HORIZON

HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma Exposed to Prior Alkylator Therapy—Subgroup Analysis

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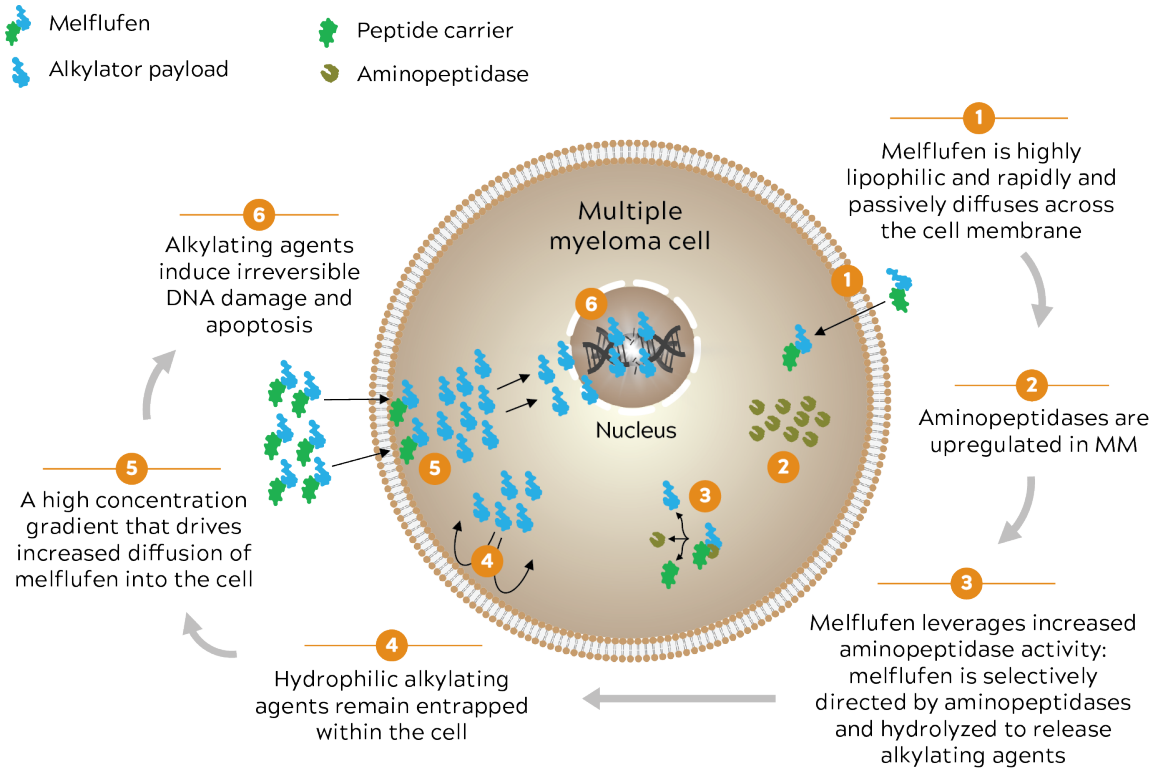
Melflufen: A First-in-Class Peptide Drug Conjugate

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



Melflufen and the MM treatment landscape:

- Despite new combination therapies being used in earlier lines of therapy, outcomes remain poor for patients with RRMM[6-8]
- Melflufen has a mechanism of action distinct from alkylators, including p53-independent cytotoxic activity, and has the potential to provide benefit to patients with RRMM[9,10]

Objective of this subgroup analysis:

To examine the **clinical activity of melflufen in a subset of patients exposed to prior alkylator therapy** in the HORIZON and O-12-M1 studies.

RRMM, relapsed/refractory multiple myeloma.

1. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019-3031. 2. Ray A, et al. *Br J Haematol*. 2016;174:397-409. 3. Wickström M, et al. *Oncotarget*. 2017;8:66641-66655. 4. Wickström M, et al. *Invest New Drugs*. 2008;26:195-204. 5. Strese S, et al. *Biochem Pharmacol*. 2013;86:888-895. 6. Moreau P, et al. *Ann Oncol*. 2017;28(suppl 4):iv52-iv61. 7. Gandhi UW, et al. *Leukemia*. 2019;33:2266-2275. 8. Moreau P, et al. *Blood Cancer J*. 2019;9:386. 9. Slipicevic et al. AACR 2020. Abstract 1843. 10. Mateos MV, et al. *J Clin Med*. 2020;9:3120.

