ANCHOR (OP-104): Melflufen Plus Dexamethasone and Daratumumab or Bortezomib in Relapsed/Refractory Multiple Myeloma Refractory to an IMiD and/or a Proteasome Inhibitor — Updated Efficacy and Safety

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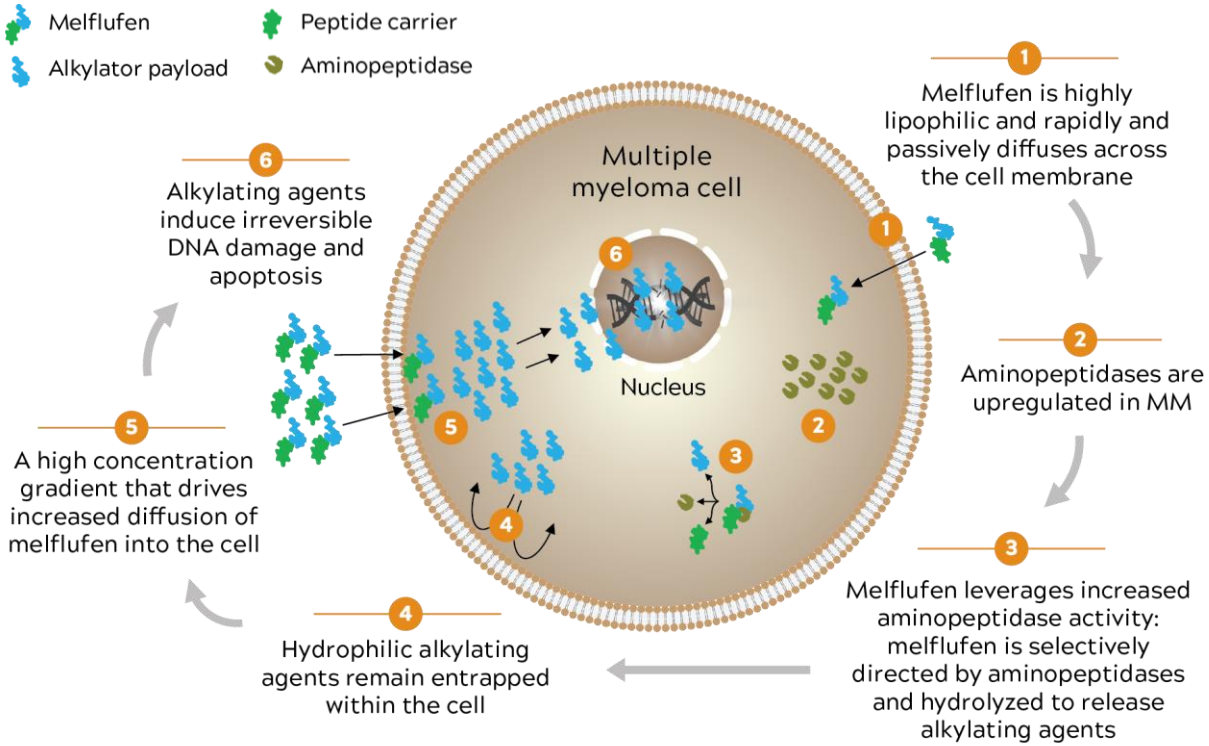
Melphalan Flufenamide (Melflufen) Is the First Aminopeptidase-Targeted Peptide-Drug Conjugate (PDC)

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 (OP-106), the activity of melflufen plus dexamethasone was further shown in heavily pretreated RRMM patients refractory to pomalidomide and/or anti-CD38 mAb therapy, with acceptable safety[6]
  - ORR was 29%; median PFS was 4.2 months, and median OS was 11.6 months
  - Grade 3/4 hematologic AEs were common (mainly neutropenia [79%], thrombocytopenia [76%], and anemia [71%]) but clinically manageable; nonhematologic AEs were infrequent

AE, adverse event; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-rate survival; 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. Richardson PG, et al. EHA 2020. Poster EP945.

