

Melflufen Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma Exposed/Refractory to Prior Alkylators – A Pooled Analysis of the O-12-M1 and HORIZON Studies



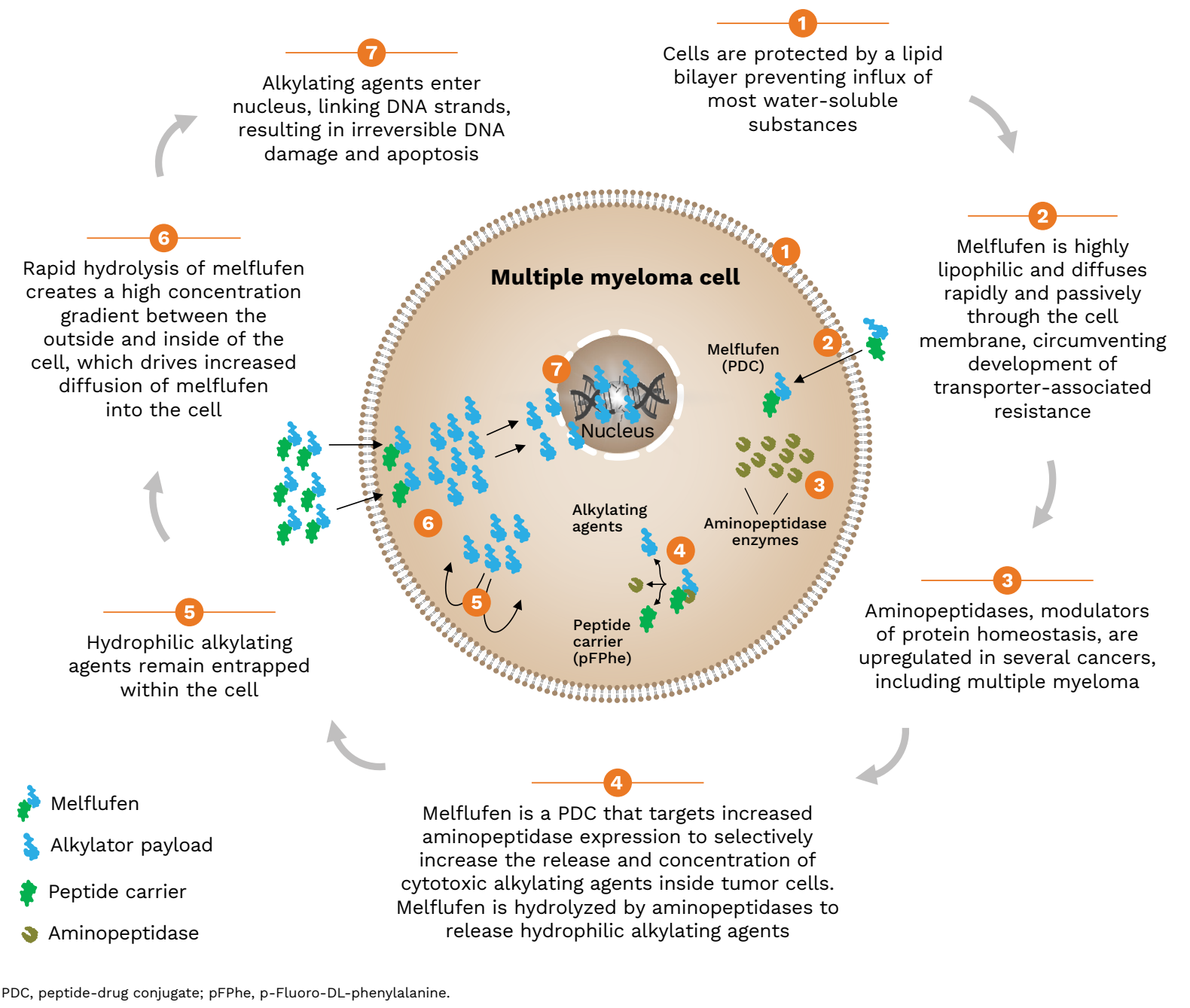
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BACKGROUND

- Despite therapeutic advances for patients with multiple myeloma (MM), outcomes are generally poor and relapses are common, highlighting the need for therapies with new mechanisms of action¹⁻⁴
 - Alkylators are an important component of MM treatment, in frontline therapy as conditioning agents prior to stem cell transplant (SCT), in combination with other agents for older or less-fit patients, and as part of salvage therapies⁵
- Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that targets aminopeptidases and thereby rapidly releases alkylating agents inside tumor cells (**Figure 1**)⁶⁻¹³
- Melflufen induces irreversible DNA damage and apoptosis via an alkylator-like, yet distinct, mechanism of cytotoxicity that is independent of p53 function and has the potential to provide therapeutic benefit for patients with relapsed/refractory MM (RRMM)^{6,12,14}
- Melflufen in combination with dexamethasone has demonstrated efficacy and a manageable safety profile in heavily pretreated and poor-risk patients with RRMM, as previously reported in the phase 2 portion of the O-12-M1 study and the phase 2 HORIZON study¹⁵⁻¹⁷
 - As many patients in the O-12-M1 and the HORIZON studies had been exposed/refractory to prior alkylators, subgroup analyses were conducted to determine if the exposed/refractory status of patients to prior alkylators impacted efficacy outcomes of subsequent treatment with melflufen plus dexamethasone