HORIZON and O-12-M1 Study Designs[1,2]

Key Eligibility Criteria

HORIZON – Adult patients with

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

Data cutoff date: January 14, 2020

O-12-M1 – Adult patients with

- RRMM refractory to last line of therapy
- ≥2 Prior lines of therapy including lenalidomide and bortezomib
- ECOG PS ≤2

Data cutoff date: October 29, 2019

Phase 2 (n=157)

Phase 2 (n=45)

Pooled (N=202)

Dosing Schedule

Melflufen 40 mg + dexamethasone 40 mg[a]
(until disease progression or unacceptable toxicity)

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

Follow-Up and Endpoints

EoT → **Follow-up for ≤24 mo**

HORIZON primary endpoints:
- ORR

Key secondary endpoints:
- CBR, PFS, OS, TTP, DOR, safety, TTR, TTP, TTNT, HRQoL

O-12-M1 (phase 2) primary endpoints:
- ORR, CBR

Key secondary endpoints:
- PFS, OS, TTP, DOR, safety

[a]Patients aged ≥75 years received dexamethasone 20 mg.

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; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; 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.

1. Richardson PG, et al. EHA 2020. Poster EP945. 2. Richardson PG, et al, *Lancet Haematol*. 2020;e395-e407.

Melflufen in Relapsed/Refractory Multiple Myeloma

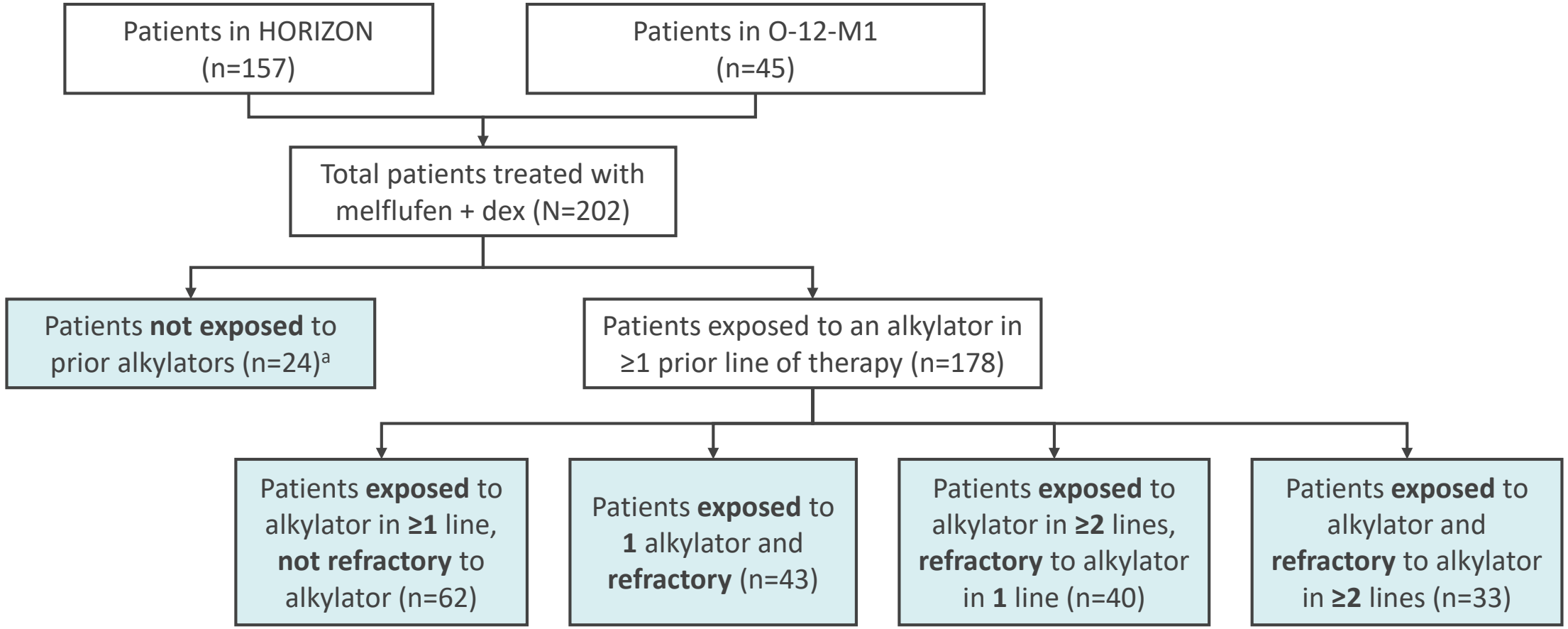
HORIZON

- **Melflufen plus dexamethasone showed meaningful efficacy and a clinically manageable safety profile** in patients with heavily pretreated RRMM as previously reported in the phase 2 portion of the O-12-M1 study and in the phase 2 HORIZON study[1,2]

