

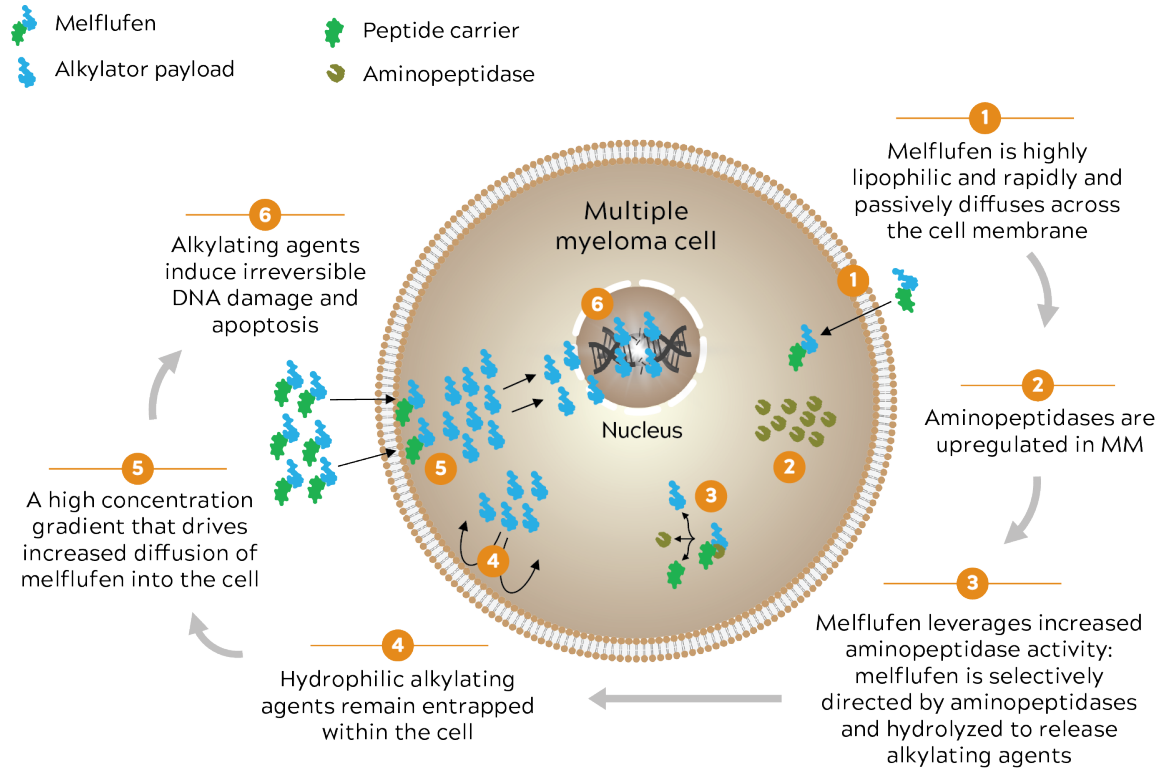
HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma—Age Subgroup Analysis of Elderly Patients

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Melflufen in Relapsed/Refractory Multiple Myeloma

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



In the pivotal, phase 2, HORIZON study, **melflufen plus dexamethasone showed clinically meaningful efficacy and a safety profile** characterized primarily by clinically manageable hematologic AEs in patients with heavily pretreated and poor-risk RRMM.⁶

Outcome⁶

Overall Population (N=157)

ORR (95% CI), %	29 (22-37)
Median OS (95% CI), mo	11.6 (9.3-15.4)
Median PFS (95% CI), mo	4.2 (3.4-4.9)
Median DOR (≥PR), (95% CI), mo	5.5 (3.9-7.6)

Patients with MM are living longer, but with the burden of symptoms and complications of prior lines of therapy and a more advanced disease.^{7,8} Older patients with RRMM are a particularly difficult-to-treat population. These patients often have comorbidities, reduced fitness levels, and are receiving concomitant medications.⁹

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

1. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019-31. 2. Ray A, et al. *Br J Haematol*. 2016;174:397-409. 3. Wickström M, et al. *Oncotarget*. 2017;8:66641-55. 4. Wickström M, et al. *Invest New Drugs*. 2008;26:195-204. 5. Strese S, et al. *Biochem Pharmacol*. 2013;86:888-95. 6. Richardson PG, et al. EHA 2020. Poster EP945. 7. Vogl DT, et al. *Leuk Lymphoma*. 2018;59:398. 8. Kumar SK, et al. *Leukemia*. 2017;31:2443. 9. Larocca A, et al. *Leukemia*. 2018;32:1697.