Figure 1. Melflufen Mechanism of Action



OBJECTIVES

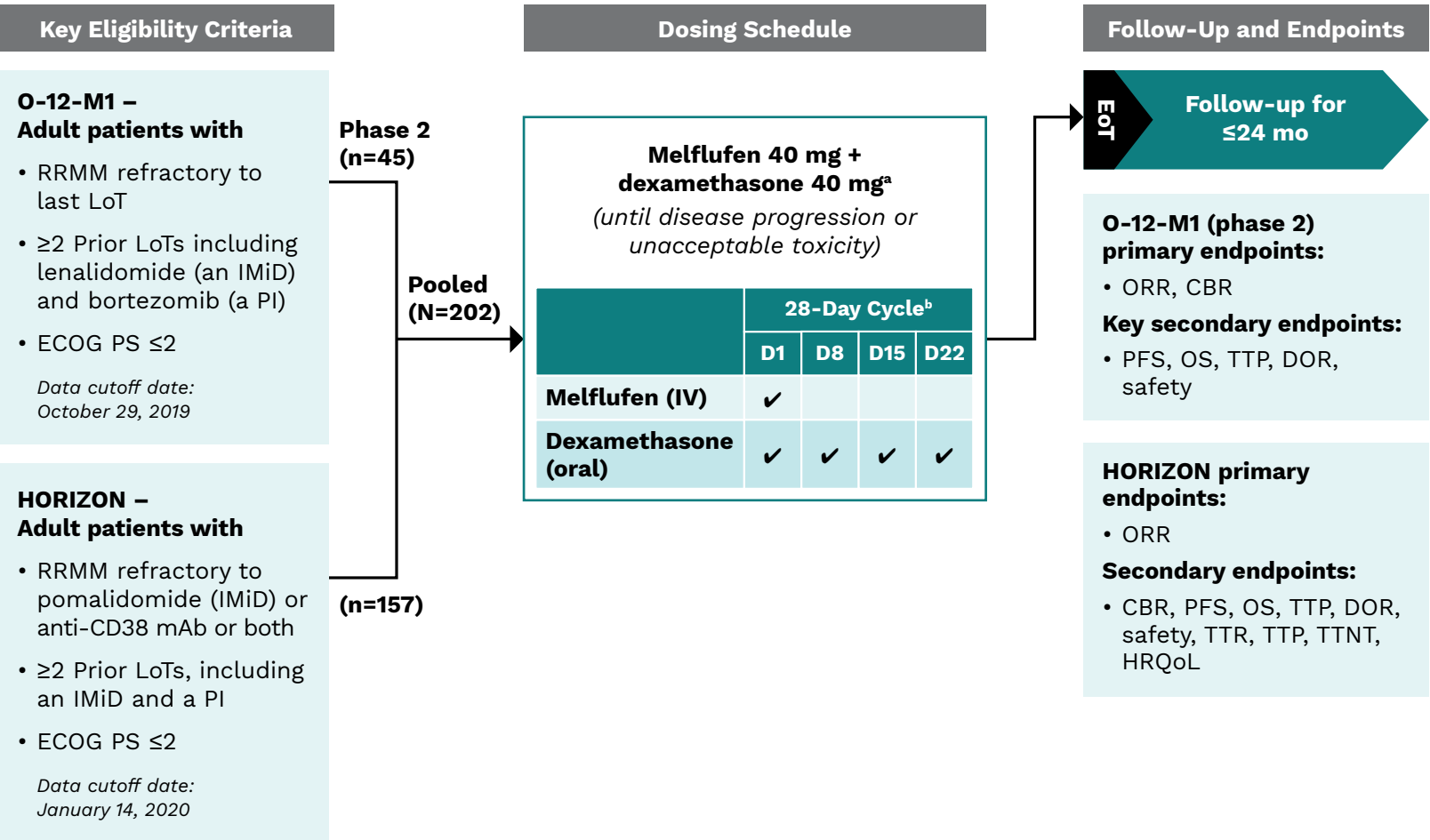
- To examine the clinical efficacy and safety of melflufen plus dexamethasone in patients exposed or exposed and refractory to prior alkylator therapy, pooled from the O-12-M1 and HORIZON studies

METHODS

- Adult patients with RRMM who had received ≥2 prior lines of therapy (LoTs) were enrolled and treated with melflufen plus dexamethasone in the O-12-M1 (n=45) and HORIZON (n=157) studies (**Figure 2**)^{16,17}
 - The primary results of O-12-M1 and HORIZON have previously been reported¹⁶⁻¹⁷
- Retrospective analyses were conducted using pooled patient data from both trials to assess patient response (N=202)
 - In the first retrospective analysis, patients were grouped by the number of prior LoTs in which they were either exposed or exposed and refractory to an alkylator received before enrollment in the respective parent trial (**Figure 3**)
 - In a separate retrospective analysis, patients were grouped by the type of prior alkylator regimen they received as standard dose, dose intense, or high dose with SCT
 - Dose intense regimens included regimens, such as DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin), VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, cyclophosphamide, and etoposide), double-alkylator regimens; or intensive-dose alkylator monotherapy, such as cyclophosphamide without SCT
 - Outcomes were also analyzed for time of progression after receiving SCT
- Refractoriness to prior alkylator was defined as disease that failed to achieve a minimal response or progressed while the patient was on primary or salvage therapy containing an alkylator or progressed within 60 days of last therapy containing an alkylator