Outcomes With Melflufen Plus Dexamethasone	HORIZON (N=157)[1]	O-12-M1 (N=45)	Pooled (N=202)
ORR (95% CI), %	29 (22.3-37.1)	31 (18.2-46.6)	30 (23.5-36.5)
Median (95% CI), mo			
PFS	4.2 (3.4-4.9)	5.7 (3.7-9.2)	4.4 (3.7-5.1)
OS	11.6 (9.3-15.4)	20.7 (11.2-33.2)	13.6 (11.2-17.6)

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 29, 2019.
ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.
1. Richardson PG, et al. EHA 2020. Poster EP945. 2. Richardson PG et al, *Lancet Haematol*. 2020;e395-e407.

Summary of Pooled Population by Prior Exposure/Refractoriness to Alkylators



Refractoriness to prior alkylator was defined as disease that failed to achieve an MR or progressed while on primary or salvage therapy containing an alkylator or progressed within 60 days of last therapy containing an alkylator.

[a]Note: 8 of 24 patients classified as 'not exposed to prior alkylators' had undergone an ASCT but information regarding the ablative regimen received (most likely melphalan 200mg/m^2) was not available for these patients.
ASCT, autologous stem cell transplant; dex, dexamethasone; MR, minimal response.

Baseline Patient Characteristics by Prior Alkylator Exposure/Refractoriness

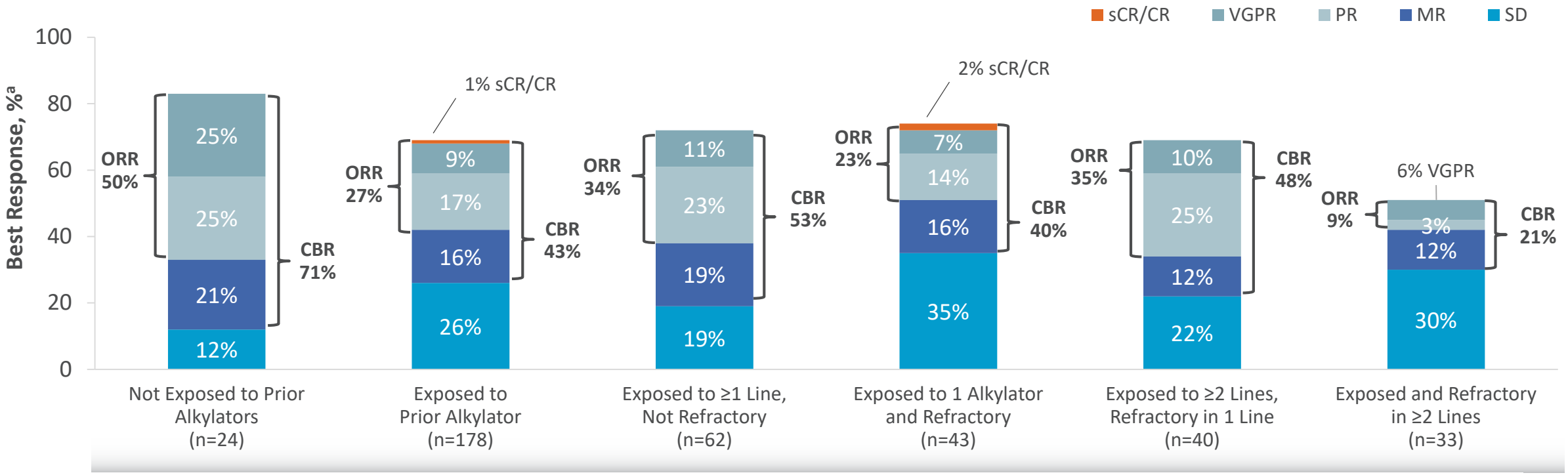
HORIZON

	Total (N=202)	Not Exposed to Prior Alkylators (n=24)	Exposed to ≥1 Line, Not Refractory (n=62)	Exposed to ≥1 Line, Refractory in 1 Line (n=83)	Exposed and Refractory in ≥2 Lines (n=33)
Age, median (range), y	65 (35-86)	69 (42-80)	64 (43-83)	65 (35-86)	66 (49-79)
Male sex, n (%)	119 (59)	16 (67)	34 (55)	46 (55)	23 (70)
High-risk cytogenetics, n (%)	79 (39)	11 (46)	21 (34)	30 (40)	14 (42)
ISS stage at study entry (I / II / III), %[a]	**39 / 33 / 24**	**50 / 33 / 12**	**47 / 42 / 10**	**36 / 25 / 35**	**21 / 36 / 30**
ECOG PS (0 / 1 / 2), %	31 / 57 / 12	29 / 58 / 12	31 / 56 / 13	35 / 58 / 7	21 / 55 / 24
Extramedullary disease, n (%)	**61 (30)**	**8 (33)**	**16 (26)**	**25 (30)**	**12 (36)**
Prior lines of therapy, median (range), n	**5 (2-14)**	**3 (2-7)**	**4 (2-10)**	**5 (2-9)**	**7 (4-14)**
Triple-class refractory, n (%)[b]	**122 (60)**	**14 (58)**	**29 (47)**	**54 (65)**	**25 (76)**
