

HORIZON (OP-106): Melflufen Plus Dexamethasone in 55 Patients With Relapsed/Refractory Multiple Myeloma With Extramedullary Disease—Subgroup Analysis

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BACKGROUND

- Extramedullary disease (EMD) is characterized by multiple myeloma (MM) cells that can grow independently of the bone microenvironment¹
- Outcomes for patients with EMD are worse than those for patients without EMD and are particularly poor in the relapsed/refractory MM (RRMM) setting²
 - Prognosis is usually poorer for patients with hematogenous-spread soft-tissue EMD than for patients with only bone-related EMD^{3,4}
- No standard therapy has been established for this population with high unmet medical need,⁴ and treatment with anti-CD38 monoclonal antibody monotherapy has shown limited activity (overall response rate [ORR], 17%)⁵
- Melphalan flufenamide (melflufen) is an investigational first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and thereby rapidly delivers and releases alkylating agents inside tumor cells (**Figure 1**)⁶⁻¹⁰
 - Melflufen has demonstrated inhibition of angiogenesis in preclinical studies^{6,10}
- In the pivotal, phase 2 HORIZON study, melflufen plus dexamethasone showed clinically meaningful efficacy and a manageable safety profile in patients with heavily pretreated RRMM, including in patients with EMD¹¹
 - ORR was 29%; median progression-free survival (PFS) was 4.2 months; median overall survival (OS) was 11.6 months; and median duration of response (DOR) in patients with a partial response (PR) or better was 5.5 months¹¹
 - Grade 3/4 hematologic treatment-emergent adverse events (TEAEs) were common (mainly neutropenia [78%], thrombocytopenia [76%], and anemia [71%]) but clinically manageable; nonhematologic TEAEs were infrequent¹¹

