

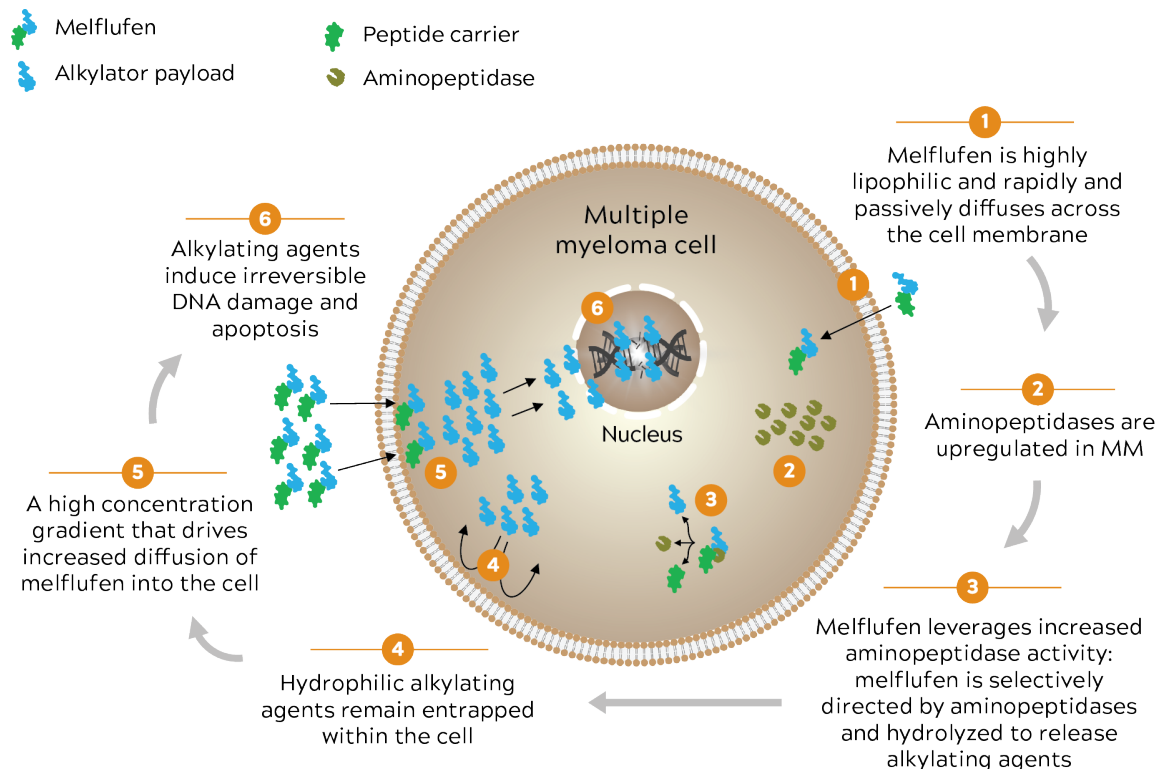
# HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma With High-Risk Cytogenetics—Subgroup Analysis

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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.**<sup>1-5</sup>



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.<sup>6</sup>

Outcome <sup>6</sup>	Overall Population (N=157)
ORR (95% CI), %	29 (22.3-37.1)
OS, median (95% CI), mo	11.6 (9.3-15.4)
PFS, median (95% CI), mo	4.2 (3.4-4.9)
DOR (≥PR), median (95% CI), mo	5.5 (3.9-7.6)

In patients with RRMM, 29%-59% have high-risk (HR) cytogenetic abnormalities that are associated with poor treatment outcomes.<sup>7,8</sup>

**Objective of this subgroup analysis:** To evaluate the cytogenetic profile in and compare the efficacy between patients with or without HR cytogenetic abnormalities in the HORIZON study.

AE, adverse event; DOR, duration of response; MM, multiple myeloma; 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. Kumar SK, et al. *Leukemia*. 2017;31:2443. 8. Gandhi UH, et al. *Leukemia*. 2019;33:2266.