Penta refractory, n (%)	68 (34)	8 (33)	15 (24)	28 (34)	17 (52)
Prior SCT, n (%)	136 (67)	8 (33)[c]	49 (79)	55 (66)	24 (73)
Progression after SCT, n/N (%)					
>12 mo	94/136 (69)	6/8 (75)	38/49 (78)	36/55 (65)	14/24 (58)
≤12 mo	42/136 (31)	2/8 (25)	11/49 (22)	19/55 (35)	10/24 (42)

- **Patients exposed or refractory to prior alkylators generally had poorer prognostic features at baseline than patients who had not been exposed to prior alkylators, including higher ISS stage and number of prior therapies**
- **Patients exposed and refractory to alkylators in ≥2 prior lines of therapy had particularly poor prognostic features**

[a]ISS stage and fluorescence in situ hybridization risk group at study entry were assessed as described (Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2969). Overall, 9 patients from the total population (N=202) had unknown/missing ISS stage at baseline. [b]Triple-class refractory is defined as refractory to or intolerant of ≥1 proteasome inhibitor, ≥1 immunomodulatory agent, and ≥1 anti-CD38 monoclonal antibody. [c]Note: 8 of 24 patients classified as 'not exposed to prior alkylators' had undergone an autologous SCT but information regarding the ablative regimen received (most likely melphalan 200mg/m2) was not available for these patients.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; SCT, stem cell transplant.

Best Response to Melflufen Plus Dexamethasone in Pooled Population by Prior Alkylator Exposure/Refractoriness Status



ORR (95% CI), %	50 (29.1-70.9)	27 (20.6-34.1)	34 (22.3-47.0)	23 (11.8-38.6)	35 (20.6-51.7)	9 (1.9-24.3)
Median DOR (95%CI), mo	6.9 (2.8-11.5)	6.7 (3.9-8.3)	5.1 (3.7-14.0)	3.9 (3.1-9.6)	7.5 (3.0-11.1)	7.6 (7.6-NE)

- **Meaningful response rates were seen in all subgroups analyzed, except for patients who were exposed and refractory to alkylators in ≥2 prior lines**
- **Durable responses were observed in all subgroups analyzed**

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 29, 2019.

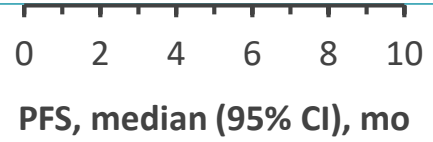
[a]Investigator-assessed best overall response per International Myeloma Working Group uniform criteria (Rajkumar SV, et al. *Blood*. 2011;117:4691-4695).

