

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

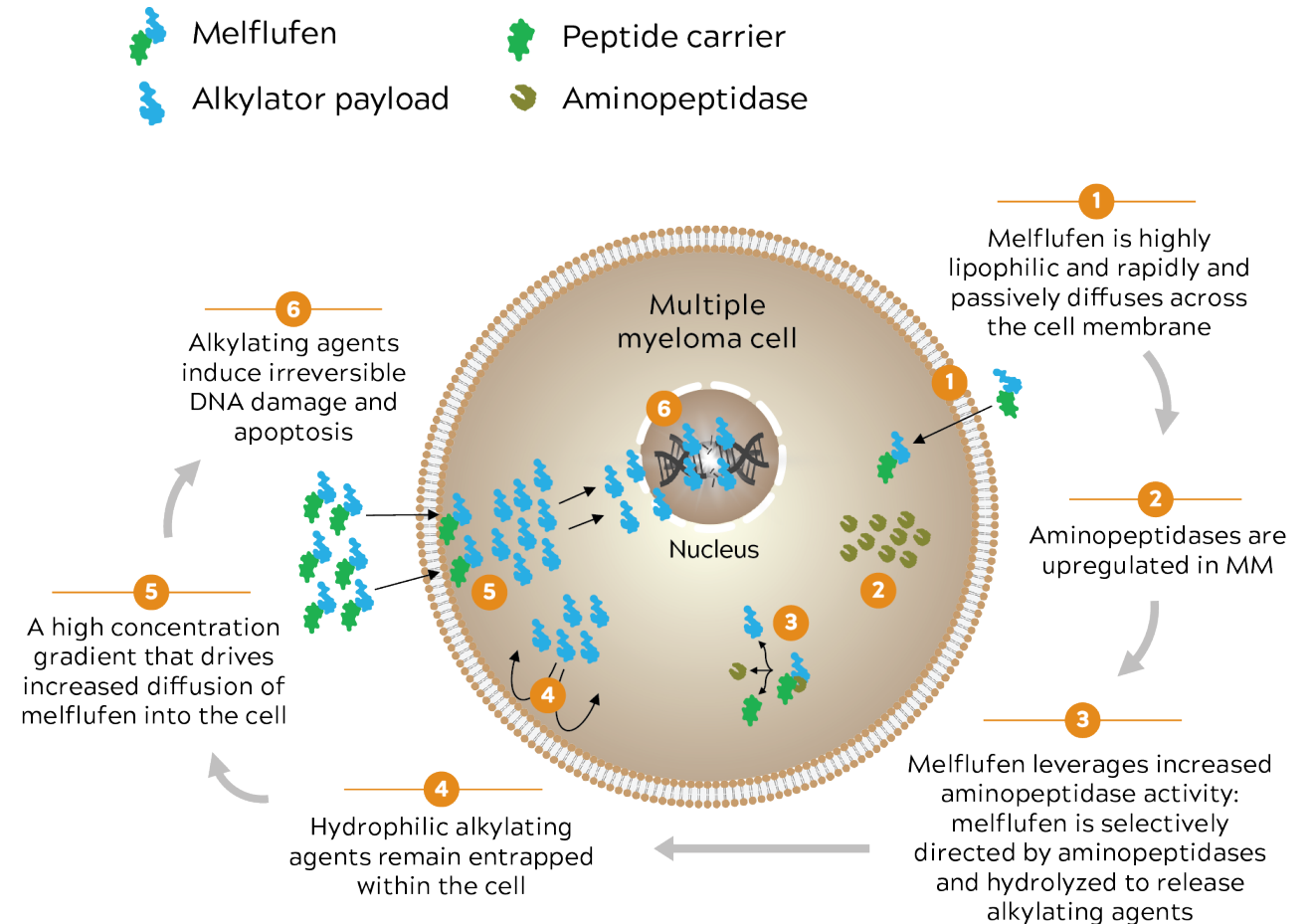
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# Melflufen: A First-in-Class Peptide-Drug Conjugate

Melphalan flufenamide (melflufen) is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**<sup>1-5</sup>

- EMD is characterized by MM cells that can grow independently of the bone microenvironment
  - Angiogenesis, cell proliferation, adhesion, migration, and invasion are all pathways that are involved in progression to EMD<sup>6</sup>
- Melflufen has demonstrated inhibition of angiogenesis in preclinical studies<sup>1,2,5</sup>



EMD, extramedullary disease; MM, multiple myeloma.