Figure 1. Melflufen Mechanism of Action

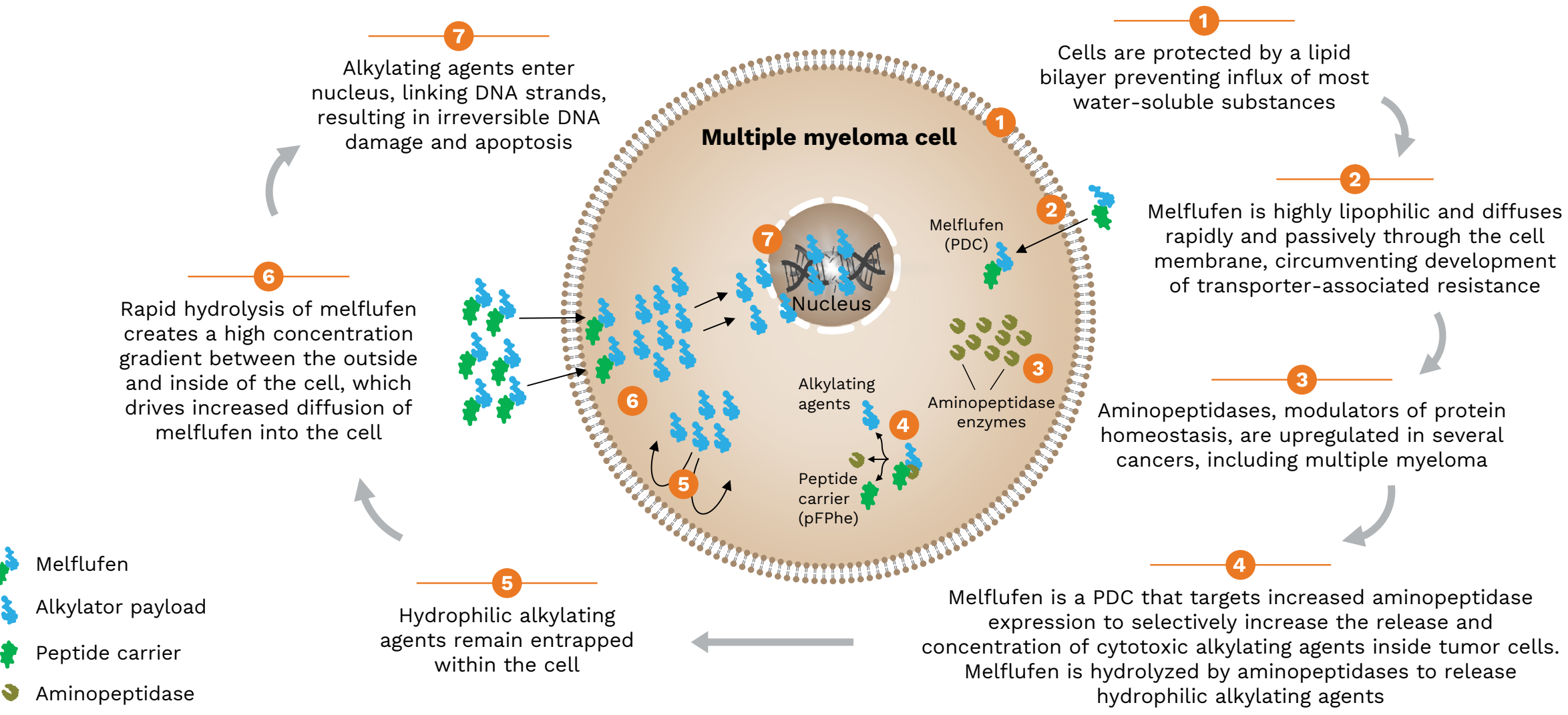
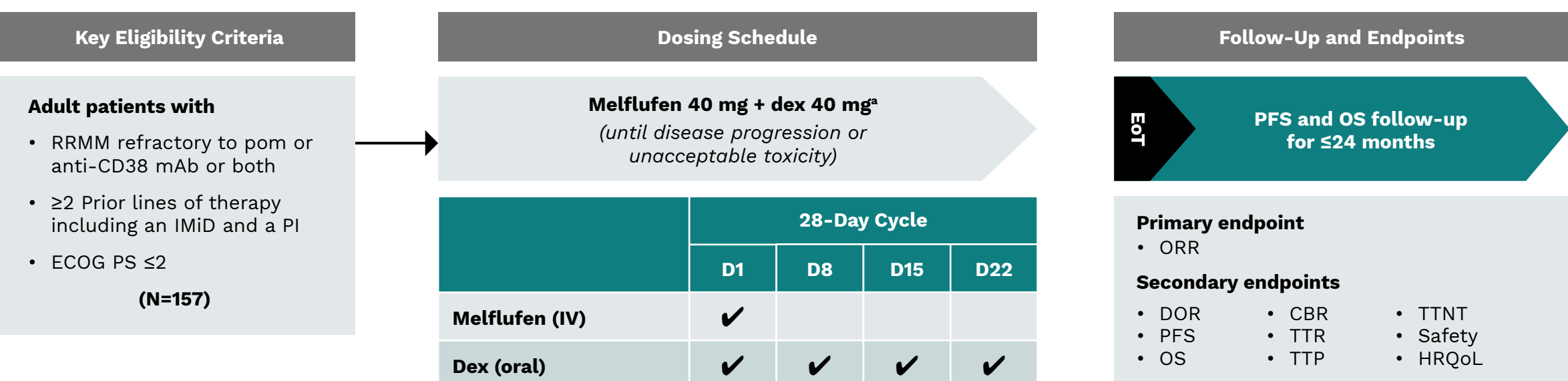


Figure 2. Phase 2 HORIZON Study Design (NCT02963493)



Data cutoff date: 14 January 2020.
*Patients aged ≥75 years received dexamethasone 20 mg.
CBR, clinical benefit rate; D, day; dex, dexamethasone; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HRQoL, health-related quality of life; IMiD, immunomodulatory agent; IV, intravenous; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pom, pomalidomide; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTR, time to progression; TTR, time to response.

OBJECTIVE

- To evaluate the efficacy and safety of melflufen plus dexamethasone in a subgroup of patients with RRMM and EMD in the pivotal, single-arm, multicenter, phase 2 HORIZON study

METHODS

- HORIZON is a pivotal, single-arm, multicenter, phase 2 study of melflufen plus dexamethasone in patients with heavily pretreated RRMM who must have received ≥2 prior lines of therapy (**Figure 2**)
- Patients received melflufen 40 mg (intravenously on day 1 of each 28-day cycle) plus dexamethasone 40 mg weekly until disease progression or unacceptable toxicity
- EMD definition and assessment
 - EMD was defined as the presence of ≥1 paraneoplastic or soft-tissue lesion based on imaging and/or clinical examination at baseline
 - Known or suspected EMD was assessed at screening (within 28 days), as clinically indicated, and to confirm response or progression according to International Myeloma Working Group uniform response criteria¹²
 - The same method of evaluation was used throughout the study (eg, by computerized tomography/magnetic resonance imaging/positron emission tomography)