ANCHOR Study Design

- ANCHOR is a Phase 1/2a, 3+3 design, dose-escalation study of melflufen plus dexamethasone in combination with either daratumumab or bortezomib
- Up to 3 dose levels of melflufen are being tested, starting at 30 mg and either increasing to 40 mg or decreasing to 20 mg based on observed DLTs
- Once the optimal dose has been established, an additional 20 patients per regimen will be recruited into the phase 2 of the study, for which the primary objective is ORR (investigator assessed according to International Myeloma Working Group criteria)
- Here, we present the interim analysis for both treatment arms as of October 19, 2020

NCT03481556

DLT, dose-limiting toxicity; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma.

ANCHOR: Melflufen Plus Dexamethasone in Combination With Bortezomib

Study Schema

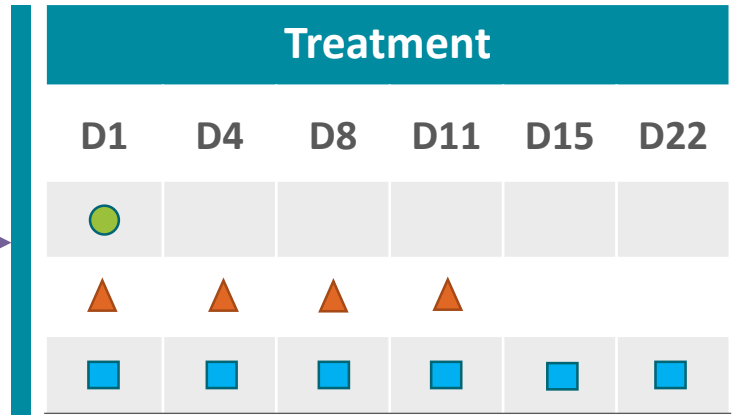
Phase 1/2, Open-Label, Multicenter Study: Bortezomib Combination Cohort

Patients with RRMM

- 1-4 prior lines of therapy
- Refractory to (or intolerant of) an IMiD and/or PI
- Aged ≥18 years
- Measurable disease
- ECOG PS ≤2
- **Not PI-refractory in last line (N=13)[a]**

NCT03481556

28-day cycles until disease progression or unacceptable toxicity



Melflufen (IV): 40/30/20 mg on day 1
Bortezomib (SC): 1.3 mg/m^2 on days 1, 4, 8, and 11
Dexamethasone (po): 20/40 mg[b]

Primary objectives

- Phase 1: Optimal dose of melflufen in combination
- Phase 2: ORR

Secondary objectives

- Best response
- DOR
- TTR
- PFS (monthly until PD)
- OS (every 3 months)
- Safety

[a]One patient was replaced due to G-CSF administration in the DLT period. [b]Dexamethasone 20 mg is administered on days 1, 4, 8, and 11 of each cycle and 40 mg on days 15 and 22 of each cycle; for patients aged ≥75 years, a 12-mg dose is administered on days 1, 4, 8, and 11 and 20 mg on days 15 and 22.

D, day; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; po, oral; SC, subcutaneous; TTR, time to response.

Melflufen Plus Dexamethasone in Combination With Bortezomib

Patients and Efficacy Outcomes (N=13)

- Median age was 72 years (range, 61-82), and median number of prior lines was 3 (range, 1-4)
  - High-risk cytogenetics were present in 44% of patients with known status[a]; 77% were refractory to last therapy, and 92% received a prior PI
- Eight patients (62%) remained on treatment at the time of data cutoff
  - Five patients discontinued treatment (2 patients due to PD, 2 patients due to other,[b] and 1 due to an AE)
- Median treatment duration was 8.7 months (range, 1.4-29.0)
- At a median follow-up time of 12.0 months, PFS data were not yet mature

	Best Confirmed Response, Patients, n							Patients, %	
Subgroup	>CR	VGPR	PR	MR	SD	PD	NA	ORR	CBR
Melflufen 30 mg (n=6)	0	1	2	0	2	0	1[a]	50	50
Melflufen 40 mg (n=7)	1	3	1	0	1	0	1[b]	71	71
Total (N=13)	**1**	**4**	**3**	**0**	**3**	**0**	**2**	**62**	**62**

[a]One patient had an unconfirmed MR in the 30-mg dose cohort.
[b]One patient had an unconfirmed SD in the 40-mg dose cohort.