1. Chauhan D, et al. *Clin Cancer Res*. 2013;19(11):3019-31. 2. Ray A, et al. *Br J Haematol*. 2016;174(3):397-409. 3. Wickström M, et al. *Oncotarget*. 2017;8(39):66641-55. 4. Wickström M, et al. *Invest New Drugs*. 2008;26(3):195-204. 5. Strese S, et al. *Biochem Pharmacol*. 2013;86(7):888-95. 6. Bhutani M, et al. *Leukemia*. 2020;34:1-20.

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 EMD.<sup>1</sup>

Outcome <sup>1</sup>	Patients (N=157)
ORR, % (95% CI)	29 (22.3-37.1)
OS, median (95% CI), months	11.6 (9.3-15.4)
PFS, median (95% CI), months	4.2 (3.4-4.9)
DOR (≥PR), median (95% CI), months	5.5 (3.9-7.6)

## Objective of this subgroup analysis

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

- Outcomes for patients with EMD are worse than those for patients without EMD<sup>2</sup>
  - A recent analysis of isatuximab plus pomalidomide and dexamethasone showed a median PFS of 4.6 months for patients with EMD and 11.5 months in the overall population<sup>3</sup>
- Outcomes for patients with EMD are particularly poor in the RRMM setting<sup>2</sup>
  - Prognosis is usually poorer for patients with hematogenous-spread soft-tissue plasmacytomas than for patients with bone-related plasmacytomas<sup>4,5</sup>
- No standard therapy has been established for this population with high unmet medical need<sup>2</sup>
  - Treatment with anti-CD38 mAb monotherapy has shown limited activity (ORR, 17%)<sup>6</sup>

DOR, duration of response; EMD, extramedullary disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory multiple myeloma.

1. Richardson et al. EHA 2020. Poster EP9453. 2. Bhutani M, et al. *Leukemia*. 2020;34(1):1-20. 3. Beksac M, et al. EHA 2020. Poster EP978. 4. Gagelmann et al. *Haematologica*. 2018;103:890. 5. Mangiacavalli et al. *Ann Hematol*. 2017;96:73. 6. Usmani et al. *Blood*. 2016;128:37-44.

HORIZON is a pivotal, single-arm, multicenter, phase 2 study of melflufen plus dexamethasone in patients with RRMM who must have received  $\geq 2$  lines of prior therapy (NCT02963493).

## Key Eligibility Criteria

### Adult patients with

- RRMM refractory to pomalidomide or anti-CD38 mAb or both
- $\geq 2$  Prior lines of therapy, including an IMiD and a PI
- ECOG PS  $\leq 2$

(N=157)

Data cutoff date: January 14, 2020

## Dosing Schedule

**Melflufen 40 mg + dexamethasone 40 mg<sup>a</sup>**  
(until disease progression or unacceptable toxicity)

	28-Day Cycle			
	D1	D8	D15	D22
Melflufen (IV)	✓			
Dexamethasone (oral)	✓	✓	✓	✓

## Follow-Up and Endpoints

EoT

PFS and OS follow-up for  $\leq 24$  mo

### Primary endpoint

- ORR

### Secondary endpoints

- DOR
- PFS
- OS
- CBR
- TTR
- TTP
- TTNT
- Safety
- HRQoL

## EMD Definition and Assessment:

- EMD was defined as the presence of  $\geq 1$  paraspinal or soft-tissue lesion based on imaging and/or clinical examination at baseline
- Known or suspected EMD were assessed at screening (within 28 days), as clinically indicated, and to confirm response or progression according to International Myeloma Working Group uniform response criteria
- The same method of evaluation was used throughout the study (eg, CT/MRI/PET)

<sup>a</sup>Patients aged  $\geq 75$  years received dexamethasone 20 mg.