RESULTS

PATIENTS

- In total, 157 patients were enrolled and treated in HORIZON (data cutoff date, 14 January 2020); of these, 55 had EMD (51% had only bone-related EMD and 49% of patients had soft-tissue related EMD)
- Baseline patient characteristics were generally similar between patients with and without EMD (**Table 1**)

Table 1. Baseline Patient Characteristics

Characteristic	EMD (n=55)	Non-EMD (n=102)
Age, median (range), years	64 (43-82)	65 (35-86)
Male sex, n (%)	31 (56)	58 (57)
High-risk cytogenetics, n (%) ^a	19 (35)	40 (39)
ISS stage (I / II / III) at study entry, % ^b	36 / 25 / 33	42 / 34 / 21
EMD at study entry, n (%) ^c	55 (100)	NA
Bone-related (only)	28 (51)	NA
Soft-tissue	27 (49)	NA
No. of prior lines of therapy, median (range)	5 (2-12)	5 (2-10)
Triple-class refractory, n (%) ^d	50 (91)	69 (68)
Refractory to ≥1 anti-CD38 mAb, n (%)	50 (91)	75 (74)
Refractory to prior alkylator therapy, n (%)	33 (60)	59 (58)

^aHigh-risk cytogenetics at study entry was based on fluorescence in situ hybridization, defined as t(4;14), del(17)(17p), and t(14;16) as described¹³; 11 patients (20%) in the EMD group and 20 patients (20%) in the non-EMD group had unknown cytogenetics. Cytogenetic assessments were not centralized.
^bAt study entry, 3 patients in the EMD group and 3 patients in the non-EMD group had unknown or missing ISS stage.
^cEMD was defined as the presence of ≥1 paraneoplastic or soft-tissue lesion based on imaging and/or clinical examination at baseline.
^dDefined as refractory to or intolerant of ≥1 proteasome inhibitor, ≥1 immunomodulatory agent, and ≥1 anti-CD38 mAb.
EMD, extramedullary disease; ISS, International Staging System; mAb, monoclonal antibody; NA, not applicable.