Data cutoff date: 19 October 2020.
[a]Four patients had unknown high-risk status by cytogenetics. [b]Grouped term "other" includes lack of efficacy (n=1) and other (n=1).
AE, adverse event; CBR, clinical benefit rate; CR, complete response; MR, minor response; NA, not assessed; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; SD, stable disease; VGPR, very good PR.

Melflufen Plus Dexamethasone in Combination With Bortezomib

Safety and Tolerability (N=13)

Grade ≥3 TRAEs[a,b]	Patients, n (%) 30 mg (n=6)	40 mg (n=7)	Total (N=13)
Any Grade ≥3 TRAE	5 (83)	7 (100)	**12 (92)**
Thrombocytopenia[c]	3 (50)	7 (100)	**10 (77)**
Neutropenia[d]	2 (33)	5 (71)	**7 (54)**
Anemia	2 (33)	4 (57)	**6 (46)**

[a]TRAEs ≥2 patients. [b]Additional grade ≥3 TRAEs that occurred in 1 patient in the 30-mg cohort included fatigue, syncope, pneumonia pneumococcal, and hypotension. Additional grade ≥3 TRAEs that occurred in 1 patient in the 40-mg cohort included hemorrhage. [c]Thrombocytopenia includes the preferred terms 'thrombocytopenia' and 'platelet count decreased'. [d]Neutropenia includes the preferred terms 'neutropenia' and neutrophil count decreased'.

- No DLTs were observed at any dose
- Grade ≥3 nonhematologic TRAEs were uncommon
- Three patients (23%) experienced serious TRAEs (pneumonia and neutropenia; thrombocytopenia and neutropenia; and syncope [1 patient each])
- One patient experienced an AE with a fatal outcome ≤30 days after last dose of study drug (cardiac failure chronic, considered unrelated to study treatment)

Data cutoff date: 19 October 2020.
AE, adverse event; DLT, dose-limiting toxicity; TRAE, treatment-related AE.

ANCHOR: Melflufen Plus Dexamethasone in Combination With Daratumumab

Study Schema

Phase 1/2, Open-Label, Multicenter Study: Daratumumab Combination Cohort

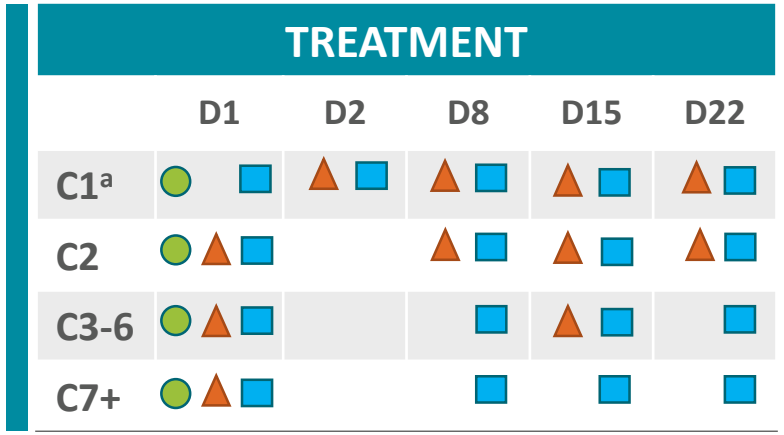
Patients with RRMM

- 1-4 prior lines of therapy
- Refractory to (or intolerant of) an IMiD and/or PI
- Aged ≥18 years
- Measurable disease
- ECOG PS ≤2
- **No prior anti-CD38 mAb therapy**

(N=33)

NCT03481556

28-day cycles until disease progression or unacceptable toxicity



Melflufen (IV): 40/30/20 mg on day 1
Daratumumab (IV): 16 mg/kg[b]
Dexamethasone (po): 40 mg weekly[c,d]

Primary objectives

- Phase 1: Optimal dose of melflufen in combination
- Phase 2: ORR

Secondary objectives

- Best response
- DOR
- TTR
- PFS (monthly until PD)
- OS (every 3 months)
- Safety

[a]In cycle 1, daratumumab is administered on day 2 due to prolonged infusion time of the first dose. [b]Administered on days 2, 8, 15, and 22 for cycle 1; days 1, 8, 15, and 22 for cycle 2; days 1 and 15 for cycles 3 to 6; and day 1 for cycles 7+. [c]For patients aged ≥75 years, a 20-mg dose is administered. [d]Oral dexamethasone may be substituted for IV dexamethasone before daratumumab infusion only.
C, cycle; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; po, oral; TTR, time to response.