CBR, clinical benefit rate; CT, computerized tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; EoT, end of treatment; HRQoL, health-related quality of life; IMiD, immunomodulatory agent; IV, intravenous; mAb, monoclonal antibody; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTP, time to progression; TTR, time to response.

# 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)
<b>High-risk cytogenetics, n (%)<sup>a</sup></b>	<b>19 (35)</b>	<b>40 (39)</b>
ISS stage (I/II/III) at study entry, % <sup>b</sup>	36 / 25 / 33	42 / 34 / 21
EMD at study entry, n (%) <sup>c</sup>	55 (100)	NA
Soft-tissue plasmacytoma	27 (49)	NA
Bone-related plasmacytoma	28 (51)	NA
No. of prior lines of therapy, median (range)	5 (2-12)	5 (2-10)
Triple-class refractory, n (%) <sup>d</sup>	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)

<sup>a</sup>High-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 described<sup>1</sup>; 11 patients (20%) in the EMD group and 20 patients (20%) in the non-EMD group had unknown cytogenetics. Cytogenetic assessments were not centralized. <sup>b</sup>At study entry, 3 patients in the EMD group and 3 patients in the non-EMD group had unknown or missing ISS stage. <sup>c</sup>EMD was defined as the presence of ≥1 paraspinal or soft-tissue lesion based on imaging and/or clinical examination at baseline. <sup>d</sup>Defined as refractory to or intolerant of ≥1 proteasome inhibitor, ≥1 IMiD, and ≥1 anti-CD38 mAb.

EMD, extramedullary disease; IMiD, immunomodulatory agent; ISS, International Staging System; mAb, monoclonal antibody; NA, not applicable.

1. Sonneveld P, et al. *Blood*. 2016;127:2955-2962.

See Mateos MV, et al. ASH 2020. #3237 for high-risk cytogenetics subgroup analysis.

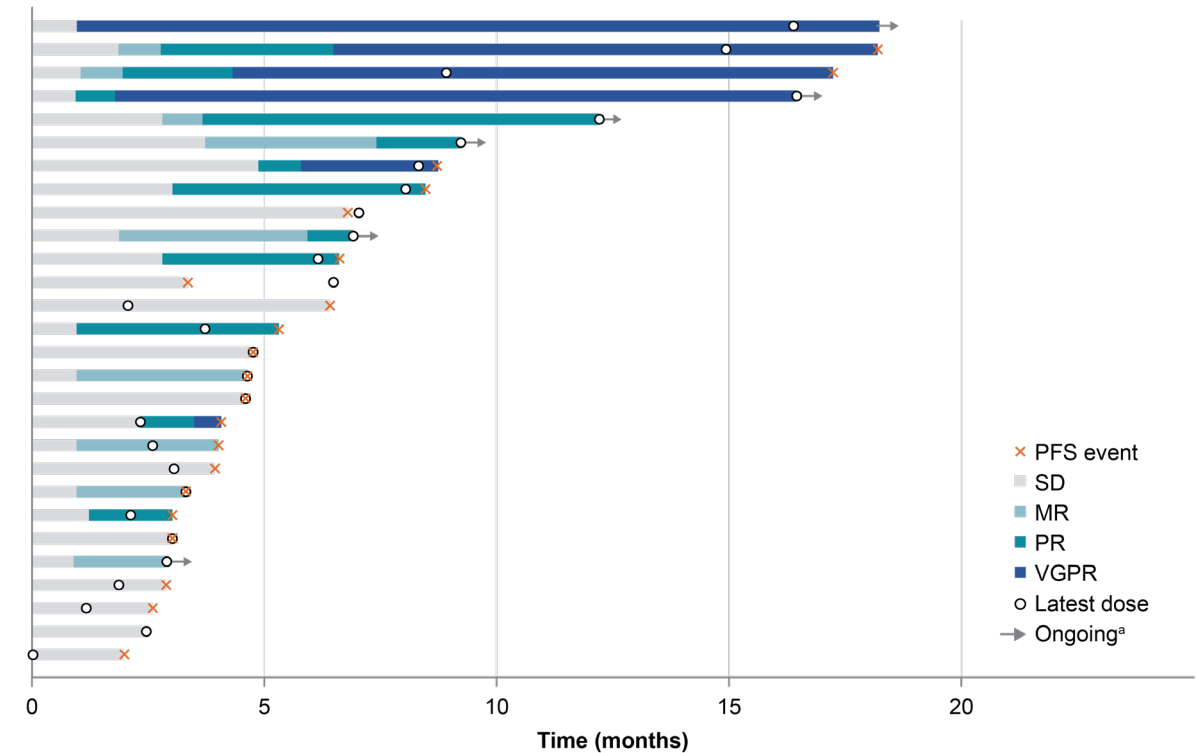
# Response in Patients With EMD and Patients Without EMD