EFFICACY

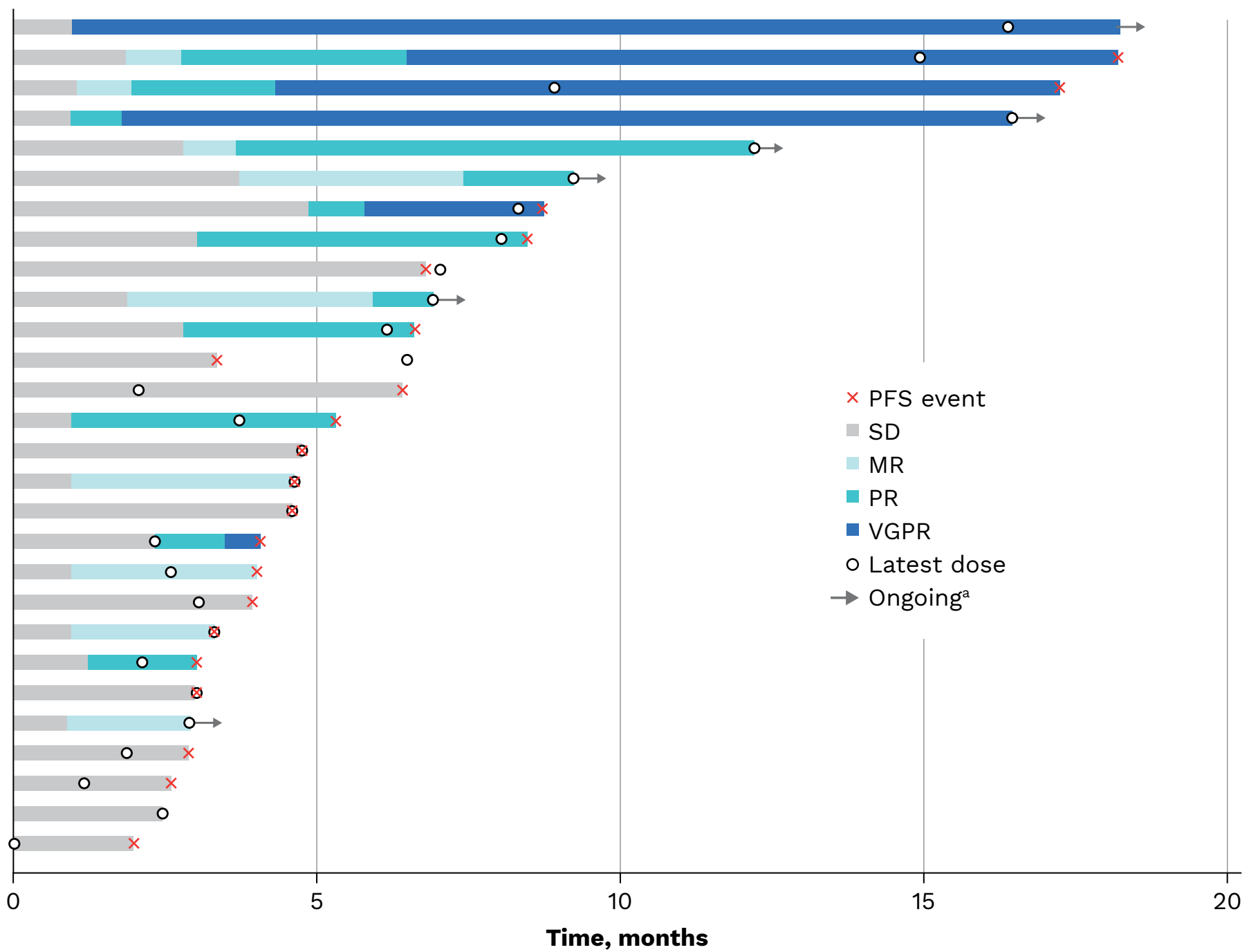
- ORR was 24% (95% CI, 13.2-37.0) in patients with EMD and 32% (95% CI, 23.4-42.3) in patients without EMD (**Table 2**)
- In patients with EMD,
 - ORR assessed by independent review committee was 27%
 - ORR was 25% (95% CI, 10.7-44.9) and the clinical benefit rate (CBR) was 32% (95% CI, 15.9-52.4) in patients with only bone-related EMD (n=28)
 - ORR was 22% (95% CI, 8.6-42.3) and the CBR was 30% (95% CI, 13.8-50.2) in patients with soft-tissue EMD (n=27)
- Responses deepened with longer treatment duration in patients with EMD (**Figure 3**)
- Median DOR was 5.5 months (95% CI, 1.8 to not evaluable) in patients with EMD and 5.1 months (95% CI, 3.7-7.5) in patients without EMD

Table 2. Response and Treatment Duration

	Patients With EMD (n=55)	Patients Without EMD (n=102)
ORR (≥PR), % (95% CI)	24 (13.2-37.0)	32 (23.4-42.3)
CBR (≥MR), % (95% CI)	31 (19.1-44.8)	53 (42.8-62.9)
Treatment duration, median (range), weeks	12 (4-79)	18 (4-99)

Investigator-assessed best overall response per International Myeloma Working Group uniform response criteria.¹²
CBR, clinical benefit rate; EMD, extramedullary disease; MR, minimal response; ORR, overall response rate; PR, partial response.