Melflufen Plus Dexamethasone in Combination With Daratumumab

Baseline Patient Characteristics (N=33)

Characteristics	30 mg (n=6)	40 mg (n=27)	Total (N=33)
Age, median (range), y	57 (49-78)	66 (35-77)	**63 (35-78)**
Sex (men / women), n (%)	3 (50) / 3 (50)	19 (70) / 8 (30)	**22 (67) / 11 (33)**
Time since diagnosis, median (range), y	3.1 (1.9-8.0)	3.9 (0.7-15.6)	**3.8 (0.7-15.6)**
No. of previous lines, median (range)	2.5 (1-3)	2.0 (1-4)	**2.0 (1-4)**
ISS at study entry, I / II / III[a], n (%)	6 (100) / 0 / 0	18 (67) / 5 (19) / 3 (11)	**24 (73) / 5 (15) / 3 (9)**
High-risk cytogenetics by FISH[b], n/N (%)	2/5 (40)	12/21 (57)	**14/26 (54)**
ECOG PS 0 / 1 / 2, (%)	50 / 33 / 17	41 / 52 / 7	**42 / 48 / 9**
Prior ASCT / alkylator exposed, n (%)	5 (83) / 5 (83)	21 (78) / 24 (89)	**26 (79) / 29 (88)**
Alkylator refractory, n (%)	1 (17)	3 (11)	**4 (12)**
IMiD refractory, n (%)	3 (50)	18 (67)	**21 (64)**
PI refractory, n (%)	0	15 (56)	**15 (45)**
Last-line refractory[c], n (%)	3 (50)	17 (63)	**20 (61)**
IMiD + PI refractory, n (%)	0	12 (44)	**12 (36)**

Data cutoff date: 19 October 2020.

[a]One patient at the 40-mg dose level had unknown ISS. [b]High-risk defined as t(4;14), t(14;16), t(14;20), del(17/17p), or gain(1q). Missing data for 1 patient at the 30-mg dose level and 6 patients at the 40-mg dose level.

[c]Failure to achieve at least a minimal response or progression on therapy within 60 days of treatment.

ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; ISS, International Staging System; PI, proteasome inhibitor.

Patient Disposition (N=33)

Disposition	30 mg (n=6)	40 mg (n=27)
On treatment at data cutoff	2 (33)	3 (11)
Discontinued treatment at data cutoff	4 (67)	24 (89)
Progressive disease	2 (33)	12 (44)
Adverse events	1 (17)	7 (26)
Other[a]	1 (17)	5 (19)

- Median follow-up: 18.4 months (95% CI, 16.2-25.9)
  - 30 mg: 28.4 months (95% CI, 18.9-NR)
  - 40 mg: 16.9 months (95% CI, 15.4-19.2)

Data cutoff date: 19 October 2020.
[a]Grouped term "other" includes lack of efficacy (n=1) in the 30-mg cohort, and in the 40-mg cohort, due to lack of efficacy and physician's decision (n=2 each) and other (n=1).
NR, not reached.

Treatment Exposure (N=33)

	30 mg (n=6)	40 mg (n=27)
No. of treatment cycles, median (range)	19 (1-32)	6 (1-27)
Treatment duration, median (range), mo	21.7 (1-30.2)	6.2 (1-27.6)
Total cumulative doses administered, median (range), mg		
Melflufen	344 (30-960)	150 (40-790)
Daratumumab	42765 (5670-75232)	16128 (3776-46800)
Dexamethasone	2280 (120-4980)	640 (160-4060)

- In total, 2 patients (33%) in the 30-mg cohort and 7 patients (26%) in the 40-mg cohort discontinued melflufen but continued with daratumumab and dexamethasone

Data cutoff date: 19 October 2020.