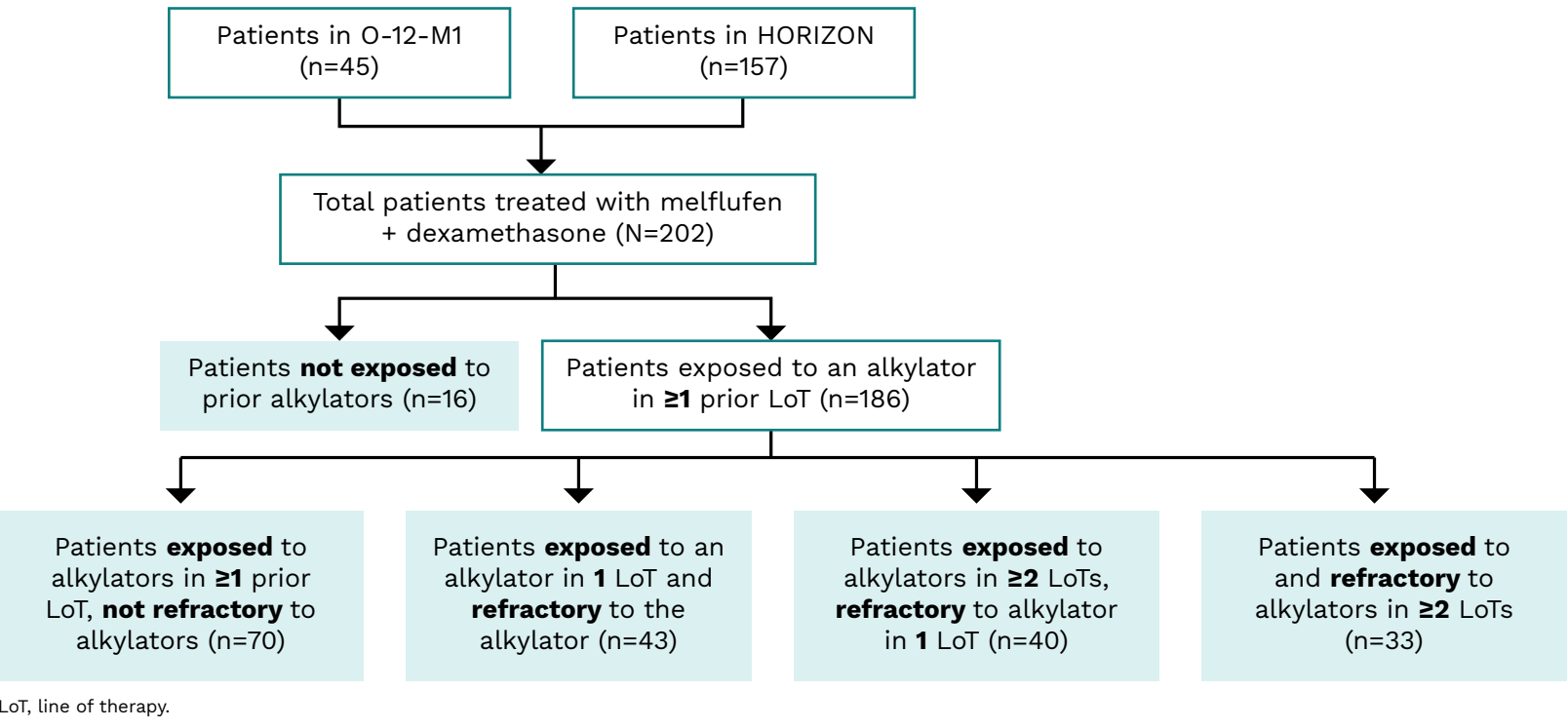
METHODS (continued)

Figure 2. HORIZON and O-12-M1 Study Designs



*Patients aged ≥75 years received dexamethasone 20 mg. *In the O-12-M1 study, 28 patients received the combination regimen in 21-day cycles and 17 patients received 28-day cycles. CBR, clinical benefit rate; D, day; 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; LoT, line of therapy; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRM, relapsed/refractory multiple myeloma; TTNI, time to next treatment; TTP, time to progression; TTR, time to response.