**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).<sup>1</sup>**

## 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

## Screening for and Establishing HR Cytogenetic Abnormalities

- At screening, cytogenetics were evaluated using plasma cells from bone marrow aspirate by interphase fluorescence *in situ* hybridization and by conventional karyotyping performed at study centers
- HR cytogenetic abnormalities were classified by the presence of t(4;14), t(14;16), t(14;20), del(17/17p), or gain(1q)<sup>2</sup>

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

CBR, clinical benefit rate; del, deletion; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EoT, end of treatment; HR, high risk; 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.

1. Richardson PG, et al. EHA 2020. Poster EP945. 2. Sonneveld P, et al. *Blood*. 2016;127:2955.

# Baseline Characteristics by HR Cytogenetic Group

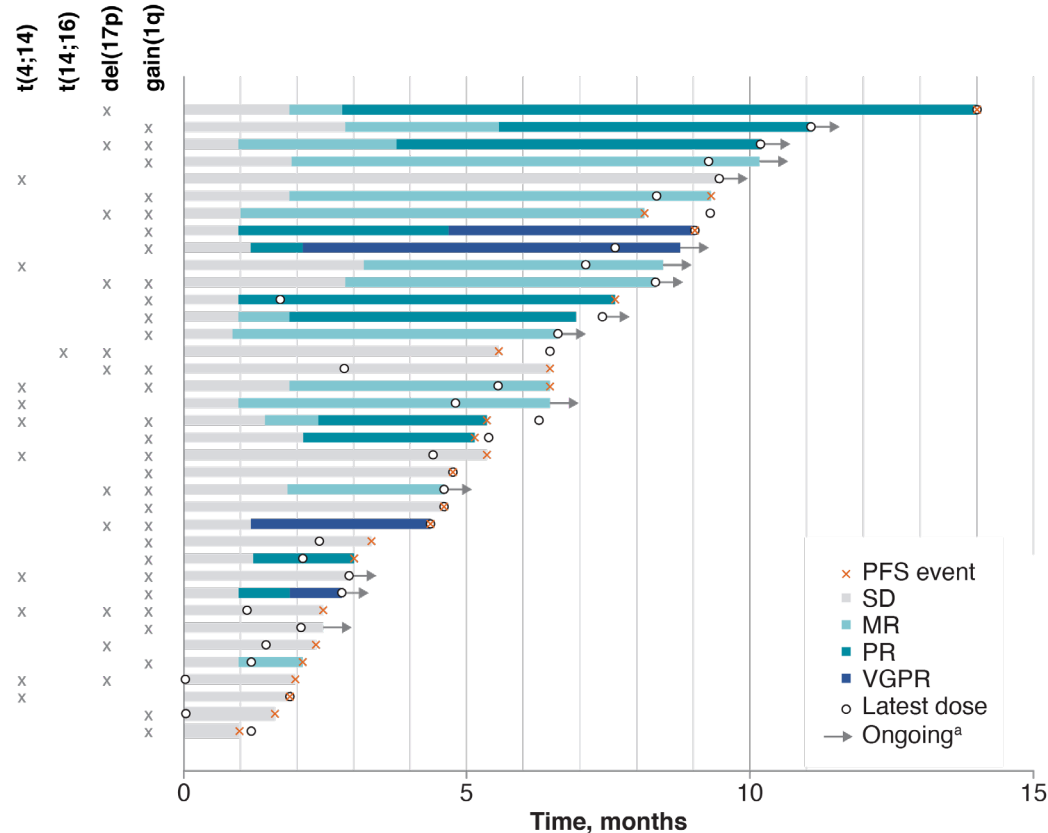
	HR Cytogenetics (n=59)	Non-HR/Unknown Cytogenetics <sup>a</sup> (n=98)
Age, median (range), y	65 (41-86)	64 (35-84)
Male sex, n (%)	35 (59)	54 (55)
ISS stage I / II / III, % <sup>b</sup>	32 / 39 / 25	45 / 27 / 24
ECOG PS 0 / 1 / 2, %	19 / 59 / 22	29 / 59 / 12
No. prior lines of therapy, median (range)	5 (2-12)	5 (2-10)
Triple-class refractory, n (%) <sup>c</sup>	41 (69)	78 (80)
Refractory to prior alkylator, n (%)	37 (63)	55 (56)
Cytogenetic abnormality, n (%)		
Gain(1q)	41 (69)	0
Del(17p)	18 (31)	0
t(4;14)	18 (31)	0
t(14;16)	4 (7)	0
t(14;20)	0	0
No. of cytogenetic abnormalities 0 / 1 / 2 / 3 / 4, %	0 / 69 / 25 / 3 / 2	100 / 0 / 0 / 0 / 0