Melflufen Plus Dexamethasone in Combination With Daratumumab

Overall Response (N=33)

Subgroup	Best Confirmed Response, Patients, n							Patients, %	
	>CR	VGPR	PR	MR	SD	PD	NA	ORR	CBR
Melflufen 30 mg (n=6)	0	4	1	0	0	0	1[a]	83	83
Melflufen 40 mg (n=27)	2	6	11	1	2	1	4[b]	70	74
Total (N=33)	**2**	**10**	**12**	**1**	**2**	**1**	**5**	**73**	**76**

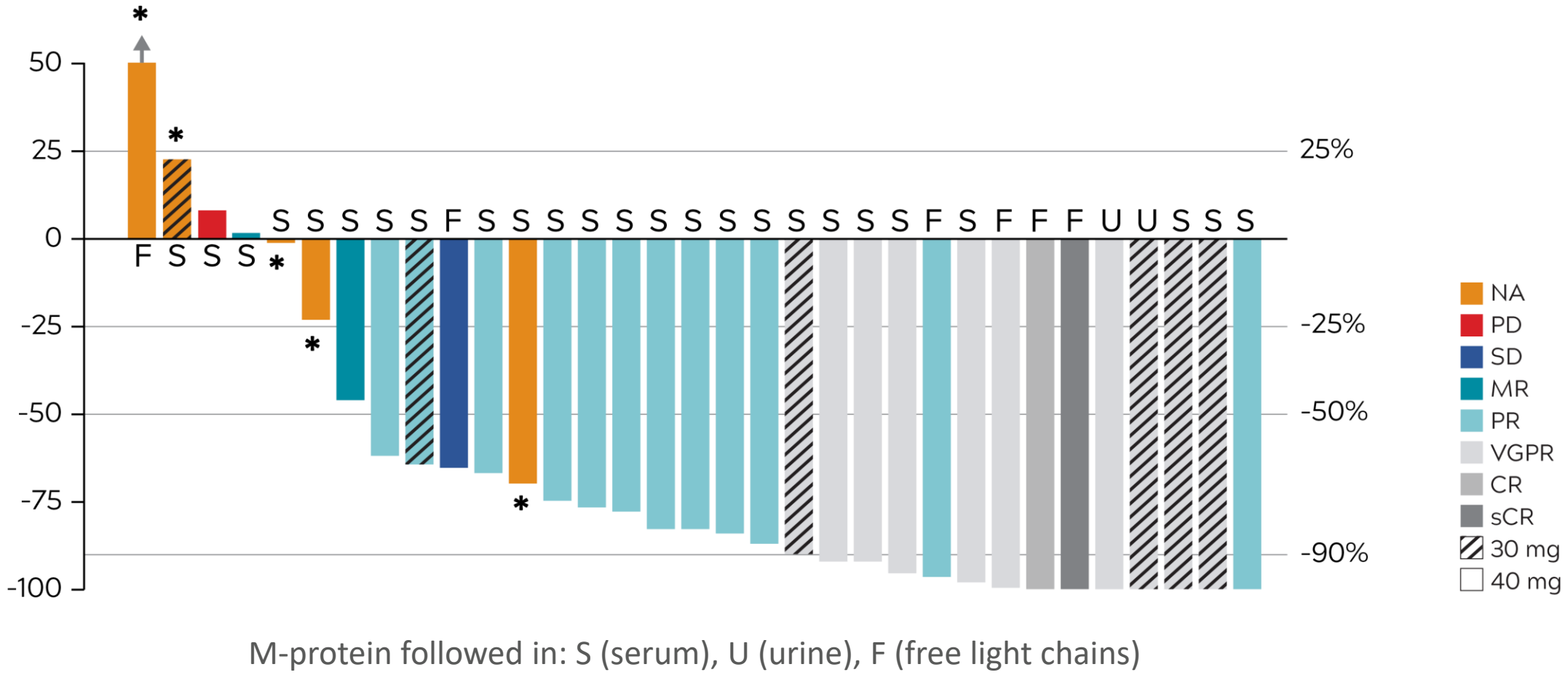
[a]One patient had an unconfirmed PD in 30-mg dose cohort.
[b]Four patients had unconfirmed responses in the 40-mg dose cohort: 2 PD, 1 SD, and 1 PR.