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

Key Eligibility Criteria:

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

(N=157)

Data cutoff date: January 14, 2020

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

PFS and OS follow-up for ≤ 24 mo

Primary endpoint

- ORR

Secondary endpoints

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

Objective of this subgroup analysis

- To evaluate the efficacy and safety of melflufen plus dexamethasone in the subset of patients with RRMM aged ≥ 75 years who were treated in the HORIZON study

^aPatients aged ≥ 75 years received dexamethasone 20 mg.

CBR, clinical benefit rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; 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; PS, performance status; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTP, time to progression; TTR, time to response.

Baseline Characteristics in Patients Aged ≥ 75 Years

	Patients Aged ≥ 75 Years (n=25)	Overall Population (N=157)
Age, median (range), y	77 (75-86)	65 (35-86)
Male sex, n (%)	13 (52)	89 (57)
ISS stage (I / II / III / unknown or missing), %	44 / 24 / 32 / 0	40 / 31 / 25 / 4
ECOG PS, n (%)		
0	5 (20)	39 (25)
1	17 (68)	93 (59)
2	3 (12)	25 (16)
No. prior lines of therapy, median (range)	5 (2-8)	5 (2-12)
Triple-class–refractory, n (%) ^a	19 (76)	119 (76)
Penta-refractory, n (%) ^b	10 (40)	59 (38)
Refractory to prior alkylator therapy, n (%)	16 (64)	92 (59)
Cytogenetic risk group, n (%)		
High risk	10 (40)	59 (38)
Standard risk	11 (44)	67 (43)
Unknown	4 (16)	31 (20)

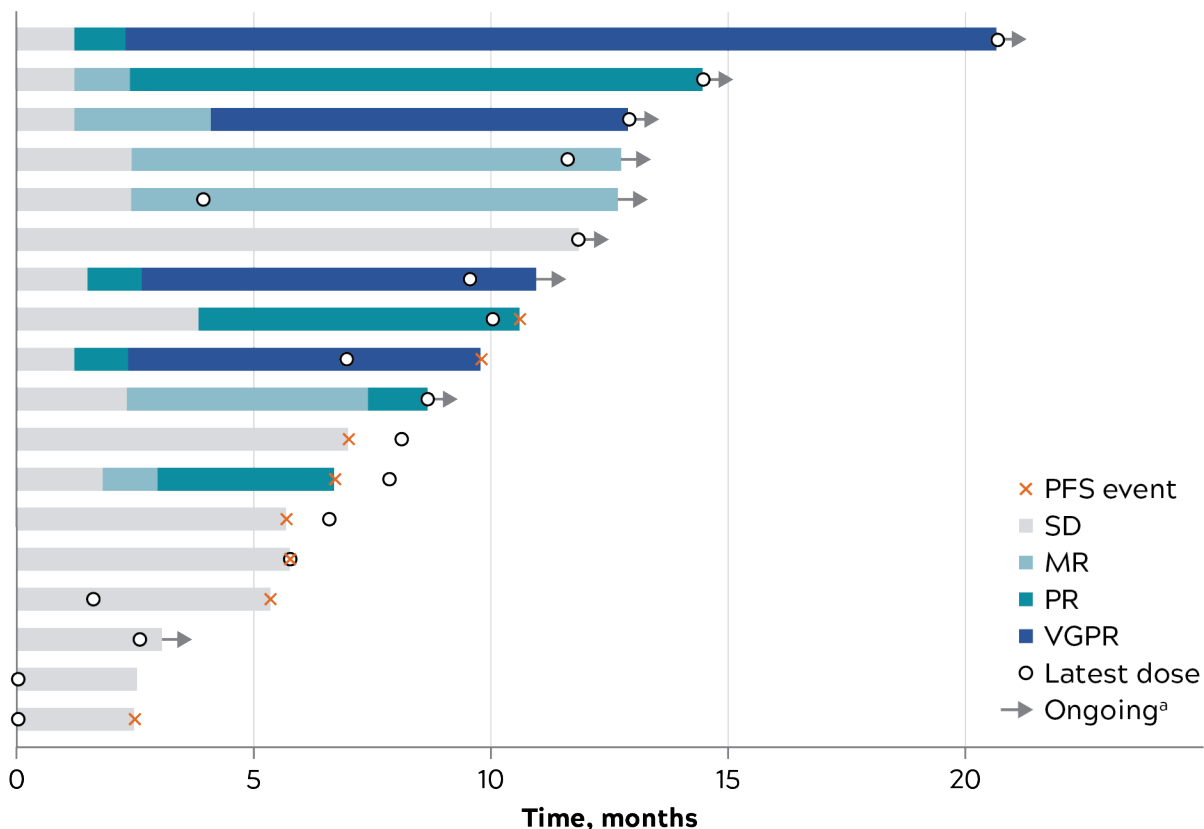
- Baseline characteristics for patients aged ≥ 75 years were generally consistent with those of the overall population