Figure 3. Summary of Pooled Population by Exposed or Exposed and Refractory Status to Prior Alkylators



RESULTS

PATIENTS

- Of 202 patients in the pooled population, 186 (92%) had been exposed to alkylator in ≥1 prior LoT and 33 (16%) had been exposed and were refractory to alkylators in ≥2 prior LoTs
 - Efficacy results for the overall pooled population are shown in **Table 1**^{15,17}
- Baseline patient characteristics are organized by status of exposed and refractory to alkylators received in prior LoTs (**Table 2**)
 - Patients who were exposed and refractory to prior alkylators had certain poorer prognostic features compared with patients who had no prior alkylator exposure, including higher International Staging System stage and number of prior LoTs
 - Patients who were exposed and refractory to alkylators in ≥2 prior LoTs had particularly poor prognostic features

Table 1. Outcomes With Melflufen Plus Dexamethasone

	O-12-M1 (N=45) ¹⁶	HORIZON (N=157) ¹⁷	Pooled Population (N=202)
ORR (95% CI), %	31 (18.2-46.6)	29 (22.3-37.1)	30 (23.5-36.5)
Median (95% CI), mo			
PFS	5.7 (3.7-9.2)	4.2 (3.4-4.9)	4.4 (3.7-5.1)
OS	20.7 (11.2-33.2)	11.6 (9.3-15.4)	13.6 (11.2-17.6)

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 28, 2019. *Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.¹⁸ CBR, clinical benefit rate; CR, complete response; DOR, duration of response; LoT, line of therapy; MR, minor response; NE, not evaluable; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.

RESULTS (continued)

Table 2. Baseline Patient Characteristics by Status (Exposed or Exposed and Refractory) to Alkylators Received in Prior LoTs

Patients by Alkylator Exposed/Refractory Status in Prior LoTs	Overall (N=202)	Not Exposed to Prior Alkylators (n=16)	Exposed in ≥1 Prior LoT (n=186)	Alkylator Exposed, Alkylator-Refractory Status (Within n=186 Group)			
				≥1 Exposed, Not Refractory (n=70)	1 Exposed, 1 Refractory (n=43)	≥2 Exposed, 1 Refractory (n=40)	≥2 Exposed, ≥2 Refractory (n=33)
Age, median (range), y	65 (35-86)	71 (61-80)	64 (35-86)	63 (42-83)	68 (55-86)	62 (35-84)	66 (49-79)
Male sex, n (%)	119 (59)	10 (62)	109 (59)	40 (57)	26 (60)	20 (50)	23 (70)
High-risk cytogenetics, n (%)	79 (39)	8 (50)	71 (38)	24 (34)	22 (51)	11 (28)	14 (42)
ISS stage at study entry (I / II / III), %^a	39 / 33 / 24	44 / 38 / 12	38 / 33 / 25	49 / 40 / 10	42 / 23 / 30	30 / 28 / 40	21 / 36 / 30
ECOG PS (0 / 1 / 2), %	31 / 57 / 12	19 / 62 / 19	32 / 56 / 12	33 / 56 / 11	35 / 60 / 5	35 / 55 / 10	21 / 55 / 24
Extramedullary disease, n (%)	61 (30)	6 (38)	55 (30)	18 (26)	15 (35)	10 (25)	12 (36)
Prior LoTs, median (range), n	5 (2-14)	3 (2-7)	5 (2-14)	4 (2-10)	5 (2-9)	6 (3-9)	7 (4-14)
Triple-class–refractory, n (%)^b	122 (60)	8 (50)	114 (61)	35 (50)	30 (70)	24 (60)	25 (76)
Penta-refractory, n (%)^c	68 (34)	4 (25)	64 (34)	19 (27)	15 (35)	13 (32)	17 (52)
Response to prior alkylator therapy, n (%)							
No response ^d	66 (33)	N/A	50 (27)	13 (19)	27 (63)	4 (10)	6 (18)
Response ≥PR ^d	136 (67)	N/A	136 (73)	57 (81)	16 (37)	36 (90)	27 (82)
Refractory ≤12 mo prior to study start ^e	71 (35)	N/A	71 (38)	0 (0)	18 (42)	26 (65)	27 (82)
Refractory to alkylator in last LoT	46 (23)	N/A	46 (25)	0 (0)	11 (26)	15 (38)	20 (61)
Prior allogeneic/autologous SCT, n (%)	136 (67)	0 (0)	136 (73)	57 (81)	23 (53)	32 (80)	24 (73)
Progression after SCT, n/N (%)							
>12 mo	94/136 (69)	N/A	94/136 (69)	44/57 (77)	16/23 (70)	20/32 (62)	14/24 (58)
6-12 mo	26/136 (19)	N/A	26/136 (19)	9/57 (16)	4/23 (17)	7/32 (22)	6/24 (25)
<6 mo	16/136 (12)	N/A	10/136 (7)	4/57 (7)	3/23 (13)	5/32 (16)	4/24 (17)
Previous alkylator treatment, n (%)							
SCT	136 (67)	N/A	136 (73)	57 (81)	23 (53)	32 (80)	24 (73)
Intensive dose	51 (25)	N/A	51 (27)	10 (14)	8 (19)	16 (40)	17 (52)
Triplet-combination	72 (36)	N/A	72 (39)	11 (16)	19 (44)	16 (40)	26 (79)
Quadruplet-combination	16 (8)	N/A	16 (9)	3 (4)	5 (12)	2 (5)	6 (18)
Single-agent alkylator ± steroid therapy	18 (9)	N/A	18 (10)	1 (1)	3 (7)	6 (15)	8 (24)
Melphalan ^f	120 (59)	N/A	120 (65)	51 (73)	13 (30)	33 (82)	23 (70)