- In patients with EMD (n=55), ORR was 24% (95% CI, 13.2-37.0), CBR was 31% (95% CI, 19.1-44.8), and median DOR was 5.5 months (95% CI, 1.8-NE)
  - ORR and CBR assessed by IRC were 27% and 33%, respectively
  - Among 50 patients with EMD and refractory to prior daratumumab, the ORR was 22%
- In the non-EMD group (n=102), ORR was 32% (95% CI, 23.4-42.3), CBR was 53% (95% CI, 42.8-62.9), and the median DOR was 5.1 months (95% CI, 3.7-7.5)

## ORR and CBR For Patients Within the EMD Group

	ORR, % (95% CI)	CBR, % (95% CI)
Bone-related plasmacytoma (n=28)	25 (10.7-44.9)	32 (15.9-52.4)
Soft-tissue plasmacytoma (n=27)	22 (8.6-42.3)	30 (13.8-50.2)

## Swim-Lane Plot for Patients With EMD Who Achieved $\geq$ SD



Median treatment duration was 12 weeks (range, 4-79) in the EMD group and 18 weeks (range, 4-99) in the non-EMD group.

Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.<sup>1</sup>

<sup>a</sup>Patient remains on study (receiving therapy or in the end-of-treatment follow-up period) and has not yet experienced a progression-free survival event.

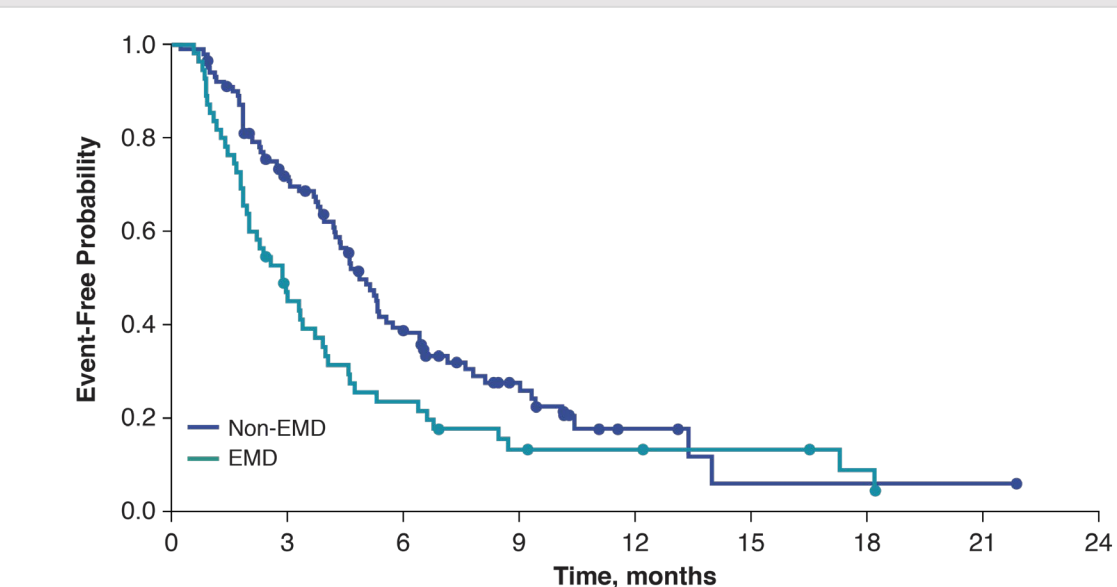
CBR, clinical benefit rate; DOR, duration of response; EMD, extramedullary disease; HR, high-risk; IRC, Independent Review Committee; MR, minimal response; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