^aRefractory or intolerant to ≥ 1 IMiD + ≥ 1 PI + ≥ 1 anti-CD38 mAb. ^bRefractory to 2 IMiD + 2 PI + 1 anti-CD38 mAb.

ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; PS, performance status.

Response in Patients Aged ≥75 Years Who Achieved ≥SD

Swim-Lane Plot for Patients Aged ≥75 Years Who Achieved ≥SD (n=18)



Best Overall Responses in Patients Aged ≥75 Years and the Overall Population

	Aged ≥75 Years (n=25)	Overall Population (N=157)
ORR, n (%) [95% CI]		
By investigator assessment	8 (32) [14.9-53.5]	46 (29) [22.3-37.1]
By IRC	8 (32) [14.9-53.5]	47 (30) [22.9-37.8]
CBR, (%) [95% CI]		
By investigator assessment	10 (40) [21.1-61.3]	71 (45) [37.3-53.4]
By IRC	10 (40) [21.1-61.3]	69 (44) [36.0-52.1]

- In patients ≥75 years old the median DOR was not reached (95% CI, 3.0-NE) and the median treatment duration was 5.5 months (range, 1-18)
- In the overall population, the median DOR was 5.5 months (95% CI, 3.9-7.6) and the median treatment duration was 3.8 months (range, 1-23)

Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.¹

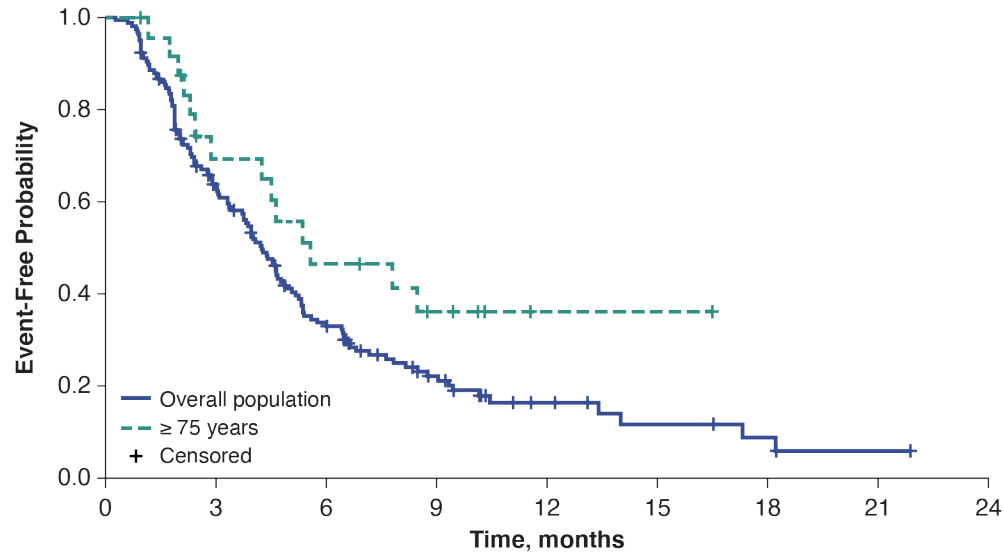
^aPatient remains on study (receiving therapy or in the end of treatment follow-up period) and has not yet experienced a progression-free survival event.