- ORR in patients was similar for both cohorts
  - 30 mg: 83%
  - 40 mg: 70%
  - 30 + 40 mg: 73%

Data cutoff date: 19 October 2020.
CBR, clinical benefit rate; CR, complete response; MR, minor response; NA, not assessed; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Melflufen Plus Dexamethasone in Combination With Daratumumab

Best M-Protein Change (N=33)



M-protein followed in: S (serum), U (urine), F (free light chains)

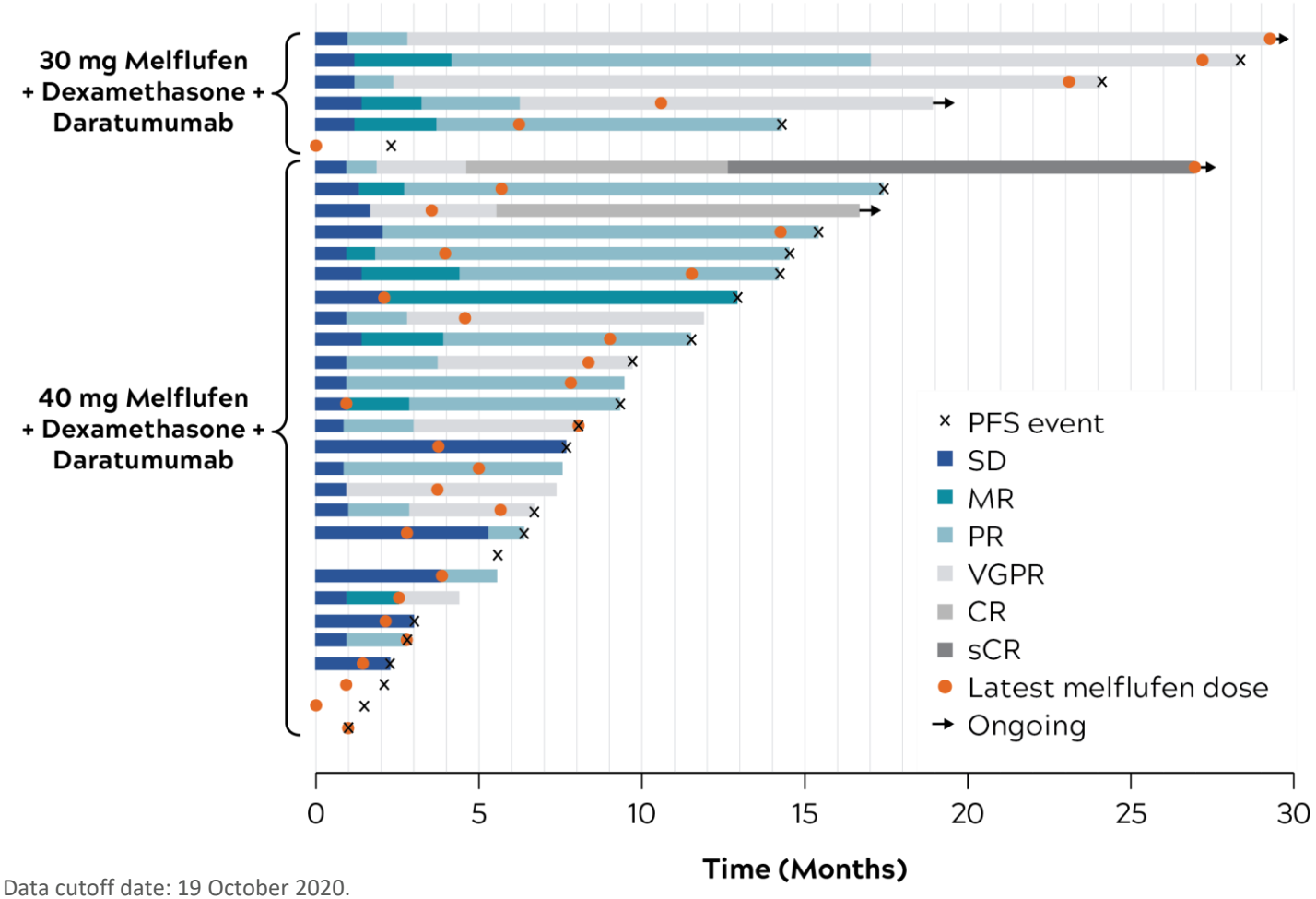
Data cutoff date: 19 October 2020.