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

# PFS and OS in Patients With EMD and Patients Without EMD



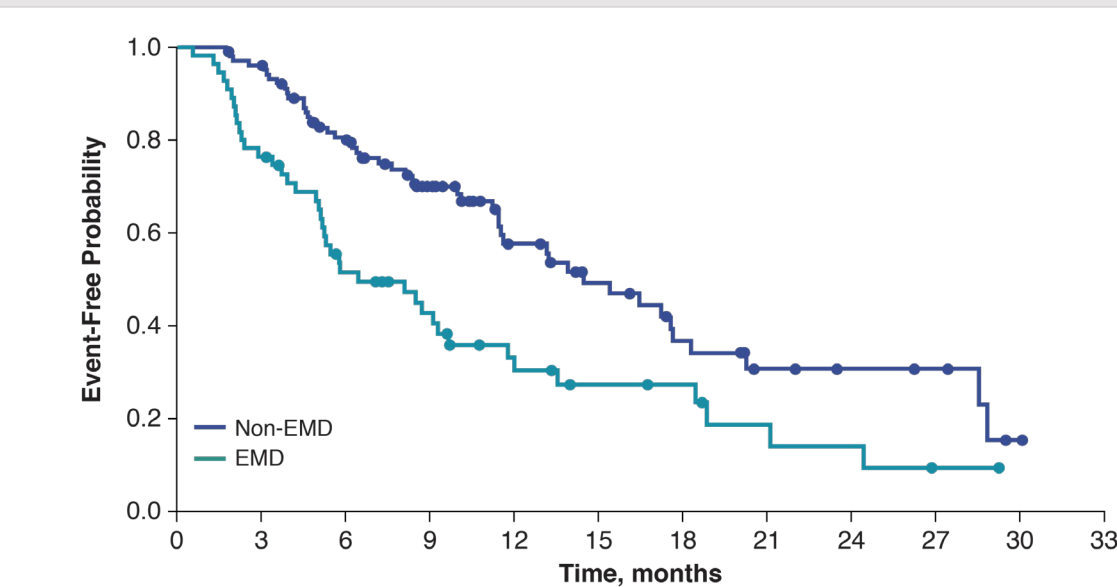
## PFS in the EMD and the Non-EMD Groups



No. at risk		0	3	6	9	12	15	18	21	24
EMD	55	24	12	6	5	4	2	0	0	0
Non-EMD	102	67	34	16	4	1	1	1	0	0

Patient Group	Patients, n	Median PFS (95% CI), mo
<b>EMD Group</b>	<b>55</b>	<b>2.9 (2.0-3.7)</b>
Bone-related	28	2.9 (2.0-4.6)
Soft-tissue	27	2.6 (1.5-3.9)
<b>Non-EMD group</b>	<b>102</b>	<b>4.9 (4.2-5.7)</b>

## OS in the EMD and the Non-EMD Groups



No. at risk		0	3	6	9	12	15	18	21	24	27	30	33
EMD	55	42	26	19	12	8	7	4	3	1	0	0	0
Non-EMD	102	97	74	50	30	21	14	8	6	5	1	0	0

Patient Group	Patients, n	Median OS (95% CI), mo
<b>EMD Group</b>	<b>55</b>	<b>6.5 (5.1-9.7)</b>
Bone-related	28	9.3 (4.2-18.5)
Soft-tissue	27	5.8 (3.9-9.1)
<b>Non-EMD group</b>	<b>102</b>	<b>14.5 (11.5-17.6)</b>