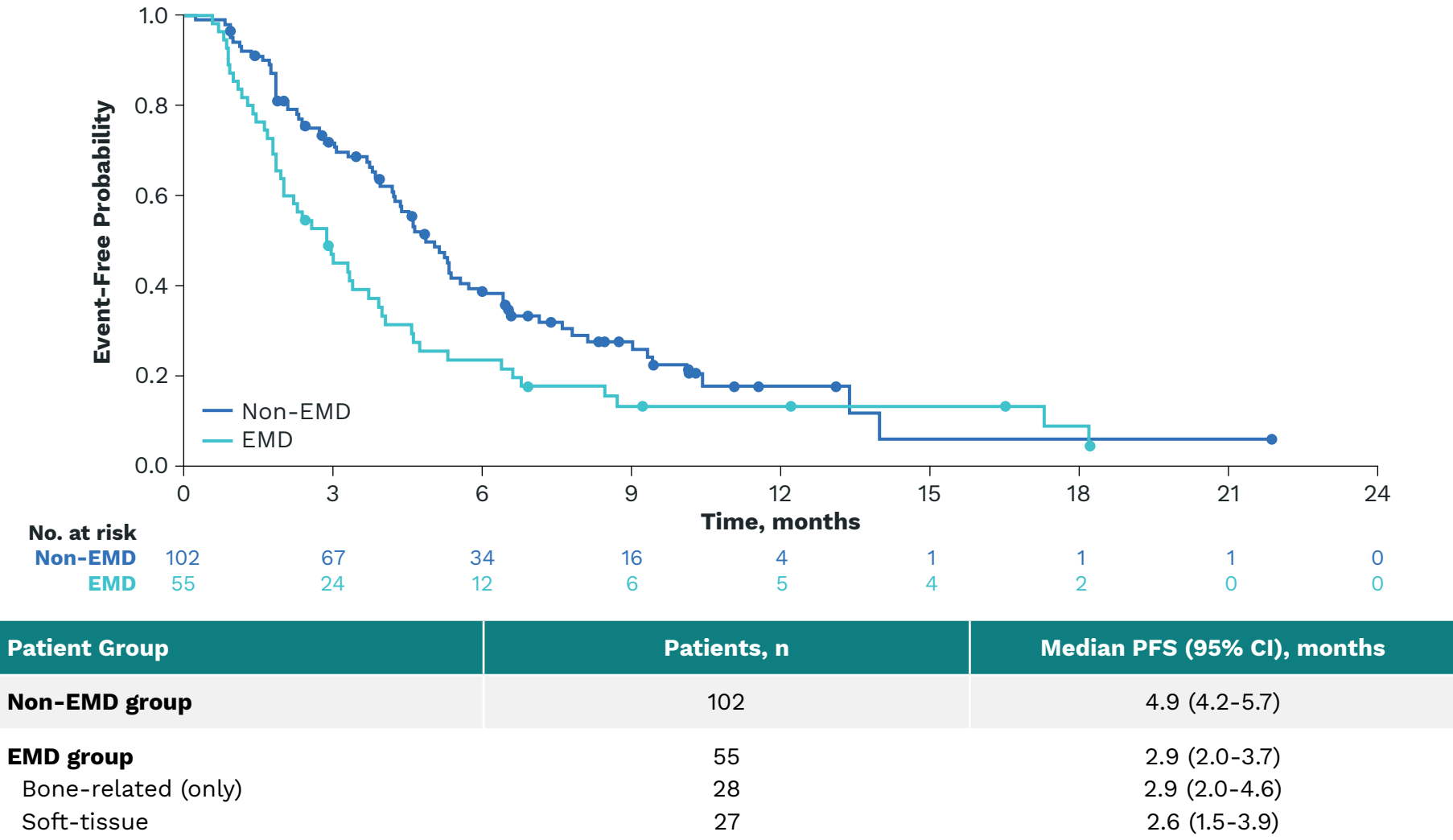
Figure 3. Response in Patients With EMD Who Achieved Stable Disease or Better



Investigator-assessed best overall response per International Myeloma Working Group uniform response criteria.¹²
*Patient remains on study (receiving therapy or in the end-of-treatment follow-up period) and has not yet experienced a PFS event.
MR, minimal response; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