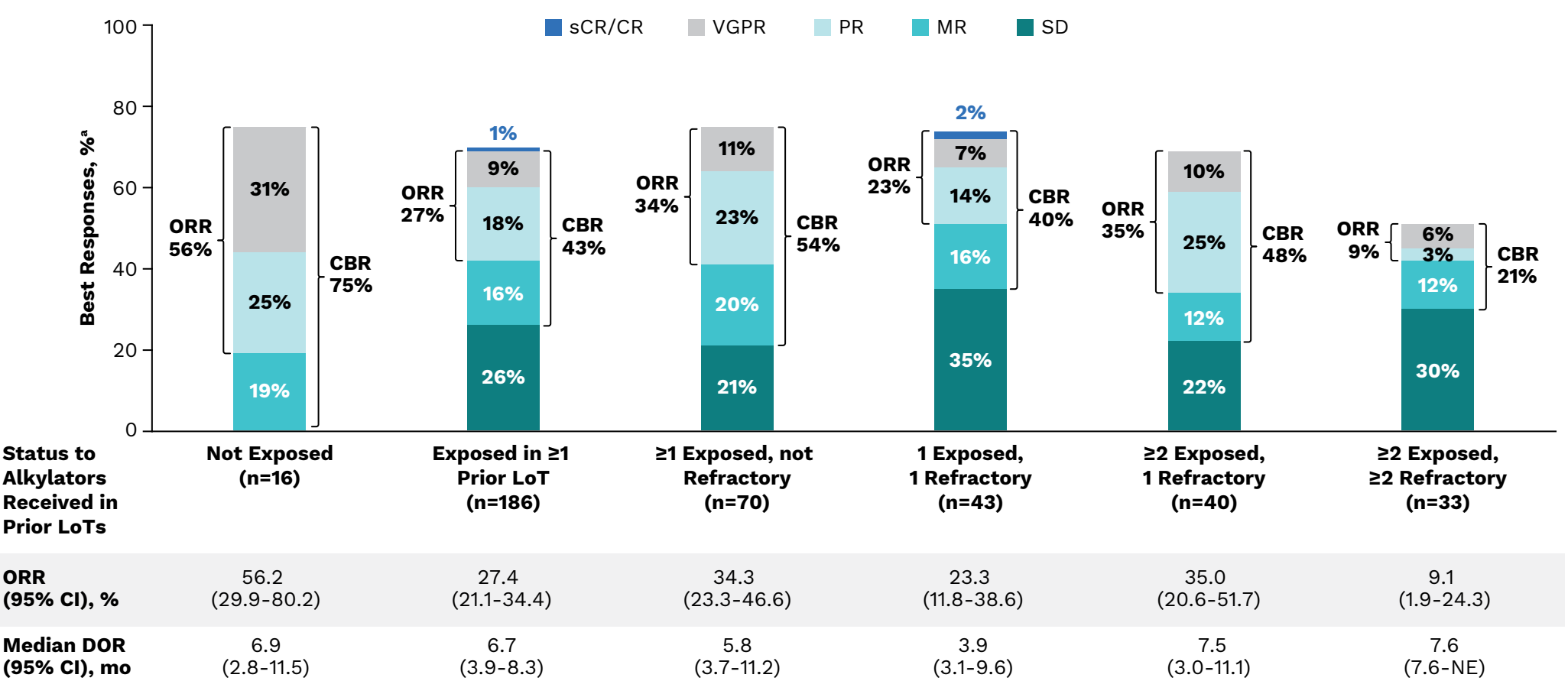
^aISS stage and fluorescence in situ hybridization risk group at study entry were assessed as described.¹⁸ Overall, 9 patients from the total population (N=202) had unknown/missing ISS stage at baseline. ^bTriple-class refractory is defined as refractory to ≥1 proteasome inhibitor, ≥1 immunomodulatory agent, and ≥1 anti-CD38 monoclonal antibody. ^cPenta-refractory is defined as refractory to ≥1 proteasome inhibitors, ≥2 immunomodulatory agents, and ≥1 anti-CD38 monoclonal antibody. ^dResponse was defined as having achieved a stringent complete response, complete response, very good PR, or PR. No response was defined as having achieved a minimal response, stable disease, progressive disease, or having a missing response assessment. ^eRefractory (within 12 months) to alkylator received during line of therapy before entering the melflufen study. ^fUsed as monotherapy or in combination therapy.

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; LoT, line of therapy; PR, partial response; SCT, stem cell transplant.