- Although baseline characteristics were generally similar between patients with and without HR cytogenetics, fewer patients with HR cytogenetics had triple-class–refractory MM (69%) than those without HR cytogenetics (80%)

<sup>a</sup>Includes patients with standard-risk cytogenetics (n=67) and patients with missing/unknown cytogenetic status (n=31). <sup>b</sup>At baseline, 2 patients (3%) in the HR cytogenetics group and 4 patients (4%) in the non-HR cytogenetics group had missing/unknown ISS stage. <sup>c</sup>Triple-class refractory is defined as refractory to or intolerant of ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 monoclonal antibody. del, deletion; ECOG, Eastern Cooperative Oncology Group; HR, high risk; ISS, International Staging System; MM, multiple myeloma; PS, performance status.

# Response by HR Cytogenetic Group

## Swim-Lane Plot for Patients in the HR Cytogenetics Group Who Achieved $\geq$ SD



- In patients with HR cytogenetics (n=59), ORR was 20% (95% CI, 11.0-32.8), CBR was 37% (95% CI, 25.0-50.9), and median DOR was 6.7 months (95% CI, 3.0-NE)
  - Responses deepened with longer treatment duration; in some patients, response was extended beyond the last dose of melflufen
- In patients with non-HR/unknown cytogenetics (n=98), ORR was 35% (95% CI, 25.4-45.0), CBR was 50% (95% CI, 39.7-60.3), and the median DOR was 5.1 months (95% CI, 3.9-7.5)

Median number of cycles of therapy initiated was 3 (1-15) in the HR cytogenetics group and 4 (1-17) in the non-HR/unknown cytogenetics 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; del, deletion; DOR, duration of response; HR, high risk; 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;117:4691-5.

# Response by Type and Number of HR Cytogenetic Features



	HR Feature <sup>a</sup>			Number of HR Features	
	Del(17p)	t(4;14)	Gain(1q)	1	≥2
n	18	18	41	41	18
ORR, n (%) [95% CI]	3 (17) [3.6-41.4]	1 (6) [0.1-27.3]	11 (27) [14.2-42.9]	9 (22) [10.6-37.6]	3 (17) [3.6-41.4]
CBR, n (%) [95% CI]	6 (33) [13.3-59.0]	4 (22) [6.4-47.6]	19 (46) [30.7-62.6]	15 (37) [22.1-53.1]	7 (39) [17.3-64.3]

- The highest response rate was observed in patients with gain(1q)