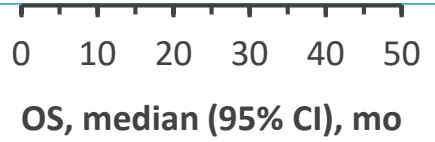
CBR, clinical benefit rate; CR, complete response; DOR, duration of response; MR, minor response; NE, not evaluable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

PFS and OS With Melflufen Plus Dexamethasone in Pooled Population by Prior Alkylator Exposure/Refractoriness Status

HORIZON

	n	PFS, Median (95%CI), mo	OS, Median (95%CI), mo
Total	202	4.4 (3.7-5.1)	13.6 (11.2-17.6)
Prior alkylator exposure/refractoriness			
Not exposed to prior alkylators	24	7.1 (3.7-9.0)	22.4 (9.6-NE)
Exposed to prior alkylator	178	4.2 (3.7-4.9)	11.8 (10.0-16.5)
Exposed to ≥1 line, not refractory	62	5.3 (4.2-7.9)	21.1 (17.2-33.2)
Exposed to 1 alkylator and refractory	43	4.6 (3.0-6.5)	11.6 (7.7-18.9)
Exposed to ≥2 lines, refractory in 1 line	40	3.7 (2.4-4.9)	10.1 (5.3-13.9)
Exposed and refractory in ≥2 lines	33	3.1 (1.7-4.0)	7.2 (4.8-13.6)





- **There was a trend towards PFS and OS being shorter with higher exposure and refractoriness to prior alkylators**
- **Results should be interpreted with caution due to limited patient numbers and poorer prognostic features with increasing exposure/refractoriness to prior alkylators**

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 29, 2019.
NE, not estimable; OS, overall survival; PFS, progression-free survival.

ORR With Melflufen Plus Dexamethasone in Pooled Population by Prior Alkylator Treatment to Which Patients Were Exposed/Refractory

HORIZON

Type of Alkylator Received in Prior Lines of Therapy Outside of SCT[a]	Exposed to Alkylator, n(%)	ORR (95% CI), %[b]	Refractory to Alkylator, n(%)	ORR (95% CI), %[b]
High-dose alkylator therapy outside of SCT[c]	51 (25)	24 (10.7-41.2)	37 (18)	24 (8.2-47.2)
Triplet-combination 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)

- **Meaningful response rates were seen in all subgroups analyzed, except for patients who were refractory to an alkylator received as part of a quadruplet-combination regimen**

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 29, 2019.

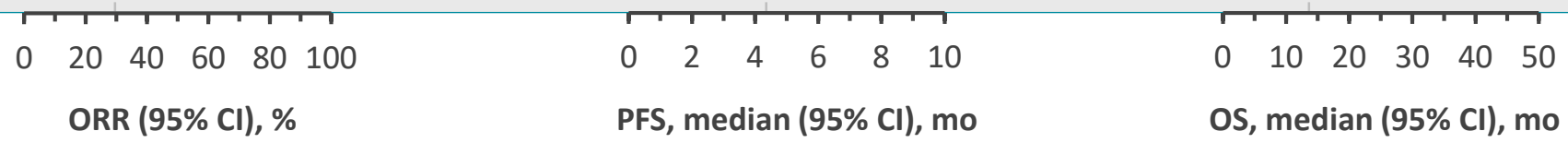
[a]Prior lines including SCT were excluded from the analysis. [b]Patients refractory to alkylators in multiple prior lines were excluded from this analysis. [c]Includes patients who received the following regimens: dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP); VDT-PACE-like regimens (eg, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide); double-alkylator regimens; or high-dose alkylator monotherapy outside of SCT.

ORR, overall response rate; SCT, stem cell transplant.

ORR, PFS, and OS With Melflufen Plus Dexamethasone in Pooled Population by Progression After SCT

HORIZON

	n	ORR (95% CI), %	PFS, median (95%CI), mo	OS, median (95%CI), mo
Overall	**202**	**30 (23.5-36.5)**	**4.4 (3.7-5.1)**	**13.6 (11.2-17.6)**
Progression after SCT				
>12 mo	94	32 (22.7-42.3)	4.6 (3.8-6.4)	13.6 (11.2-18.9)
<12 mo	42	19 (8.6-34.1)	3.4 (2.1-4.9)	11.2 (5.4-18.3)
6-12 mo	26	23 (9.0-43.6)	4.0 (1.9-5.3)	13.9 (5.4-18.5)
2-6 mo	10	0 (0.0-30.8)	2.2 (0.7-2.9)	4.9 (1.5-11.2)
<2 mo	6	33 (4.3-77.7)	6.4 (1.0-NE)	19.0 (9.7-NE)



- **The effects of melflufen and dexamethasone were of similar magnitude in patients progressing after SCT**
- **Due to small sample size, results should be interpreted with caution**

Data cutoff dates: HORIZON - January 14, 2020; O-12-M1 - October 29, 2019.
NE, not estimable; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant.