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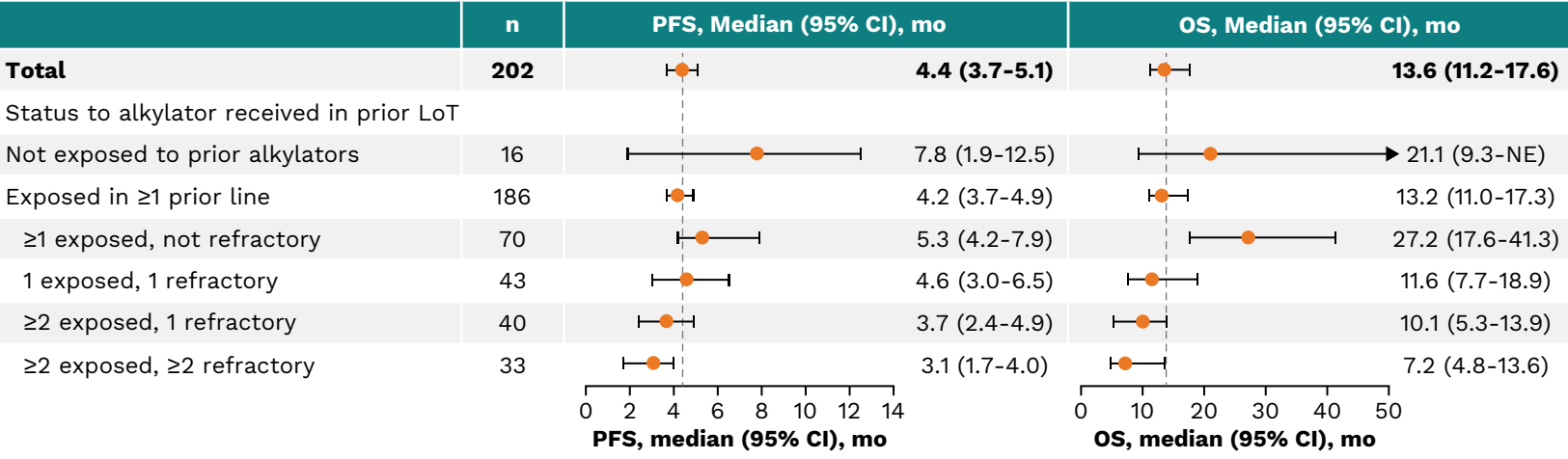
- Meaningful and durable responses were observed in all subgroups analyzed by number of prior LoTs (**Figure 4**)
- Patients with fewer prior LoTs in which they were exposed or exposed and refractory to alkylators, generally had longer progression-free survival (PFS) and overall survival (OS; **Figure 5**)
 - Only those exposed and refractory to alkylators in ≥2 prior LoTs had a reduced overall response rate (ORR) of 91%
 - Results should be interpreted with caution due to limited patient numbers and poorer prognostic features with increasing prior LoTs in which patients were exposed and refractory to alkylators

Figure 4. Best Response by Exposed or Exposed and Refractory Status to Alkylators Received in Prior LoTs



Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 28, 2019. *Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.¹⁸ CBR, clinical benefit rate; CR, complete response; DOR, duration of response; LoT, line of therapy; MR, minor response; NE, not evaluable; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.

Figure 5. PFS and OS by Exposed or Exposed and Refractory Status to Alkylators Received in Prior LoTs



Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 28, 2019. NE, not estimable; OS, overall survival; PFS, progression-free survival.

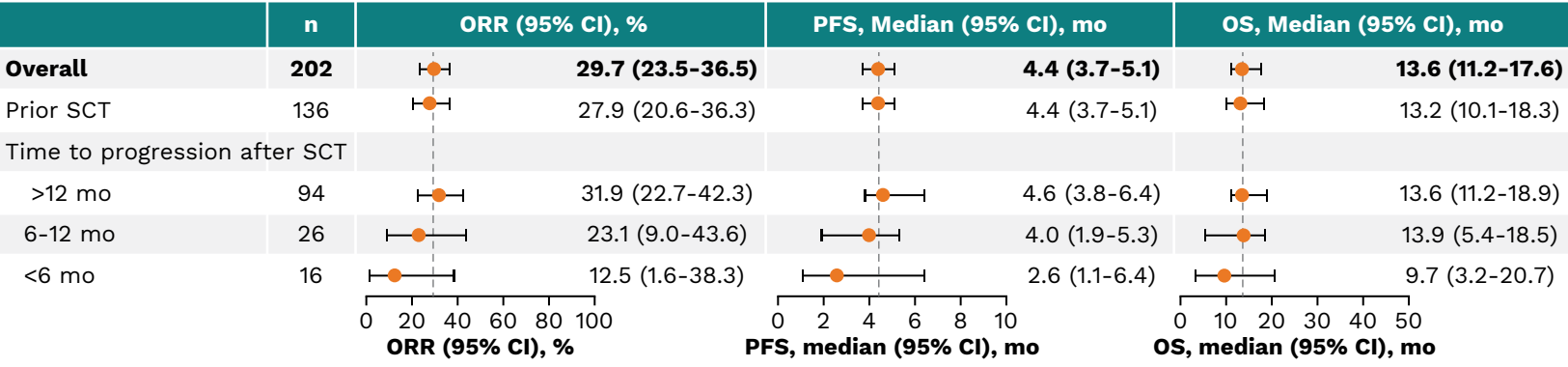
- Meaningful response rates were observed in patients treated with intensive-dose and standard-dose alkylating regimens (not including high-dose alkylator regimens with SCT; **Table 3**)
 - Response rates in patients receiving alkylators as part of a quadruplet regimen were limited
- Outcomes were also assessed by time of progression following high-dose therapy with SCT (**Figure 6**)
 - The effects of melflufen and dexamethasone were of similar magnitude in the overall group compared with patients with prior SCT and patients progressing ≥12 months after SCT
 - Due to small sample size, the results should be interpreted with caution