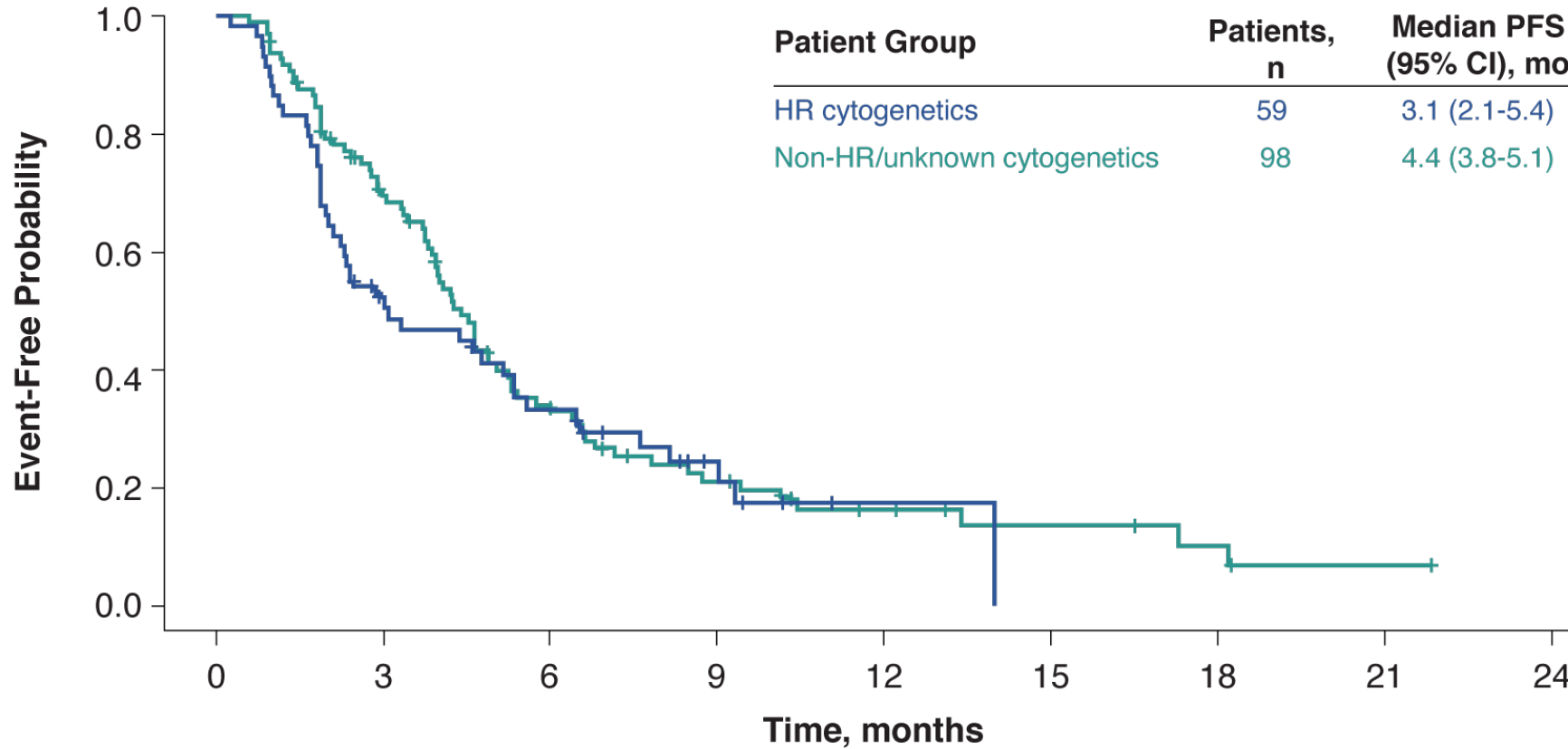
Investigator-assessed best overall response per International Myeloma Working Group uniform criteria.<sup>1</sup>

<sup>a</sup>Patients may have had >1 co-occurring cytogenetic abnormality.

CBR, clinical benefit rate; del, deletion; HR, high risk; ORR, overall response rate.

1. Rajkumar SV, et al. *Blood*. 2011;117:4691-5.

# PFS by HR Cytogenetic Group



	Number at risk								
	0	3	6	9	12	15	18	21	24
<b>HR cytogenetics</b>	59	28	17	7	1	0	0	0	0
<b>Non-HR/unknown cytogenetics</b>	98	63	29	15	8	5	3	1	0

HR, high risk; PFS, progression-free survival.

# PFS and OS by Type and Number of HR Features

Patient Group	Patients, n	PFS, Median (95% CI), mo	OS, Median (95% CI), mo
HR cytogenetics	59	3.1 (2.1-5.4)	11.5 (8.5-13.6)
Del(17p)	18	2.4 (1.9-6.5)	11.5 (3.6-14.5)
T(4;14)	18	2.3 (1.8-5.4)	8.4 (3.3-11.5)
Gain(1q)	41	4.6 (2.5-6.5)	11.8 (9.3-21.1)
1 HR feature	41	2.4 (1.9-4.8)	11.6 (7.7-21.1)
≥2 HR features	18	5.4 (2.2-6.5)	11.5 (4.5-14.5)
Non-HR/unknown cytogenetics	98	4.4 (3.8-5.1)	13.2 (8.1-17.6)

- Although outcomes were generally consistent among patients with HR cytogenetic features, patients with gain(1q) appeared to derive the most benefit from melflufen plus dexamethasone therapy