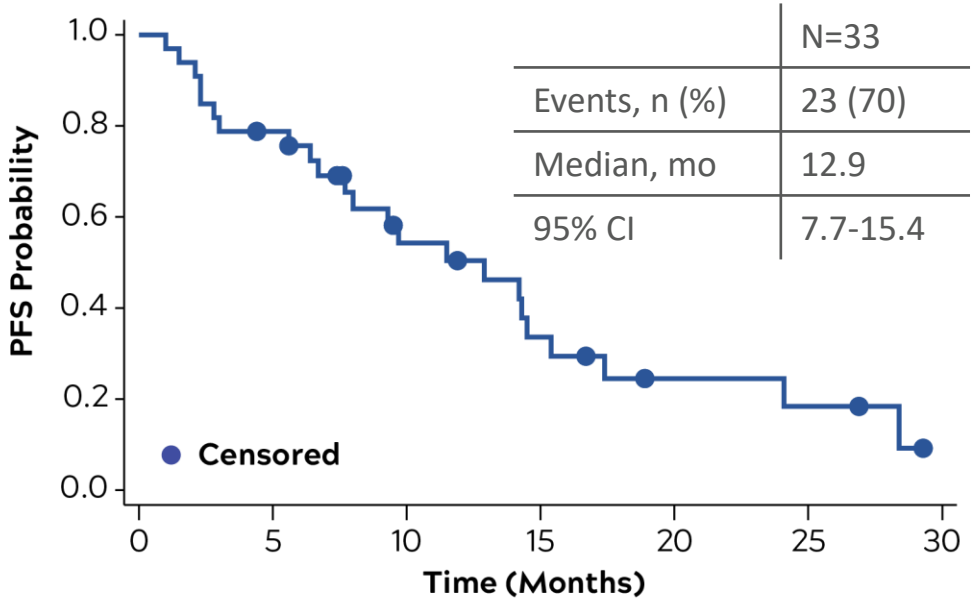
Response categories refer to best confirmed response. Asterisk denotes patients with unconfirmed responses.

CR, complete response; PD, progressive disease; PR, partial response; MR, minimal response; NA, not assessed; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

Melflufen Plus Dexamethasone in Combination With Daratumumab

Swimmer Plot and Progression-Free Survival (N=33)





	N=33
Events, n (%)	23 (70)
Median, mo	12.9
95% CI	7.7-15.4

- Median DOR was 12.6 months (95% CI, 7.6-24.2), with 5 of 33 patients still ongoing at the time of data cutoff (2 patients on melflufen 30 mg and 3 patients on melflufen 40 mg)
- At a median follow-up of 18.9 months, median PFS was 12.9 months (95% CI, 7.7-15.4)
- The OS data were immature at the median follow-up of 18.4 months

Data cutoff date: 19 October 2020.

CR, complete response; DOR, duration of response; MR, minor response; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

Melflufen Plus Dexamethasone in Combination With Daratumumab

Safety and Tolerability (N=33)

Grade ≥3 TRAEs[a,b]	Patients, n (%) 30 mg (n=6)	40 mg (n=27)	Total (N=33)
Any Grade ≥3 TRAE	5 (83)	24 (89)	**29 (88)**
Thrombocytopenia[c]	3 (50)	21 (78)	**24 (73)**
Neutropenia[d]	5 (83)	17 (63)	**22 (67)**
Anemia	3 (50)	5 (19)	**8 (24)**
Lymphopenia	0 (0)	2 (7)	**2 (6)**
Febrile neutropenia	1 (17)	1 (4)	**2 (6)**
Pneumonia	0 (0)	2 (7)	**2 (6)**

[a]TRAEs ≥2 patients combined across both cohorts (preferred term). [b]Additional grade ≥3 TRAEs that occurred in 1 patient in the 30-mg cohort included and in 1 patient in the 40-mg cohort included leukopenia, pancytopenia, fatigue, upper respiratory tract infection, infusion related reaction, blood alkaline phosphatase increased, muscular weakness, agitation, sepsis, and hypertension. [c]Thrombocytopenia includes the preferred terms 'thrombocytopenia' and 'platelet count decreased pooled together'. [d]Neutropenia includes the preferred terms 'neutropenia' and 'neutrophil count decreased' pooled together.