Table 3. ORR With Melflufen Therapy in Patients Who Received Dose Intensive and Standard Dose Alkylator Therapy in Prior LoTs

Type of Alkylator Received in Prior LoTs Outside of SCT	Exposed to Alkylator, n (%) ^a	ORR (95% CI), % ^a	Refractory to Alkylator, n (%) ^a	ORR (95% CI), % ^a
Intensive-dose alkylator therapy^b	51 (25)	24 (10.7-41.2)	37 (18)	24 (8.2-47.2)
Triple-class–refractory therapy including an alkylator	72 (36)	30 (17.7-45.8)	55 (27)	32 (16.7-51.4)
Quadruplet-combination therapy including an alkylator	16 (8)	40 (12.2-73.8)	11 (5)	17 (0.4-64.1)
Single-agent alkylator ± steroid therapy	18 (9)	40 (12.2-73.8)	13 (6)	29 (3.7-71.0)

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 28, 2019. ^aAll patients who received an alkylator outside of an SCT setting were included in the analysis, but prior lines associated with SCT were excluded from the analysis. ^bPercentage of the total pooled population (N=202). ^cPatients refractory to alkylators in multiple prior lines were excluded from this analysis. ^dIncludes patients who received the following regimens: dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP); VDT-PACE-like regimens (eg, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide); double-alkylator regimens; or intensive-dose alkylator monotherapy outside of SCT.

Figure 6. Outcomes With Melflufen Therapy for Patients Who Underwent SCT (n=136) by Time to Progression Following the SCT



Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 28, 2019. ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant.

SAFETY

- The safety profile of melflufen plus dexamethasone in the O-12-M1 and HORIZON trials was similar between patients exposed or exposed and refractory to prior alkylators and patients with no prior alkylator exposure (**Table 4**)
- Treatment-emergent adverse events (TEAEs) were mostly hematologic, reversible, and clinically manageable (**Figure 7**)
- Nonhematologic TEAEs were infrequent and primarily grade 1/2

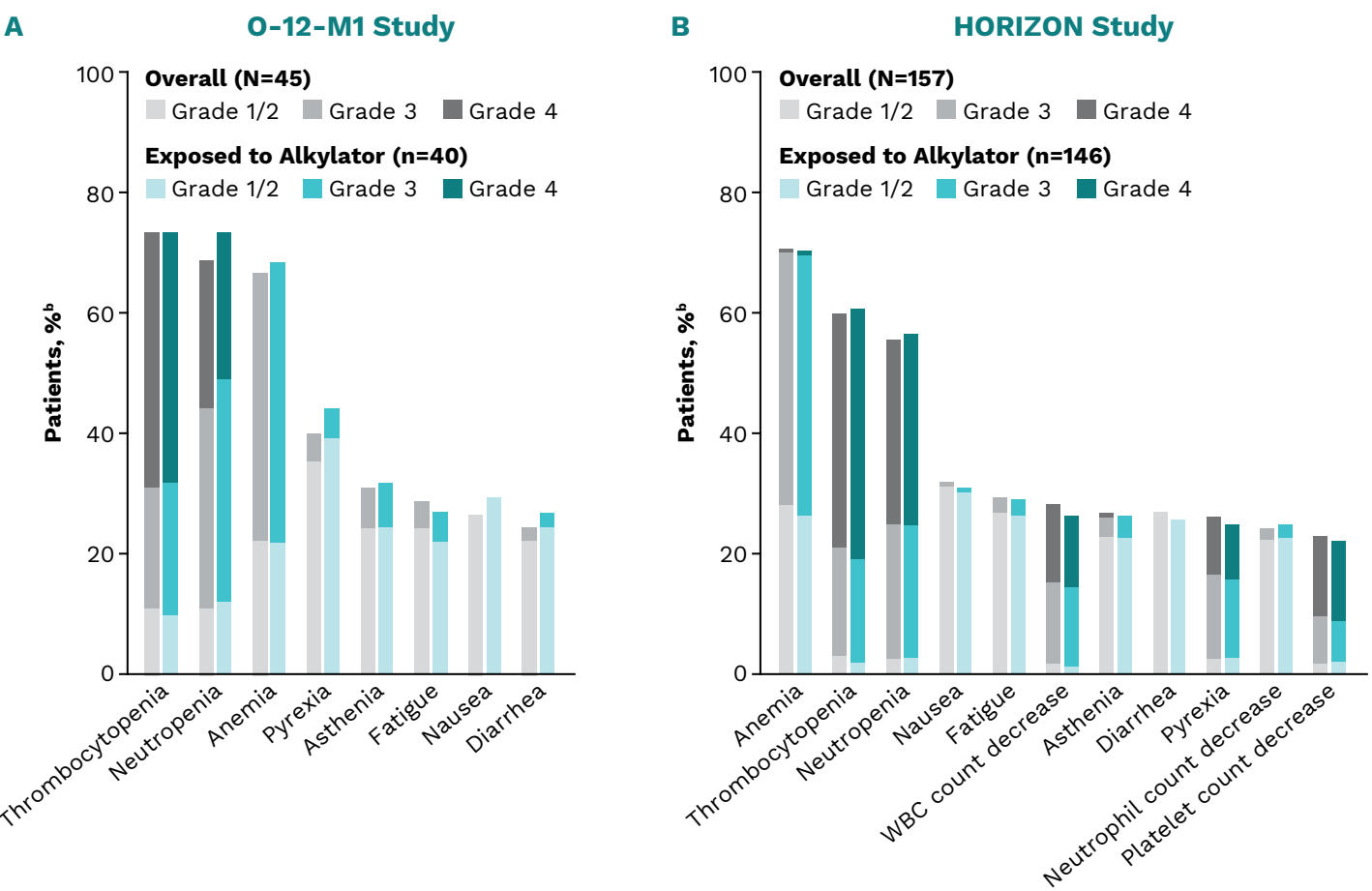
Table 4. Overview of TEAEs With Melflufen Plus Dexamethasone