CBR, clinical benefit rate; DOR, duration of response; IRC, Independent Review Committee; MR, minimal response; NE, not estimable; 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 Aged ≥75 Years

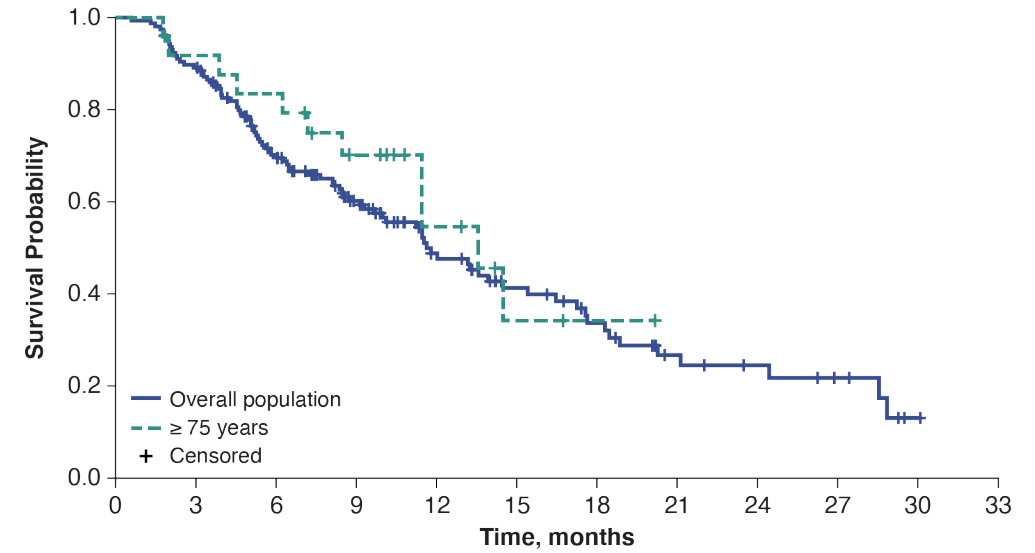
PFS in Patients Aged ≥75 Years and the Overall Population



No. at risk (no. censored)		0	3	6	9	12	15	18	21	24
Overall population	157	91	46	22	9	5	3	1	0	0
≥75 years	25	15	10	6	1	1	0	0	0	0

	Events, n/N	Median PFS (95% CI), mo
Patients Aged ≥75 Years	14/25	5.6 (2.9-NE)
Overall Population	121/157	4.2 (3.4-4.9)

OS in Patients Aged ≥75 Years and the Overall Population



No. at risk (no. censored)		0	3	6	9	12	15	18	21	24	27	30	33
Overall population	157	139	100	69	42	29	21	12	9	6	1	0	0
≥75 years	25	22	20	14	7	3	2	0	0	0	0	0	0

	Events, n/N	Median OS (95% CI), mo
Patients Aged ≥75 Years	11/25	13.6 (8.5-NE)
Overall Population	88/157	11.6 (9.3-15.4)

- PFS and OS in patients aged ≥75 years were consistent with that in the overall population