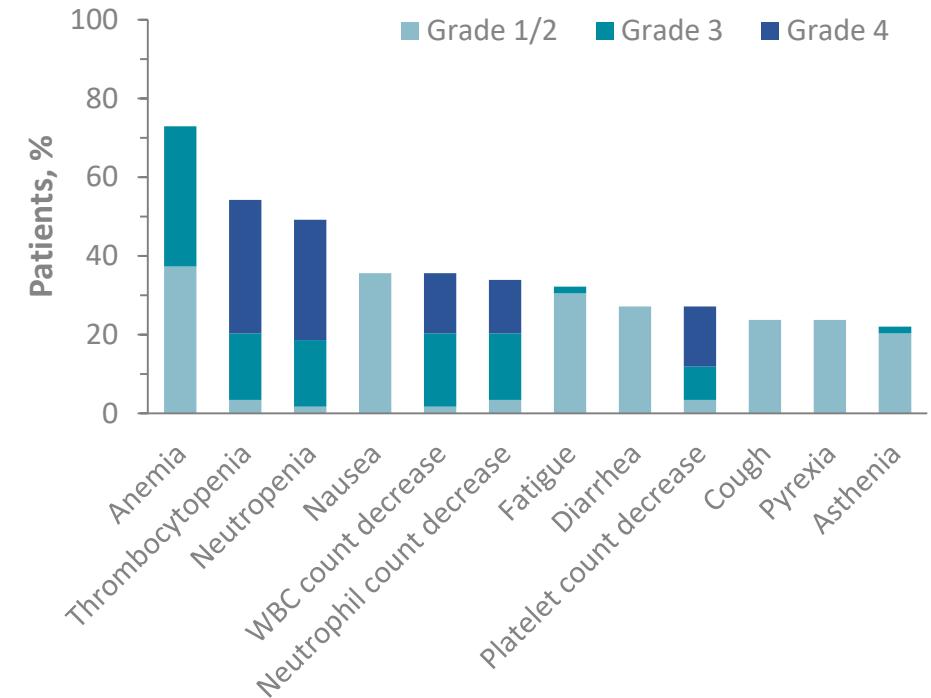
## Summary of TEAEs by HR Cytogenetic Group

Patients With TEAE, n (%) <sup>a</sup>	HR Cytogenetics (n=59)	Non-HR/Unknown Cytogenetics <sup>b</sup> (n=98)
Grade ≥3 TEAEs	56 (95)	94 (96)
TEAEs leading to melflufen discontinuation	11 (19)	23 (23)
Occurring in ≥2 patients in either group		
Thrombocytopenia	5 (8)	11 (11)
Acute kidney injury	2 (3)	0 (0)
Pneumonia	2 (3)	1 (1)
Neutropenia	1 (2)	4 (4)
Febrile neutropenia	0 (0)	2 (2)
TEAEs leading to melflufen dose reduction	14 (24)	28 (29)
TEAEs leading to melflufen dose delay	28 (47)	69 (70)
Any SAE	33 (56)	47 (48)

The safety profile of melflufen plus dexamethasone in patients with HR cytogenetics was consistent with that in the overall population<sup>1</sup>

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

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



- Fatal TEAEs occurred in 4 (7%) patients with HR cytogenetics and in 6 (6%) patients with non-HR/unknown cytogenetics
  - None were considered related to melflufen

<sup>a</sup>AEs are coded to preferred term using MedDRA, version 19.1. <sup>b</sup>Includes patients with standard-risk cytogenetics (n=67) and patients with missing/unknown cytogenetic status (n=31).

AE, adverse event; HR, high-risk; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event; WBC, white blood cell.

1. Richardson PG, et al. EHA 2020. Poster EP945.

- In HORIZON, melflufen plus dexamethasone demonstrated clinically meaningful efficacy and a manageable safety profile in patients with advanced RRMM, including patients with HR cytogenetics
  - Durable responses were observed among patients with HR cytogenetics, including in patients with  $\geq 2$  cytogenetic abnormalities and gain(1q)
- The safety profile of melflufen plus dexamethasone in patients with HR cytogenetics was consistent with that of previous reports.<sup>1,2</sup> No new safety concerns were identified
- These data are encouraging and support further evaluation of melflufen plus dexamethasone in patients with RRMM and with HR cytogenetics

HR, high risk; RRMM, relapsed/refractory multiple myeloma.

1. Richardson PG, et al. *Lancet Haematol*. 2020;7:e395-407. 2. Richardson PG, et al. EHA 2020. Poster EP945.

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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](#), [3214](#), [3477](#) (posters)
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