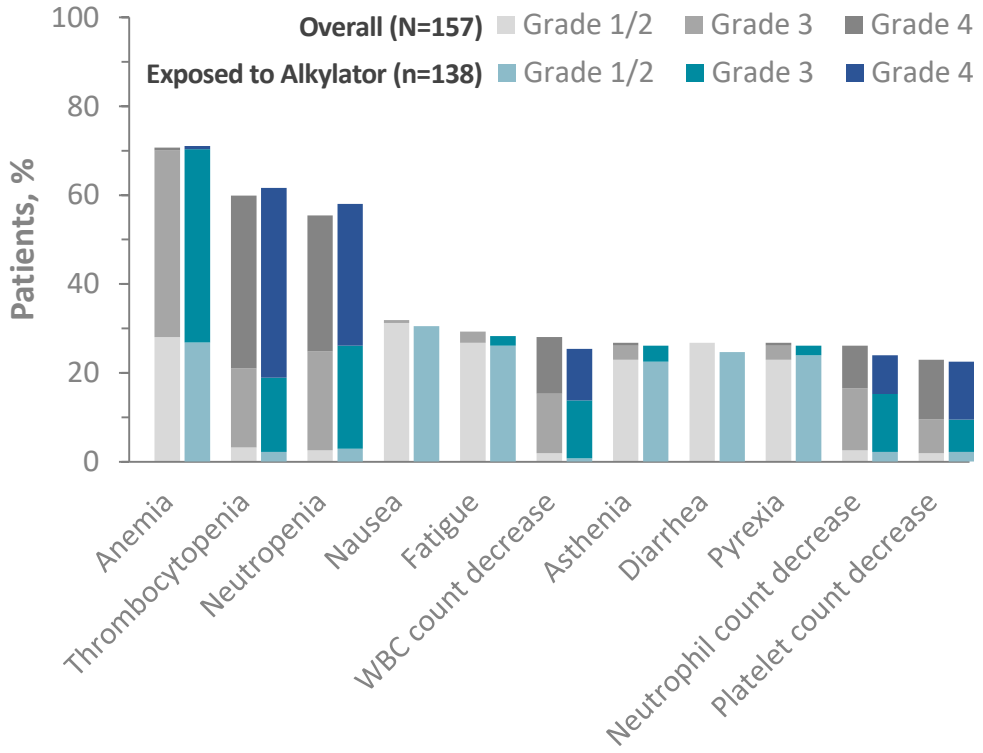
Overview of TEAEs With Melflufen Plus Dexamethasone

Patient Subgroup	Grade 3/4 TEAE, n (%)[a]
HORIZON (N=157)	140 (89)
Exposed to prior alkylator (n=138)	123 (89)
Refractory to prior alkylator (n=92)	80 (87)
Not exposed to high-dose alkylator (n=129)	115 (89)
O-12-M1 (N=45)	38 (84)
Exposed to prior alkylator (n=40)	34 (85)
Refractory to prior alkylator (n=24)	18 (75)
Not exposed to high-dose alkylator (n=22)	19 (86)

The safety profile of melflufen plus dexamethasone in HORIZON and O-12-M1 was similar in patients exposed and/or refractory to prior alkylators and those not exposed to an alkylator

- Hematologic TEAEs were the most common toxicity but were mostly reversible and clinically manageable
- Nonhematologic TEAEs were infrequent and primarily grade 1/2

Most Common TEAEs (Occurring in ≥20% of Patients) in Patient Exposed to Prior Alkylator (n=138) and the Overall Population (N=157) in HORIZON



[a]AEs are coded to preferred term using Medical Dictionary for Regulatory Activities, version 19.1.
TEAE, treatment-emergent adverse event; WBC, white blood cell.

Conclusions

- In this pooled retrospective analysis, melflufen plus dexamethasone demonstrated clinically meaningful efficacy and a manageable safety profile in patients previously exposed and refractory to alkylators and with advanced RRMM
- Most patients had RRMM that was at least triple-class–refractory, and 30% had extramedullary disease at relapse
- Durable responses were observed in all patients refractory to alkylators including patients refractory to alkylators in multiple lines of prior therapy and patients refractory to high-dose alkylator regimens (eg, DCEP and VDT-PACE)
- There was no clinically relevant difference in the ORR between the alkylator-refractory subgroups studied, except for a trend towards lower ORR in patients with RRMM refractory to alkylators in multiple prior lines of therapy; this subgroup had poorer prognostic factors and more advanced disease, which may have affected their chance to respond to therapy
- Taken together, these results are intriguing, support the activity of melflufen in heavily pretreated patients with RRMM exposed to prior alkylators, and should be verified in larger cohorts

DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplant; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide.