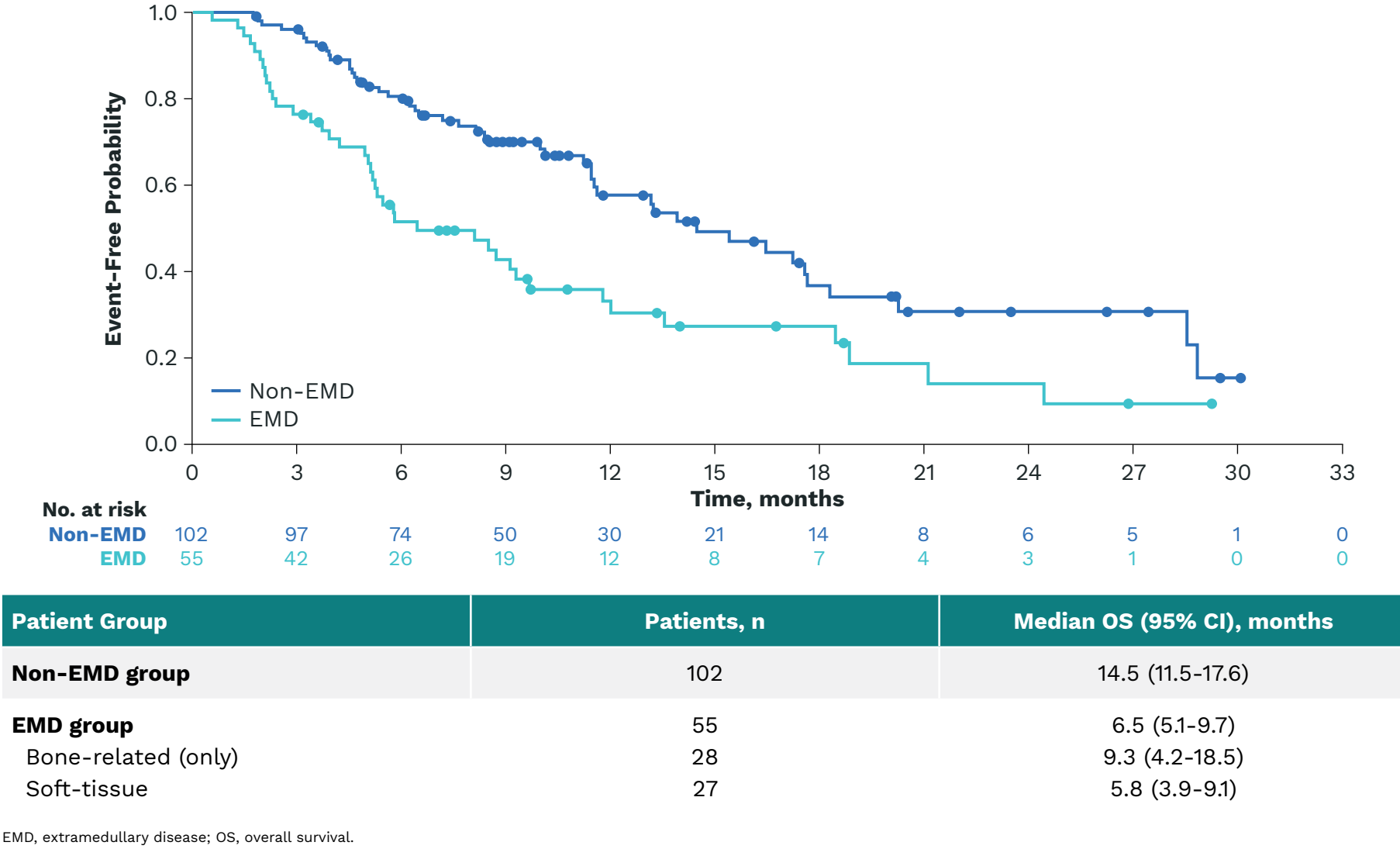
- Median PFS was 2.9 months in patients with EMD and 4.9 months in patients without EMD (**Figure 4**)
 - Median PFS was 2.9 months in patients with only bone-related EMD and 2.6 months in patients with soft-tissue EMD
- Median OS was 6.5 months in patients with EMD and 14.5 months in patients without EMD (**Figure 5**)
 - Median OS was 9.3 months in patients with only bone-related EMD and 5.8 months in patients with soft-tissue EMD

Figure 4. PFS in Patients With EMD and Patients Without EMD



EMD, extramedullary disease; PFS, progression-free survival.

Figure 5. OS in Patients With EMD and Patients Without EMD



EMD, extramedullary disease; OS, overall survival.