Patient Subgroup	Grade 3/4 TEAE, n (%) ^a
O-12-M1 (N=45)	
Exposed to prior alkylator (n=41)	38 (84)
Refractory to prior alkylator (n=24)	18 (75)
Not exposed to high-dose alkylator (n=22)	19 (86)
HORIZON (N=157)	
Exposed to prior alkylator (n=145)	140 (89)
Refractory to prior alkylator (n=92)	130 (90)
Not exposed to high-dose alkylator (n=129)	115 (89)

^aAEs are coded to preferred term using Medical Dictionary for Regulatory Activities, version 19.1.

TEAE, treatment-emergent adverse event.

Figure 7. Most Common TEAEs in Patients Exposed to Prior Alkylators and the Overall Population in O-12-M1 (A) and HORIZON (B)^a



^aOccurring in ≥10% of O-12-M1 and ≥20% of HORIZON patients. ^bAEs are coded to preferred term using Medical Dictionary for Regulatory Activities, version 19.1. TEAE, treatment-emergent adverse event; WBC, white blood cell.

CONCLUSIONS

- Patients in this pooled analysis had RRMM that was multirefractory to prior alkylators and with negative prognostic features, including the majority with triple-class–refractory disease and one-third with extramedullary disease at the time of study entry
- In this pooled retrospective analysis, melflufen and dexamethasone demonstrated clinically meaningful efficacy and a manageable safety profile in patients with RRMM, who were previously exposed and refractory to alkylators
- Meaningful and durable responses were observed in patients refractory to prior alkylators, including in patients exposed and refractory to alkylators as standard-dose, intensive-dose, and high-dose therapy with SCT, as well as patients with alkylator exposure in multiple LoTs
- Efficacy results were similar between alkylator-refractory subgroups, including ORR, PFS, and OS, except for a trend toward a lower ORR in patients refractory to alkylators in multiple prior LoTs, which may be attributed to poorer prognostic features and advanced disease in this subgroup at baseline
- Prior alkylator exposure, including being refractory to prior alkylators, did not adversely impact the efficacy and safety of melflufen therapy in RRMM
- Taken together, these results support the activity of melflufen in heavily pretreated patients with RRMM exposed to alkylators in prior LoTs and should be verified in larger cohorts

REFERENCES

- Munoz P, et al. *Blood*. 2019;133:2286-2295.
- Gandhi U, et al. *Leukemia*. 2019;33:2286-2295.
- Ray A, et al. *J Hematol Oncol*. 2019;12:297-309.
- Nguyen H, et al. *Hematol Oncol*. 2019;28:285-294.
- Kumar SK, et al. *Leukemia*. 2017;31:2443-2448.
- Chen C, et al. *Leukemia*. 2019;33:295-303.
- Robak P, et al. *Cancer Treat Rev*. 2016;42:199-208.
- Munoz P, et al. *Blood*. 2019;133:2286-2295.
- Chaudhury D, et al. *Clin Oncol*. 2017;29:3079-3085.
- Alvarado M, et al. *J Clin Oncol*. 2017;35:4645-4655.
- Wickham M, et al. *Biochem Pharmacol*. 2010;79:1281-1290.
- Buller J, et al. *J Drug Target*. 2003;11:393-395.
- Ray A, et al. *J Hematol Oncol*. 2019;12:297-309.
- Nguyen H, et al. *Hematol Oncol*. 2019;28:285-294.
- Kumar SK, et al. *Leukemia*. 2017;31:2443-2448.
- Chen C, et al. *Leukemia*. 2019;33:295-303.
- Robak P, et al. *Cancer Treat Rev*. 2016;42:199-208.
- Munoz P, et al. *Blood*. 2019;133:2286-2295.
- Chaudhury D, et al. *Clin Oncol*. 2017;29:3079-3085.
- Alvarado M, et al. *J Clin Oncol*. 2017;35:4645-4655.
- Wickham M, et al. *Biochem Pharmacol*. 2010;79:1281-1290.

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