- No DLTs were observed at any dose
- 15 patients (45%) experienced SAEs, most commonly pneumonia (12%); influenza (9%); and parainfluenza virus infection, sepsis, urinary tract infection, and febrile neutropenia (6% each)[a]
  - 30 mg: 4 patients (67%)
  - 40 mg: 11 patients (41%)
- Four AEs with fatal outcomes
  - 30 mg: sepsis (unrelated to study treatment)
  - 40 mg: sepsis (possibly related to melflufen), and cardiac failure chronic and and general physical health deterioration (unrelated to study treatment)[b]

Data cutoff date: 19 October 2020.

[a]Treatment-related SAEs in the 30-mg cohort included febrile neutropenia (1 patient) and in the 40-mg cohort, pneumonia (3 patients) and febrile neutropenia, pancytopenia, sepsis, upper respiratory tract infection, and pyrexia (1 patient each). [b]Event occurred 2 days after last exposure to study treatment; cause of death was reported as progressive disease.

AE, adverse event; DLT, dose-limiting toxicity; SAE, serious AE; TRAE, treatment-related AE.

Melflufen Plus Dexamethasone in Combination With Daratumumab

Dose Reductions and Discontinuations Due to AEs (N=33)

	30 mg (n=6)	40 mg (n=27)
Any TEAEs leading to melflufen dose reduction, n (%)	3 (50)	18 (67)
Time to first dose reduction due to AE, median, mo (95% CI)	6.2 (1.4-NR)	3.7 (2.7-4.6)
Most common AEs leading to dose reduction, n (%)		
Thrombocytopenia[a]	2 (33)	15 (56)
Neutropenia[b]	1 (17)	7 (26)
Most common AEs leading to treatment discontinuation of any study drug,[c] n (%)		
Thrombocytopenia[a]	1 (17)	11 (41)
Neutropenia[b]	1 (17)	2 (7)
Sepsis	1 (17)	1 (4)
Anemia	0 (0)	2 (7)

[a]Thrombocytopenia includes the preferred terms 'thrombocytopenia' and 'platelet count decreased'.
[b]Neutropenia includes the preferred terms 'neutropenia' and 'neutrophil count decreased'.
[c]Additional AEs leading to treatment discontinuation of any study drug in the 30-mg cohort included influenza and in the 40-mg cohort included pancytopenia, weight increased, pneumonia, chronic cardiac failure, right ventricular hypertrophy, asthenia, fall, head injury, insomnia, and hiccups.

Data cutoff date: 19 October 2020.
AE, adverse event; NR, not reached; TEAE, treatment-emergent AE.

ANCHOR: Conclusions

- Melflufen plus dexamethasone as a triplet regimen with daratumumab or bortezomib in heavily pretreated RRMM was well tolerated, with a similar safety profile as when used as a doublet (melflufen plus dexamethasone)[1,2]
  - Grade 3/4 TRAEs were mostly hematologic and clinically manageable with dose reductions
- No DLTs were observed across both regimens and melflufen dose levels
- Both combinations demonstrated encouraging activity
  - ORR was 73% in combination with daratumumab and 62% in combination with bortezomib
  - Median PFS was 12.9 months in combination with daratumumab
- For the daratumumab arm, the safety and efficacy analysis has determined that melflufen at 30 mg should be the recommended dose with daratumumab in future studies
- The bortezomib arm of ANCHOR is still recruiting, and the RP2D is yet to be determined

DLT, dose-limiting toxicity; ORR, overall response rate; PFS, progression-free survival; R2PD, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; TRAE, treatment-related adverse event.

1. Richardson P, et al. *Lancet Haematol*. 2020;7:e395-e407. 2. Richardson P, et al. EHA 2020. Abstract EP945.

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