SAFETY

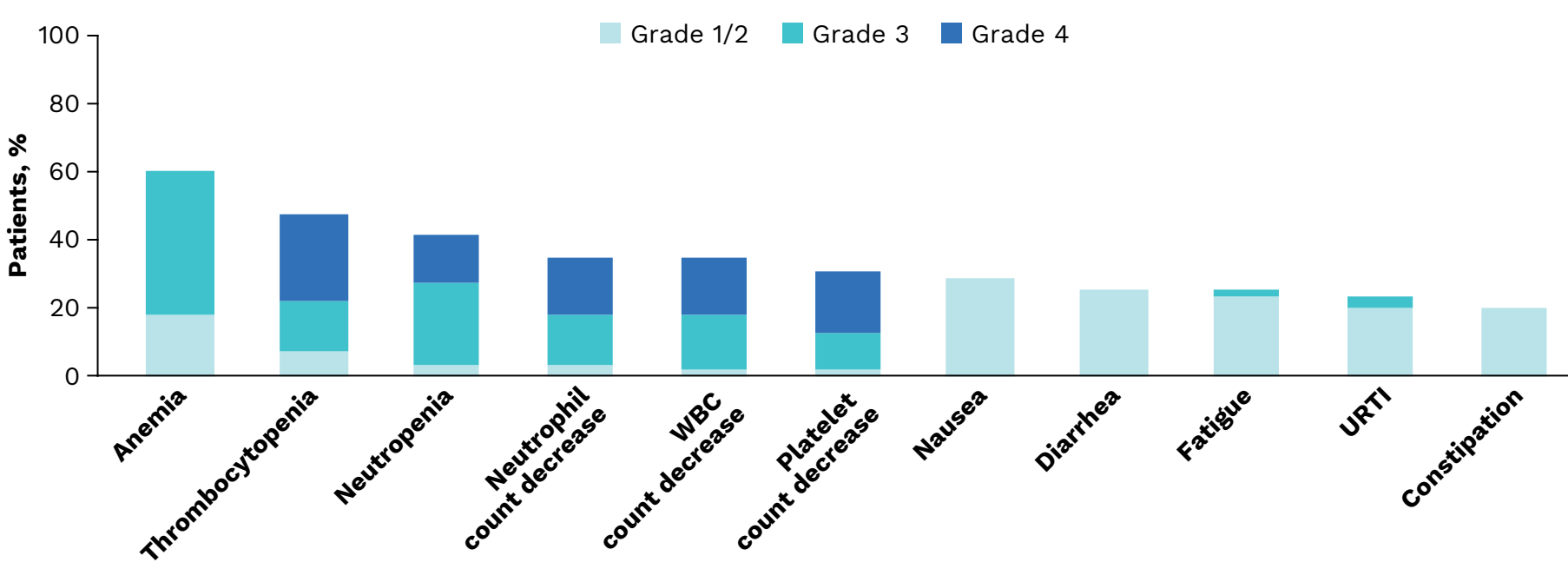
- The safety profile of melflufen plus dexamethasone in patients with EMD was consistent with that in the overall HORIZON population (**Table 3**), and no new safety signals were identified in patients with EMD¹¹
 - The most common TEAEs were hematologic in nature (**Figure 6**)
 - Nonhematologic TEAEs were primarily grade 1/2
 - Fatal TEAEs occurred in 8 patients (15%) with EMD and none were considered related to melflufen

Table 3. Summary of TEAEs in Patients With EMD

Patients With TEAE, n (%)	Patients With EMD (n=55)
Any TEAE ^a	55 (100)
Grade 3/4 TEAEs	43 (78)
TEAEs leading to melflufen discontinuation	13 (24)
Occurring in ≥2 patients	
Thrombocytopenia	5 (9)
General physical health deterioration	2 (4)
Any SAE	38 (69)

^aAdverse events are coded to preferred term using MedDRA version 10.1.
EMD, extramedullary disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Figure 6. Most Common TEAEs Occurring in ≥20% of Patients With EMD^a



^aAdverse events are coded to preferred term using MedDRA version 10.1.
EMD, extramedullary disease; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; WBC, white blood cell.

CONCLUSIONS

- EMD, particularly in the RRMM setting, is associated with poor patient outcome and is not well investigated¹
- This retrospective subgroup analysis from HORIZON represents the largest cohort of patients with EMD evaluated to date in a prospective clinical trial
- Melflufen plus dexamethasone showed activity in patients with advanced RRMM with EMD, a population with high unmet medical need, in the HORIZON study
- The safety profile of melflufen plus dexamethasone in patients with EMD was consistent with that of previous reports and consisted primarily of hematologic TEAEs that were clinically manageable with dose modification and supportive care^{11,24}
 - Nonhematologic TEAEs were mostly grade 1/2 and did not result in treatment discontinuation
- Results support continued evaluation of melflufen-based combination therapies for this population

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