celgene and Bristol-Myers Squibb. MN: honoraria from Celgene; consulting/advisory role with Novartis, Celgene, Pfizer, and Jazz Pharmaceuticals. JB: honoraria from Celgene, Amgen, and Janssen. MC: no conflicts of interest to report. HC: research funding from Oncopeptides. JL: honoraria from Celgene, Takeda, Amgen, Janssen, Gilead, Karyopharm, Mundipharma, Carsten, Novartis, Oncopeptides, and AbbVie. AK: consulting/advisory role with Celgene, Janssen, Amgen, and Takeda. CM: honoraria from Amgen, Celgene, Gilead, Janssen, Incyte, Takeda, and Verastem. AP: honoraria from Celgene and Amgen; consulting/advisory role with Celgene. JZ: honoraria from Bristol-Myers Squibb and Celgene; consulting/advisory role with Alnylam, Prothena, Amgen, Takeda, Celgene, Caelum, and Oncopeptides; research funding from Bristol-Myers Squibb and Celgene. NP: honoraria from Amgen, Celgene, Janssen, Takeda, and The Binding Site; consulting/advisory role with Amgen, Celgene, Janssen, and Takeda; research funding from Celgene and Janssen; membership on an entity's Board of Directors or advisory committee and speakers' bureau for Celgene. JM, ST, HZ: employment and equity ownership with Oncopeptides. MV: honoraria from Janssen, Celgene, Amgen, and Takeda; consulting/advisory role with Janssen, Celgene, Amgen, Takeda, GSK, AbbVie, and Oncopeptides.