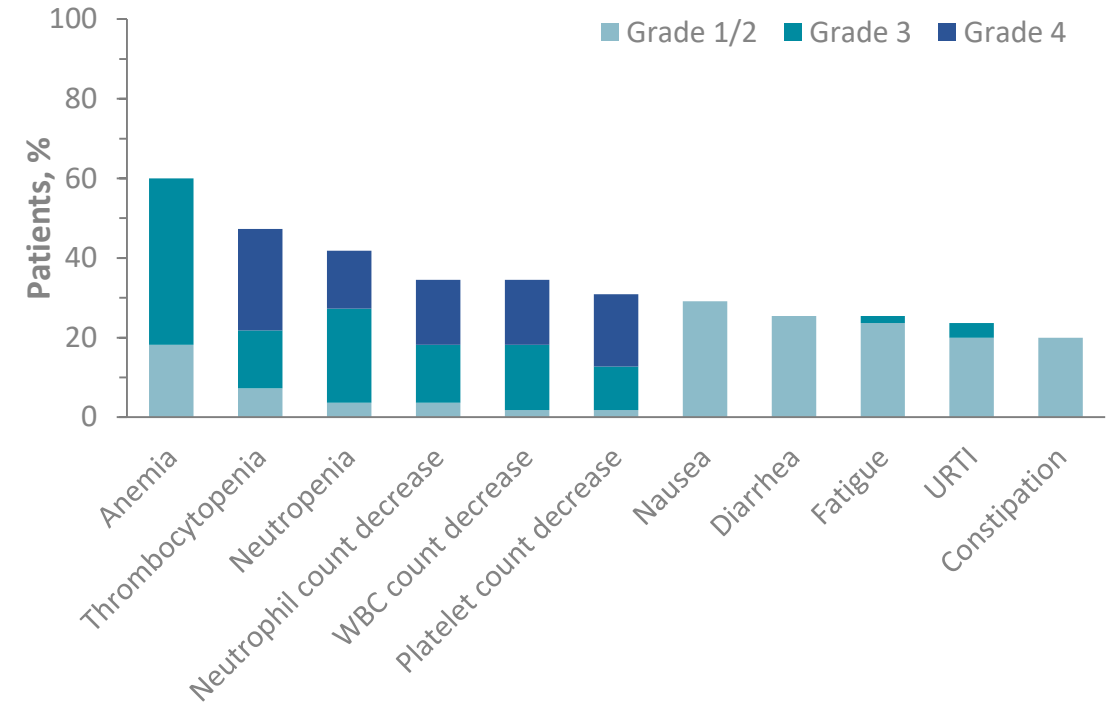
DOR, duration of response; EMD, extramedullary disease; OS, overall survival; PFS, progression-free survival.

## Summary of TEAEs in Patients With EMD

Patients With TEAE, n (%)	Patients With EMD (n=55)
Any TEAE <sup>a</sup>	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)

- Fatal TEAEs occurred in 8 patients (15%) with EMD; none were considered related to melflufen

## Most Common TEAEs (Occurring in ≥20% of Patients)



The safety profile of melflufen plus dexamethasone in patients with EMD was consistent with that in the overall population

- The most common TEAEs were hematologic
- Nonhematologic TEAEs were primarily grade 1/2

<sup>a</sup>Adverse events are coded to preferred term using MedDRA, version 19.1.

EMD, extramedullary disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; WBC, white blood cell.

- EMD, particularly in the RRMM setting, is associated with poor patient outcome and is not well investigated<sup>1</sup>
- 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<sup>1,2</sup>
  - 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

EMD, extramedullary disease; RRMM, relapsed/refractory multiple myeloma; TEAE, treatment-emergent adverse event.

1. Bhutani M, et al. *Leukemia*. 2020;34:1-20. 2. Richardson et al. EHA 2020. Poster EP945. 3. Richardson PG, et al. *Lancet Haematol*. 2020;7:e395-e3407.

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- **Melflufen is being discussed in other presentations at this meeting:**
  - Melflufen plus dexamethasone and daratumumab or bortezomib, abstract: [417](#) (oral)
  - Melflufen plus dexamethasone, abstracts: [2293](#), [2321](#), [2564](#), [3237](#), [3477](#) (posters)
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