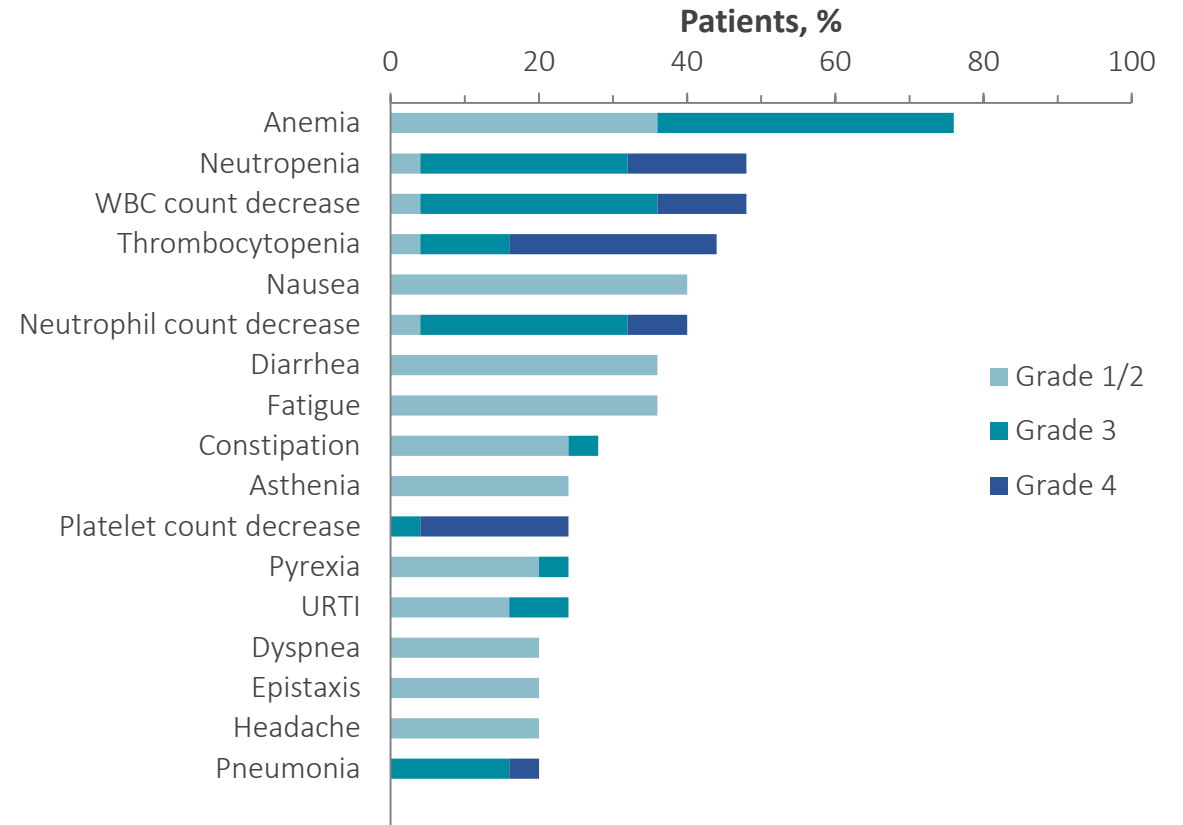
NE, not estimable; OS, overall survival; PFS, progression-free survival.

Summary of TEAEs

Patients With TEAE, n (%) ^a	Patients Aged ≥75 Years (n=25)	Overall Population (N=157)
Worst grade 3/4 TEAEs	24 (96)	140 (89)
TEAEs leading to melflufen discontinuation	6 (24)	34 (22)
Thrombocytopenia	2 (8)	16 (10)
Pneumonia	2 (8)	3 (2)
Bone pain	1 (4)	2 (1)
Febrile neutropenia	1 (4)	2 (1)
Neutropenia	1 (4)	5 (3)
Platelet count decrease	1 (4)	1 (1)
Any SAE	10 (40)	77 (49)
Fatal TEAEs	0	10 (6)

- No new safety signals were identified in older patients

Most Common AEs (Occurring in ≥20% of Patients) in Patients Aged ≥75 Years



^aAdverse events are coded to preferred term using MedDRA, version 19.1.

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

- Patients aged ≥ 75 years with heavily pretreated RRMM who received melflufen, once monthly infusion, plus weekly dexamethasone in HORIZON demonstrated clinically meaningful efficacy and a manageable safety profile
 - Durable responses were observed among older patients and were consistent with those in the overall population treated in HORIZON¹
- The safety profile of melflufen plus dexamethasone in patients aged ≥ 75 years was consistent with that of previous reports^{1,2}
- The most common AEs were hematologic AEs that were clinically manageable with supportive care and dose modifications
 - Nonhematologic AEs were primarily grade 1/2
- Further study is warranted to confirm these data suggesting that melflufen may be an efficacious, convenient, and tolerable therapy for older patients (aged ≥ 75 years) with advanced RRMM who have limited treatment options

AE, adverse event; RRMM, relapsed/refractory multiple myeloma.

1. Richardson PG, et al. EHA 2020. Poster EP945. 2. 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: [2321](#), [2564](#), [3214](#), [3237](#), [3477](#) (posters)

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