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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, 2564, 3214, 3237, 3477 (posters)

Baseline Patient Characteristics by Prior Alkylator Exposure/Refractoriness

HORIZON

	Total (N=202)	Not Exposed to Prior Alkylators (n=24)	Exposed to ≥1 Prior Alkylator (n=178)	Exposed to ≥1 Line, Not Refractory (n=62)	Exposed to 1 Alkylator and Refractory (n=43)	Exposed to ≥2 Lines, Refractory in 1 Line (n=40)	Exposed and Refractory in ≥2 Lines (n=33)
Age, median (range), y	65 (35-86)	69 (42-80)	64 (35-86)	64 (43-83)	68 (55-86)	62 (35-84)	66 (49-79)
Male sex, n (%)	119 (59)	16 (67)	103 (58)	34 (55)	26 (60)	20 (50)	23 (70)
High-risk cytogenetics, n (%)	**79 (39)**	**11 (46)**	**68 (38)**	**21 (34)**	**22 (51)**	**11 (28)**	**14 (42)**
ISS stage at study entry (I / II / III), %[a]	**39 / 33 / 24**	**50 / 33 / 12**	**37 / 33 / 25**	**47 / 42 / 10**	**42 / 23 / 30**	**30 / 28 / 40**	**21 / 36 / 30**
ECOG PS (0 / 1 / 2), %	31 / 57 / 12	29 / 58 / 12	31 / 57 / 12	31 / 56 / 13	35 / 60 / 5	35 / 55 / 10	21 / 55 / 24
Extramedullary disease, n (%)	**61 (30)**	**8 (33)**	**53 (30)**	**16 (26)**	**15 (35)**	**10 (25)**	**12 (36)**
Median prior lines of therapy (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)**	**14 (58)**	**108 (61)**	**29 (47)**	**30 (70)**	**24 (60)**	**25 (76)**
Penta refractory, n (%)	68 (34)	8 (33)	60 (34)	15 (24)	15 (35)	13 (32)	17 (52)
Response to prior alkylator therapy, n (%)							
No response	71 (35)	—	47 (26)	10 (16)	27 (63)	4 (10)	6 (18)
Response	131 (65)	—	131 (74)	52 (84)	16 (37)	36 (90)	27 (82)
Refractory ≤12 mo of study start	71 (35)	—	71 (40)	0 (0)	18 (42)	26 (65)	27 (82)
Refractory to alkylator in last line	46 (23)	—	46 (26)	0 (0)	11 (26)	15 (38)	20 (61)
Prior allogeneic/autologous SCT, n (%)	136 (67)	8 (33)	128 (72)	49 (79)	23 (53)	32 (80)	24 (73)
Progression after SCT, n/N (%)							
>12 mo	94/136 (69)	6/8 (75)	88/128 (69)	38/49 (78)	16/23 (70)	20/32 (62)	14/24 (58)
6-12 mo	26/136 (19)	2/8 (25)	24/128 (19)	7/49 (14)	4/23 (17)	7/32 (22)	6/24 (25)
2-6 mo	10/136 (7)	0 (0)	10/128 (8)	3 /49 (6)	2/23(9)	2/32 (6)	3/24 (12)
<2 mo	6/136 (4)	0 (0)	6/128 (5)	1/49 (2)	1/23 (4)	3/32 (9)	1/24 (4)

- **Patients exposed or refractory to prior alkylators generally had poorer prognostic features at baseline than patients who had not been exposed to prior alkylators, including higher ISS stage and number of prior therapies; patients exposed and refractory to alkylators in ≥2 prior lines of therapy had particularly poor prognostic features**

[a]ISS stage and fluorescence in situ hybridization risk group at study entry were assessed as described (Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2969). Overall, 9 patients from the total population (N=202) had unknown/missing ISS stage at baseline. [b]Triple-class refractory is defined as refractory to or intolerant of ≥1 proteasome inhibitor, ≥1 immunomodulatory agent, and ≥ anti-CD38 monoclonal antibody.

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; SCT, stem cell transplant.